Studies towards the Total Synthesis of Natural Products: 
CR377 and Dolabriferol

A thesis submitted for the fulfillment of the degree of

Doctor of Philosophy

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Flinders University

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Adelaide, Australia

November 2015
Declaration

‘I declare that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge does not contain any material previously published or written by another person except where due reference is made in the text.’

Clark Nash

November 2015
I would first and foremost like to thank Associate Professor Mike Perkins for giving me the opportunity to be a part of his illustrious research group that I had admired throughout my forensic and analytical chemistry degree. This opportunity has given me the chance to develop my professional career and succeed in this field of chemistry that I am passionate about, and for that I thank you ‘Dr Mike’. I would also like to thank ‘Dr Mike’ for the amount of knowledge he has passed on to me during my time at Flinders University, and for allowing me the freedom to discover and scope out some of the subtleties of organic synthesis within these natural product research projects.

I would also like to extend my gratitude to the School of Chemistry and Physics’ many academic, technical and administrative staff and fellow post graduate students during my time spent at Flinders University. Your teachings and support gave me the skills and foundation I required to pursue and be successful during these post graduate studies. In particular, I would like to thank Associate Professors Martin Johnston and Claire Lenehan who have both been closely involved in my chemistry career to date; passing on their vast chemistry knowledge and life experiences has been invaluable.

To Christine my amazing wife, your continual support during this time has been immense, in that if it weren’t for your “keep going you can do this” external motivation I know I would not have been able to achieve this award. To my extended family support group (Mum, Dad, Paige, Patrick, Grandma & Grandad Odgers and Nash, the Carroll’s and the Merrill’s) your continual encouragement, belief and “is there something I can do to help” attitude has played a huge role in my pursuit of a PhD and my other study achievements to date.
Presentations

The following list represents presentations given on research outlined in this thesis at various symposia.

Towards the Stereoselective Synthesis of Polyektide Natural Products: CR377 and Dolabriferol.


A Retro-Claisen Approach towards the Total Synthesis of Dolabriferol.


A Retro-Claisen Approach towards the Total Synthesis of Dolabriferol.

Abstract

Natural product chemistry has been at the forefront of organic chemistry since the late 20th century with natures’ seemingly endless supply of compounds that display different types of structural complexity and biological activity. Synthesis of these intriguing natural products as a result has been one of organic chemistry’s main sources for innovation. Chapter one of this thesis introduces polyketide natural products, including their structure, biosynthesis and potent biological activities. This chapter also discusses the current strategies employed by synthetic chemists towards synthesis of polyketide natural products, with a detailed focus on both the acylation and aldol reactions. These well established chemical transformations feature heavily in polyketide synthesis and were used extensively in this dissertation.

Chapter two describes the synthesis attempts towards synthesis of CR377 (9), a polyketide natural product with a unique six-membered unsaturated tricarbonylmethane system isolated from the Fusarium Species by Brady et al. The main attempts focused on the synthesis of an acyclic tricarbonyl precursor 127 and a cyclic pyrone precursor 204, following the successful synthesis of their respective model compounds 139 in 31% (two steps), and 201 in 70% yield. Aldehyde 131 was synthesised in 33% overall yield in five linear steps from ethyl-(S)-lactate (132), and was the central focus in accessing both synthetic approaches towards the natural product. Unfortunately, incorporation of the structurally unique exocyclic double bond either caused oxidation, intramolecular conjugate addition or decomposition problems in the final stages of each synthesis strategy.
Chapter three details the structural determination of an unexpected Swern oxidation product 242 observed during an attempt towards the total synthesis of CR377 (9). Synthesis of a model unsaturated β-hydroxy ester 243 produced an analogous result 252 following the standard Swern oxidation oxalyl chloride-DMSO protocol. Structural determination was achieved by synthesis of a m-nitroaniline conjugate addition product 253 in 60% yield, which following single crystal X-ray diffraction confirmed the α,α-dichlorinated products. Swern oxidation of structurally diverse β-acyl or β-keto alcohols also gave their respective dichlorinated products in moderate to excellent yields, as a result of electrophilic chlorination.
Chapter four describes an unrefined total synthesis of marine polypropionate dolabriferol (10), which utilised a retro-Claisen rearrangement as the pivotal transformation to install the unusual ester linkage. The strategy adopted towards dolabriferol (10) involved use of lactate derive ketone 82 to install all but one of the required stereocentres in the natural product. Complete silyl deprotection of trione 400 led to the formation of trioxaadamantane 403, whose contribution as an intramolecular protecting group led to the exclusive formation of ester 405 following extended exposure to base. Hydrogenolysis of the benzyl ether protecting group in ester 405 allowed the final cyclisation to occur completing the total synthesis of dolabriferol (10) in 0.63% overall yield from methyl-3-hydroxy-2-methylpropionate in 17 linear steps.
# Glossary

A number of common, non-standard abbreviations have been used throughout this thesis. Given here are the abbreviations followed by the standard name.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Standard Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>BF$_3$.OEt$_2$</td>
<td>boron trifluoride-diethyl ether complex</td>
</tr>
<tr>
<td>BH$_3$.SMe$_2$</td>
<td>borane-dimethyl sulfide complex</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
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<tr>
<td>t-BuOH</td>
<td>tertiary-butanol</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>butyl lithium</td>
</tr>
<tr>
<td>Bz$_2$O</td>
<td>benzoic anhydride</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deuterated chloroform</td>
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<tr>
<td>C$_6$D$_6$</td>
<td>deuterated benzene</td>
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<tr>
<td>CH$_2$Cl$_2$</td>
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<td>CH$_3$CO$_2$H</td>
<td>acetic acid</td>
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<tr>
<td>COSY</td>
<td>$^1$H–$^1$H correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
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<tr>
<td>δ</td>
<td>chemical shift (ppm)</td>
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<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
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</tr>
<tr>
<td>DIBALH</td>
<td>diisobutylaluminium hydride</td>
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<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
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<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin Periodinane</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>eq</td>
<td>equivalents</td>
</tr>
<tr>
<td>et al</td>
<td>et alia (and others)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
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<td>iPr₂Net</td>
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</tr>
<tr>
<td>J</td>
<td>coupling constant (Hz)</td>
</tr>
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</tr>
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<tr>
<td>KMnO₄</td>
<td>potassium permanganate</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamine</td>
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<td>Full Form</td>
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<tr>
<td>LiHMDS</td>
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<td>literature</td>
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<tr>
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</tr>
<tr>
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<td>methanol</td>
</tr>
<tr>
<td>MgBr₂·OEt₂</td>
<td>magnesium bromide diethyl ether complex</td>
</tr>
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<td>millimole</td>
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<td>mole</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>sodium borohydride</td>
</tr>
<tr>
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<td>sodium hydroxide</td>
</tr>
<tr>
<td>NEt₃</td>
<td>triethylamine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate (triflate)</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>PMB</td>
<td>\textit{para}-methoxybenzyl</td>
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<td>PMB-Cl</td>
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<td>\textit{para}-methoxyphenyl</td>
</tr>
<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>R_f</td>
<td>retention factor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>-------------</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SmI$_2$</td>
<td>samarium(II) iodide</td>
</tr>
<tr>
<td>Sn(OTf)$_2$</td>
<td>tin(II) trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TAS-F</td>
<td>tris(dimethylamino)sulfur (trimethylsilyl)difluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBS-Cl</td>
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</tr>
<tr>
<td>TBSOTf</td>
<td>tert-butyldimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TESOTf</td>
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<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>triflic acid</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TiCl$_4$</td>
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<tr>
<td>Ti(PrO)$_4$</td>
<td>titanium tetraisopropoxide</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
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<td>TMSCl</td>
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<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
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</table>
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Appendix 1
Chapter One

Introduction to Polyketide Natural Products:
Formation, Biological Applications and Current Synthetic Approaches

This chapter introduces polyketide natural products, their biosynthesis and potent biological activities. The chapter also details the post condensation reaction transformations that lead to the formation of active secondary metabolites. Also discussed are the current strategies employed by the modern synthetic chemist towards the synthesis of polyketide natural products, with a focus directed towards the acylation and aldol reactions for asymmetric polyprenionate assembly.

**Acylation Reaction**

\[
\begin{align*}
\text{Ketone} & \xrightarrow{\text{Enolisation}} \text{Metal Enolate} & \text{O} & \text{O} & \text{R}_1 & \text{R}_2 \\
\text{Acylated Product} & \text{R}_1 & \text{R}_2 & \text{O} & \text{O}
\end{align*}
\]

**Aldol Reaction**

\[
\begin{align*}
\text{Ketone} & \xrightarrow{\text{Enolisation}} \text{Metal Enolate} & \text{O} & \text{H} & \text{R}_2 & \text{R}_2 \\
\text{Aldol Product} & \text{R}_1 & \text{R}_2 & \text{O} & \text{OH} & \text{R}_3
\end{align*}
\]
1.1 Polyketide Natural Products

1.1.1 The Rise of Terrestrial and Marine Polyketide Natural Products

Natural product chemistry came to the forefront of organic chemistry in the late 20\textsuperscript{th} century with nature’s seemingly endless supply of structurally complex terrestrial and marine polyketide natural products.\textsuperscript{1} As a result, the total synthesis of these intriguing natural products has continued to be one of the main sources for innovation in organic chemistry.

Interest from the scientific community came as these natural products were shown to possess quite potent biological activities including anticancer, antifungal, antibiotic, anti-inflammatory and antiviral properties.\textsuperscript{2} This prosperous feature however remains obstructed as compounds obtained from their natural source are only ever isolated in microgram to milligram quantities. This impediment provides current synthetic chemists with the challenge of developing new stereocchemical strategies for the total synthesis of these bioactive natural products, providing sufficient material for further biological and chemical analysis.

1.1.2 The Continual Search for New Natural Products

Since the late 20\textsuperscript{th} century natural products have been the source of the most active ingredients used in medicine. From 1994 half of all drugs approved were primarily based on natural products, with 13 natural product based drugs approved between 2005 and 2007.\textsuperscript{3} Currently, there are over 100 natural product based drugs in clinical development particularly in the area of anticancer agents.\textsuperscript{3,4}

The increase in the number of severely immunosuppressed patients over the last 10 years has resulted from the AIDS epidemic\textsuperscript{5} and also medicinal technologies in the form of aggressive anticancer therapies. Treatment of these immunosuppressed patients has in part led to increased reports of drug resistance,\textsuperscript{6} and hence it is of the greatest imperative that new biologically active compounds be discovered and synthetically produced to provide new materials for chemical and biological testing.
1.1.3 Structure and Biosynthesis

Polyketides are all structurally related, in that they are all synthesised by nature by the decarboxylative Claisen condensation of organic acids which predominately incorporate acetate, propionate and butyrate units. The successive reaction of these groups results in the final linear polyketide structure having alternate oxygenated and alkyl substituents with multiple contiguous stereocentres.2

As a result, polyketide natural products can be highly complex in structure containing numerous heterocyclic ring systems and stereocentres like discodermolide (1),7 rapamycin (2)8 and erythromycin (3)9 or they can consist of simpler structures like resveratrol (4)10 and pteroenone (5)11 (Figure 1.1).

\[ \text{Figure 1.1: The different levels of complexity of polyketide natural products} \]
1.1.4 Polyketide Synthases

Polyketide synthases (PKS) are the class of enzymes that are responsible for the overall structure and functionality of a polyketide natural product. These synthases condense small simple carboxylic acids including acetate, propionate and to a lesser extent butyrate units into linear polyketide chains, in a similar manner to the biosynthesis of fatty acids.

A generalised schematic of polyketide biosynthesis shows the loading of a short chain carboxylic acid thioester “starter unit” and a thioester of an “extender unit” using an acyl transferase (AT) onto an acyl carrier protein (ACP), and a ketosynthase domain (KS). The decarboxylation of the “extender unit” followed by a Claisen-type condensation is the key carbon-carbon bond forming step catalysed by the ketosynthase (KS) domain. Selective keto-reduction (KR), dehydration (DH) and enoyl reduction (ER) synthases can then vary the functionality of the ketone prior to being transferred back to the ketosynthase (KS) to facilitate further chain extension steps.

Figure 1.2: A schematic of PKS facilitated polyketide biosynthesis

The initial Claisen-type condensations along with manipulations to the β-ketone functionality are repeated until the polyketide chain has reached its desired length. The polyketide synthases that are present control the desired chain length, stereochemistry outcome, level of reduction and the initial cyclisation pattern of the polyektide chain. As a result, polyketides are more highly functionalised than their fatty acid counterparts, and hence are far more reactive, which often leads to intramolecular reactions/cyclisations. As shown in Figure 1.3, denticulatin A (6) shows an example of reduced, eliminated, and completely reduced functionality, as well as a hemiacetal moiety.
Diemenensin A (7)\textsuperscript{19} also displays evidence of eliminated and completely reduced functionality, as well as a β-pyrone ring system. While siphonarin A (8)\textsuperscript{20} contains a γ-pyrone ring and a complex spiroacetal.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{polyketide_natural_products}
\caption{Polyketide natural products displaying the high levels of functionalisation formed by PKS}
\end{figure}

1.1.5 Cyclisation Modes

Polyketides are believed to exist as linear chains that can undergo rearrangements and cyclisations to form the most stable thermodynamic product.\textsuperscript{21} Rearrangements and cyclisations can occur via a number of different mechanisms that include: Claisen condensation, retro-Claisen condensation, nucleophilic addition and intramolecular cycloaddition reactions.

Polyketide natural products commonly contain ketal or pyrone functionality,\textsuperscript{22} for example CR377 (9)\textsuperscript{23} and dolabriferol (10),\textsuperscript{24} (Figure 1.4) which arise from the nucleophilic attack of an alcohol onto a carbonyl further down an acyclic precursor.\textsuperscript{22} The formation of these cyclic compounds is best understood by retrosynthetic analysis of the cyclic moieties, and thus determining a potential acyclic precursor. These potential linear precursor compounds usually can have a significant number of cyclisation modes as a result of the presence of multiple nucleophilic (hydroxyl) and electrophilic (carbonyl) sites.
Introduction to Polyketide Natural Products

Figure 1.4: Pyrone and ketal functionality shown by polyketide natural products CR377 (9) and dolabriferol (10)

The formation of these cyclic structures is generally under thermodynamic control relating to oxidation state of the carbon centres and the absolute configuration of the hydroxyl and methyl stereocentres within the acyclic precursor. This means that where multiple cyclisations are possible the final structure isolated will be the most thermodynamically stable. Natural products siphonarin B (11) and caloundrin B (12) are metabolites isolated from Siphonaria, zelandica, and perfectly illustrate how thermodynamic stability and the relative configuration of stereocentres in an acyclic precursor impact the potential modes of cyclisation. Both products can be formed by an almost identical precursor 13 and 14 (epimeric at Cα) using cascade reactions (Figure 1.5).

Figure 1.5: Thermodynamic cyclisation modes of two diastereomeric acyclic precursors

Formation of a hemiacetal moiety from an acyclic precursor product is well understood and in cases where multiple cyclisation paths are present, deliberation for the thermodynamic requirements of the product can be invoked to determine which cyclisation mode dominates. Additionally, in some
cases the initially formed hemiacetal is subject to further transformations. This can be seen in the comparison of maurenone (15) and dolabriferol (10) synthetic pathways (Figure 1.6).

The dihydropyrone containing maurenone (15) isolated from S.maura,\textsuperscript{26,27} appears to form from the initial cyclisation pattern of acyclic precursor 16 to produce hemiacetal 17, this acetal 17 is then subject to dehydration to give maurenone (15). Dolabriferol (10) isolated from Dolabridera dolabrifera\textsuperscript{24} is one of the rare marine polypropionates not to possess a contiguous backbone.\textsuperscript{28} This disruption within dolabriferol (10) appears to form from a retro-Claisen fragmentation of the hemiacetal 18 precursor, which eventuates from a linear precursor 19 to form the acyclic ester 20. The ester 20 then undergoes hemiketalisation of the alcohol onto the carbonyl to produce dolabriferol (10). Although both maurenone (15) and dolabriferol (10) have been suggested to arise from similar β-hydroxy-β-dicarbonyl systems, the reactivity of the proposed hemiacetal intermediate is quite different. Maurenone’s hemiacetal 17 undergoes an elimination mechanism to produce the unsaturated γ-pyrene with no retro-Claisen product detected. The dolabriferol hemiacetal 18 that results from the cyclisation of linear precursor 19 undergoes an exclusive retro-Claisen rearrangement to form the acyclic ester 20. These two distinct outcomes demonstrate why it is often difficult to predict the eventual products of β-hydroxy-β-dicarbonyl cyclised systems found in nature.
1.1.6 Methods for Natural Product Polyketide Synthesis

The isolation and structural elucidation of a large number of novel bioactive polyketide natural products, along with the requirement for new potent therapeutic medicines has driven the development of polyketide synthesis since the early 2000s. Past medicinal incidents involving the administration of racemic compounds, where one enantiomer has displayed toxic health effects has led to the current norm that all new novel drugs are dispensed as stereochemically pure compounds. This required structural precision has led to a resurgence in the asymmetric synthesis of polyketide natural products. Recently, many research undertakings have been based around improving both the regioselectivity and stereoselectivity of carbonyl and carbon-carbon bond forming reactions. Selective reduction of carbonyl compounds and olefins have been extensively reviewed in the literature and due to the limited examples in this thesis shall not be discussed. The acylation reaction is used broadly in synthetic community as a carbon-carbon forming reaction for the attachment of an acyl group into the compound, and this route was used extensively in Chapter Two. The aldol reaction, also a regular tool for the current synthetic chemist is a concurrent carbon-carbon bond forming reaction and carbonyl reduction in one and was used
extensively in Chapters Three and Four within the dissertation. As a result, an overview of the synthetic power of both the acylation and aldol reactions has been chosen to lead into this work.

1.2 The Acylation Reaction

1.2.1 Acylation Reactions towards Synthesis of Natural Products

Acylation has been at the center of synthesis towards polyketide natural products since the discovery of electrophilic\textsuperscript{36,37} and nucleophilic\textsuperscript{58} substitution reactions. The necessity to incorporate this structural functionality along with its synthetic ease to create carbon-carbon bonds has seen acylation reactions used extensively towards natural product synthesis.

As shown above, (Figure 1.2) nature uses an acetylationing reaction for chain extension during polyketide biosynthesis.\textsuperscript{16,39} The current synthetic chemist often tries to develop synthetic approaches that closely mimic nature’s processes. As a result, carbon-carbon and carbon-heteroatom bond formations have been successfully created by employing a range of developed acylation conditions. The acylation reaction is the process of inserting an acyl group, and this can be achieved using either electrophilic or nucleophilic substitution processes.

1.2.2 Friedel-Crafts Acylation

Electrophilic aromatic substitution (commonly referred to as Friedel-Crafts acylation) was developed by Charles Friedel and James Craft in 1877\textsuperscript{37} to successfully attach acyl groups to aromatic systems. This acylation reaction requires the use of either acyl halides or anhydrides which form reactive electrophiles in the presence of a strong metal catalyst, like aluminium trichloride (AlCl\textsubscript{3}). The most common example of Friedel-Crafts acylation is the acetylation of benzene (21)\textsuperscript{40} with acetyl chloride (22) in the presence of AlCl\textsubscript{3} to form acetophenone (23) (Figure 1.7). Friedel-Crafts acylation has also been successfully employed towards the synthesis of numerous natural products.\textsuperscript{41-44}
1.2.3 Nucelophilic Acylation

Nucleophilic acyl substitution was used extensively in Chapter Two, and refers to reactions that involve the addition of nucleophiles to acyl derivatives. Nucleophiles include: alcohols, amines and enolates that displace the leaving group of an acyl halide, anhydride or ester via a step-wise addition/elimination mechanism. As nucleophiles have the ability to react with a variety of acyl derivatives, this has enabled the successful intermolecular\(^{45,46}\) and intramolecular\(^{47-50}\) intermediate bond formation for a range of natural products.

Acyl derivatives react with nucleophiles via an addition based mechanism forming a tetrahedral intermediate. The reaction can be accelerated by acidic conditions, which enhance the carbonyl’s electrophilic nature, or in basic media, which provide a more reactive anionic nucleophile.

In acidic conditions (Figure 1.8), the carbonyl 24 of the acyl derivative is protonated, activating it towards nucleophilic attack. Nucleophilic attack of the acyl carbonyl 25 creates a tetrahedral intermediate 26. Then there exists a proton shift from the nucleophile to the leaving group. This tetrahedral intermediate 27 then collapses ejecting the protonated leaving group to give the new protonated carbonyl 28. This carbonyl loses a hydrogen atom to give the nucleophilic substituted product 29. As the final step of this mechanism is the loss of a proton, nucleophilic acyl substitution reactions are thought to be catalytic in acidic conditions.
Introduction to Polyketide Natural Products

![Diagram of acyl substitution mechanisms](image)

**Figure 1.8**: Nucleophilic acyl substitution mechanism in acidic conditions

In basic conditions (Figure 1.9), the nucleophile attacks the acyl carbonyl 30 forming a tetrahedral alkoxide intermediate 31. This intermediate immediately collapses and eliminates the leaving group to produce the substitution product 32. It is possible for nucleophilic acyl substitution reactions to be catalytic in base, but they will not be if the leaving group is a weaker base than the nucleophile. This mechanism although not proven has been accepted by oxygen-18 isotope labeling experiments of ethyl propionate.

![Diagram of basic conditions](image)

**Figure 1.8**: Nucleophilic acyl substitution mechanism in basic conditions

### 1.2.4 Reactivity of Acyl Derivatives

There are four types of acyl derivatives with acid halides the most reactive, followed by anhydrides, esters and amides. One major factor in determining the reactivity of acyl derivatives is their leaving group ability, which is related to acidity. Weak bases are better leaving groups than strong bases, thus the chloride ion is a superior leaving group to the acetate ion, and hence acid chlorides are more reactive than anhydrides. Another factor that determines reactivity is the ability for the acyl derivative to form resonance contributors. Amides possess two resonance structures; both contribute to the overall structure so much so that the carbon to nitrogen bond possesses significant double bond character. Esters though exhibit less resonance stabilisation than amides, and hence the formation of the tetrahedral intermediate and subsequent loss of this resonance is not as unfavourable as it is with the nucleophilic substitution of amides. Following this, anhydrides possess...
weaker resonance stabilisation as the resonance effect is split between two carbonyls. In acyl halides there is almost no resonance; hence they are the most reactive of the acyl derivatives.

Due to these differences in reactivity conversion of one acyl derivative into another is generally restricted to the ones outlined in Figure 1.10.\textsuperscript{51,52} For example an anhydride can be easily prepared from an acyl halide via an acetate anion addition, and amides can be simply synthesised from any of the more reactive carbonyl derivatives. Conversion of an ester into an acyl halide though is a difficult task that involves hydrolysis of the ester to the carboxylic acid followed by chlorination.

![Figure 1.10: Reactivity of acyl derivatives](image)

Although alcohols\textsuperscript{53,54} and amines\textsuperscript{55,56} are used extensively in nucleophilic acyl substitution reactions towards synthetic products, the focus for the remainder of this section shall look at the nucleophilic addition of enolates on acyl derivatives. This focus is due to the effort encompassed in Chapter Two, where construction of the tricarbonylmethane functionality of CR377 (9) was targeted heavily through the acylation of cyclic and acyclic 1,3-dicarbonyl systems.

### 1.2.5 Addition of Enolates to Acyl Derivatives

In general carbonyls that contain an α-hydrogen have the ability to exist as a mixture of the enol\textsuperscript{33} and ketone\textsuperscript{34} tautomers.\textsuperscript{57} Enolates\textsuperscript{35} are prepared through the deprotonation of the carbonyl derivative’s α-hydrogen, producing an anion which is delocalised over both carbon and oxygen (Figure 1.11).\textsuperscript{58} For successful enolate addition the enolate must be generated in high concentration through the addition of a strong non-nucleophilic base in dry solvent. Strong bases like lithium diisopropylamide (LDA), sodium hydride (NaH), sodium amide (NaNH\textsubscript{2}) and 1,8-diazabicycloundec-7-ene (DBU) are all commonly employed for the preparation of such enolates. Alkyl lithiurns and
Grignard reagents can be used but are often avoided as they can rapidly and irreversibly add directly to carbonyl groups.

![Figure 1.11: Keto-enol tautomeration and preparation of reactive enolates](image)

An enolate 35 is an extremely nucleophilic substrate that can undergo nucleophilic alkylation\textsuperscript{59,60} for example by reaction with ethyl bromide to give a butanone product 36. The same enolate 35 can also react by nucleophilic acylation\textsuperscript{61,62} with acetyl chloride (22) to form the corresponding 1,3-dicarbonyl product 37 (Figure 1.12). Asymmetric ketone enolates though can lead to a mixture of thermodynamic and kinetic products. Low temperature generally favours the less substituted kinetic product while room temperature and above reactions favour the thermodynamic reaction product.

![Figure 1.12: Nucleophilic alkylation and acylation of enolates](image)

**1.2.6 Methods for the Formation of 1,3-Dicarbonyls**

1,3-Dicarbonyls are important compounds in synthetic organic chemistry.\textsuperscript{63,64} This functionality is seen readily in numerous biologically active natural products, or as key intermediates towards such species. As can be seen from above, (Figure 1.12) the ideal method for the preparation of 1,3-
dicarbonyls is addition of an acyl derivative to a previously prepared enolate anion at low
temperature. The main synthetic methods for the preparation of 1,3-dicarbonyls \[38^{65,66}\] (Figure 1.13) involve; modification of the classic Claisen condensation where acylation of a ketone \[39\] with an
ester \[40\] using an alkoxide base. The current method of choice involves the use of \(\text{LDA}\); a strong non-
nucleophilic base to generate the enolate followed by addition of an acid chloride \[41\].

![Figure 1.13: The main synthetic methods for the preparation of 1,3-dicarbonyls 38](image)

The main associated problems regarding the Claisen condensation method are: requires a large excess of acylating agent, elevated temperatures, removal of the alcohol by-product and that only modest yields are achieved. Increased yields have been reported through the use of sodium hydride or lithium hydride instead of the alkoxide base for this reaction, however this alteration is not applicable for substrates with other weakly acidic functionality.\[^{67}\] In terms of the LDA method; issues regarding weakly acidic functionality still remain, requires excess enolate formation (2-3eq), can give \(O\)-acylation and bis-acylation products, making it inherently inefficient. This stems from the fact that the \(pK_a\) of the 1,3-dicarbonyl product (=9-13) is much more acidic than the parent ketone \(pK_a\) (=20) resulting in the product quenching unreacted enolate as the product is formed. These methods associated with the formation of 1,3-dicarbonyl compounds have relied solely on hard enolisation procedures,\[^{67}\] in recent times the use of soft enolisation techniques\[^{68,69}\] like \(\text{MgBr}_2\cdot\text{OEt}_2\), \(\text{CH}_2\text{Cl}_2\) and \(\text{iPr}_2\text{NEt}\) under atmospheric conditions have been used to achieve robust formation of 1,3-diketones. These acylation methodologies can be extended to the formation of tricarboxymethane systems,\[^{70-73}\] as with these methods it is possible to form bis-acylation products \[41\]. Even though formation of
1,3-dicarbonyl enolates 42 is relatively straightforward, the stability gained through the extra resonance contributors with the anion predominately positioned between the two carbonyls in a pseudo six-membered ring can cause acylation on carbon to be quite complex (Figure 1.14).

![Diagram of acylation methods](image)

**Figure 1.14:** Extension of acylation methods to the synthesis of tricarbonylmethane systems.

As described above, the acylation reaction is a prevalent source for the construction of carbon-carbon bonds. The ability of nucleophilies to react with acyl derivatives to generate complex structural functionalities has led to its constant use in the synthesis of intricate polyketide natural products. The addition of acyl derivatives to chelated metal enolates has led to the swift formation of 1,3-dicarbonyls 37 and 1,3,3-tricarbonyl 41 motifs.

The use of enolate chemistry has also been central to stereoselective control and formation of new carbon-carbon bonds in the traditional aldol reaction towards achieving total synthesis of natural products. The aldol reaction was also used heavily throughout this dissertation, and as such this reaction is the focus of the following section.

### 1.3 The Aldol Reaction

#### 1.3.1 Stereochemical Control towards Synthesis of Natural Products

There have been numerous methods developed over the last 40 years into inducing high levels of stereochemical control in synthesising new polyketide derived natural products. The aldol reaction has been one of the most influential developed methods for the formation of carbon-carbon bonds.
Like acylation; the aldol reaction has been known to the synthetic chemist since 1872, but still remains a high priority on many research programs to target the new and more complex natural products, which continue to be isolated. These complex natural products motivate research programs to develop innovative and improved methods of stereoselective synthesis, and better understandings of acyclic stereocontrol.

The aldol reaction (between an acyclic aldehyde and acyclic ketone) has been employed as a powerful synthetic tool used when particular stereochemistry is required. The biosynthesis of polypropionate natural products which is known to proceed through the condensation of acetate, propionate and to a lesser extent butyrate units, gives rise to a linear carbon backbone that possesses alternating methylation and oxygenation. The potential stereochemical arrays that can result from this biosynthetic pathway has allowed for the aldol reaction to be manipulated to provide better strategies for stereoselective controlled chain extension sequences.

The aldol reaction usually involves the formation of a ketone enolate by use of either a strong base or by the combination of a Lewis acid and weak base. This enolate most commonly reacts with aldehydes to form the new carbon-carbon bond with a potential two new stereogenic centres. To demonstrate the aldol’s reaction power, if an ethyl-type ketone \(43\) enolate reacts with an aldehyde \(44\) it has the potential to produce preferentially one of four possible isomers \((45-48)\) (Figure 1.15). If all designated R substituents \((R_1 \text{ to } R_3)\) are achiral then the reaction can produce two sets of enantiomeric pairs \((45/46 \text{ or } 47/48)\), or if any of the R groups are chiral then all four potential products will be diastereomers.
The modern aldol reaction has been highly developed in the area of controlling the stereoinduction exhibited by the reaction to enable one of the four products shown above to be synthesised selectively. It has been shown that by controlling the geometry of the ketone enolate, through addition of a strong base, or by Lewis acid coordination can prove essential in obtaining stereoselective aldol reactions.

1.3.2 Enolate Geometry:

It has been demonstrated that the syn vs. anti stereoselectivity observed from aldol reactions can predominately be directly related to the geometry of the enolate. This, in turn, explains that control of the respective enolate geometry is vital for achieving aldol products selectively. In general, it has been well documented that enolate reactions of achiral ethyl ketones (49/50) with achiral aldehydes 51, (Z)-enolates 49 provide syn aldol adducts and (E)-enolates 50 produce anti aldol adducts.

To further illustrate the stereochemical relationship that (Z)-enolates 49 generally produce syn-aldol adducts and that (E)-enolates 50 produce anti-aldol products, one can consider the six-membered Zimmermann-Traxler transition states (Figure 1.16). As can be seen, reactions at the Re face of the
(Z)-enolate 49 with the Si face of the aldehyde 51 will proceed via TS1 to give a syn-aldol product 52 (plus the enantiomer from the enantiomeric transition state). Similarly, the reaction of the Re face of the (Z)-enolate 49 with the Re* face of the aldehyde 51 via TS2 produces an anti-adduct 53 (plus enantiomer from the enantiomeric transition state). In this case the formation of the syn-adduct 52 from TS1 is considered favoured as the alkyl group (R₃) of the aldehyde is in the preferred equatorial position. On the other hand, TS2 leading to the formation of the anti aldol adduct 53 encounters a destabilizing 1,3 diaxial/steric interaction between the alkyl group of the enolate (R₁) and the aldehyde alkyl group (R₃). This interaction results in TS1 having a lower energy than that of TS2, and thus (Z)-enolates preferentially produce syn-aldol products. From Figure 1.16, it can be seen that this premise also applies to (E)-enolates preferentially reacting with aldehydes via TS3 as opposed to TS4, giving the anti-aldol adduct 54 and not the syn-adduct 55. Once again, this is rationalised by the fact that TS4 is destabilised by the similar 1,3 diaxial/steric interactions between alkyl group of the enolate (R₁) and alkyl group of the aldehyde (R₃).
As discussed above, enolate geometry plays a major part in predicting the stereochemistry of mixed aldol based reactions. Years of research has uncovered conditions for selective enolate formation and the corresponding enolate geometry. As a result, enolate geometry can be determined by the following: 1). the base; 2). the Lewis acid; 3). the metal coordinated to the oxygen of the enolate; 4). ketone substituents; 5). ligands attached the coordinated metal; 6). general reaction conditions.

It is not possible to directly study all created enolates, and the enolate geometry is often determined by the resultant stereochemistry obtained in the respective aldol products. However, the ability to
capture lithium metal complexes with trimethylsilyl chloride (TMSCl) as relatively stable silyl enol ethers has allowed the study of lithium enolate geometry through $^1$H NMR spectroscopy. This research has observed that more ($E$)-enolate is formed when the size of the base ligands increase, and that more ($Z$)-enolate is created as the ketone’s substituents also increase.$^{83-85}$

Similar to lithium, boron enolates have also been studied considerably to determine their enolate geometry.$^{79,80}$ The combination of small ligands, a good leaving group attached to the boron and the addition of a sterically hindered amine generates ($Z$)-enolates. Whereas sterically demanding ligands, a poor leaving group attached to boron and the addition of a less hindered amine base produces ($E$)-enolates.

The ability to successfully predict and manipulate enolate geometry has allowed the development of aldol methodology towards the construction of stereochemically pure building blocks required for natural product synthesis.

**1.3.3 Π-Facial Selectivity**

Stereocontrol of the aldol reaction requires enolisation conditions that provide either the ($Z$) or ($E$)-enolate. The ratio of syn to anti-aldol products can be highly influenced by control of the respective enolate geometry. In cases where all the ketone and aldehyde substituents ($R_1$, $R_2$ and $R_3$) are achiral the transition state that corresponds to the product will also be accompanied by the transition state that leads to the enantiomeric product. This leads to the formation of racemic aldol product mixtures, as shown in Figure 1.17.
To preferentially form one enantiomeric product over the other requires $\pi$-facial selectivity displayed by either the enolate or the aldehyde involved. $\pi$-facial selectivity occurs when one face of either the enolate or the aldehyde is preferred over the other preventing reaction of the opposing transition state. The best way to influence $\pi$-facial selectivity is by creating asymmetry within the aldol reaction by combination of reagents, substrates and or auxiliary control. These individual factors or a combination of all three have substantial impact on the overall syn or anti-stereochemical result for the corresponding aldol reaction.

1.3.4 Reagent Control

An aldol reaction between two achiral fragments requires reagent control to achieve the desired selectivity. In this instance the asymmetry required is incorporated in the form of a chiral reagent, catalyst or solvent. The most common illustration of reagent control is exhibited with boron mediated aldols, where the asymmetry is introduced as chiral based ligands attached to boron. Years of scientific research has produced numerous chiral boron Lewis acids for creating enantioselective excess in aldol additions. Some examples of chiral boron enantioselective reagents (Figure 1.18) that require some preparation are the borolones (56-59) developed by Masamune$^{86,87}$ and Reetz$^{88,89}$ respectively, and a diazaborolidine 60 reagent developed by Corey$^{90-92}$. Another three examples of chiral boron reagents is the menthone-derived ligands 61 employed by Gennari$^{93-95}$ and the isopinocampheyl-derived ligands 62 and 63 which were introduced by Brown$^{96,97}$ for stereoselective hydroboration and asymmetric reductions. These enantioselective boron reagents have also been
used and reviewed extensively by Paterson\textsuperscript{98,99} for the purposes of asymmetric aldol additions towards natural product synthesis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.18}
\caption{Common asymmetric boron reagents for aldol reactions}
\end{figure}

1.3.5 Substrate Control

Substrate control, by the inclusion of chiral based ketones and to a lesser extent aldehydes can also increase the π-facial selectivity in aldol reactions. In these cases the substrate’s chirality is retained in the final product and influences the π-facial selectivity, which in turn differentiates between the competing transition states. This asymmetry creates either favourable stabilising intramolecular hydrogen bonds or destabilising steric or unstable lone pair interactions, which in turn determines the lowest energy conformation the aldol reaction will proceed through. This allows the current synthetic chemist to predict the outcome and the resultant stereochemistry exhibited by the final product. Substrate control was best demonstrated by Paterson \textit{et al}\textsuperscript{100} when he employed α-methyl chiral ketones (S)-64 (used in Chapter 4) to react with aldehydes to give highly selective \textit{anti-anti-}aldol adducts (Figure 1.19).
The (E)-enolate 65 of α-methyl chiral (S)-ketone 64 was prepared by reaction at -78°C with dicyclohexylboron chloride and triethylamine in diethyl ether. This enolate 65 was then reacted with aldehydes at -78°C for two hours to form the highly selective anti-anti aldol adduct 66. The formation of the extremely selective anti-anti aldol product 66 was determined to be due to substrate control. To rationalise this transition states TS6 and TS7 (Figure 1.19) were analysed, and looking at TS6, it would initially appear as if it would be disfavoured with the benzyloxymethylene functionality pointed towards the center of the transition state. This arrangement though allows the resultant α-hydrogen to proceed over the enolate methyl substituent, which in turn minimises the 1,3-diaxial strain. The other transition state TS7 which gives the syn-anti aldol adduct 67 is disfavoured due to lone pairs repulsion of the benzyloxy oxygen and the enolate oxygen atoms.

Paterson showed that the (Z)-enolates of α-methyl ketones 64 when complexed with titanium and tin Lewis acids display excellent diastereoselectivity towards syn-syn aldol adducts 101 (Figure 1.20). When titanium (IV) 68 and tin (II) enolates 69 of α-methyl (S)-ketone 64 are reacted in similar conditions with methacrolein, as stated above the syn-syn adduct predominates. This implies that both the titanium (IV) 68 and tin (II) enolates 69 display the same mode of stereoinduction, but Paterson 101 showed that the tin (II) enolate 69 produces a higher level of diastereoselectivity in comparison to the titanium (IV) enolate 68 and believes that the additional benzyloxy oxygen
bonding towards the tin (II) enolate 69 is favoured more than that of the titanium (IV) enolate 68. Regardless of the high levels of diastereorecontrol achieved in the above-mentioned tin-based aldol reactions, the involvement of tin (II) triflate has serious drawback for this methodology because of the expense and operational complexity associated to this Lewis acid. In 2005, Solsona\textsuperscript{102} developed a soft titanium Lewis acid (\textsuperscript{1}PrO)TiCl\textsubscript{3} that rivaled the yields and diastereomeric ratios seen with tin based chemistry. Once again, it was noted that the additional chelation of the β-protecting group during the transition state increased the diastereoselectivity towards the syn-syn product 70. Furthermore, the impact of the titanium Lewis acid used in the enolisation step on the stereochemical outcome of the aldol reaction is noteworthy as this clearly proves that choice of ligands must be carefully evaluated. As a matter of fact, the incorporation of different ligands in the titanium (IV) not only alters its acidity but also affects the structure of the resulting enolate complex, and has a dramatic influence on the aldol transition state.
Introduction to Polyketide Natural Products

Figure 1.20: Anti vs. Syn aldol additions of α-methyl chiral (S)-ketone 64

Around the same time that Paterson and coworkers\textsuperscript{100} discovered the \textit{anti-anti}-aldol adduct 66, Evans\textsuperscript{103,104} had decided to extend his previous research on oxazolidinones \textbf{79-82} to create β-ketoimides \textbf{71\textsuperscript{105}} as chiral auxiliaries for highly selective aldol reactions (Figure 1.21). While the result of using dicyclohexylboron chloride with triethylamine furnished the \textit{anti-anti}-aldol product \textbf{72} similar to Paterson’s studies,\textsuperscript{100} it was the variants seen during the \textit{syn}-aldol reactions that generated significant interest. Evans and coworkers\textsuperscript{106} were able to show that the titanium (IV) and tin (II) enolates of β-ketoimide \textbf{71} have an opposing sense of stereoisoduction. The titanium (IV) enolate still
leads to the *syn-syn*-product 73 similar to above, but the tin (II) enolate produces the *anti-syn*-adduct 74. Transition state predictions have been made to suggest why this contradicting behavior between tin (II) enolates was observed by Evans and Paterson; however to date there has still been no genuine accepted theory for this difference in selectivity.

![Figure 1.21: Evans’ β-ketoimides 71 as chiral auxiliaries for highly selective aldol reactions](image)

The above chiral ketones developed by Paterson and Evans have significantly impacted on the ability for highly complex molecules to be synthesised using the aldol reaction. The capability to synthesise *syn-syn*, *anti-syn* and *anti-anti* motifs plus the power to predict the stereochemical outcome of these aldol reactions has led to this propionate chemistry being employed towards the successful synthesis of many natural products.\(^{107-113}\)

Previous discussion has outlined that ketone or aldehyde chirality will impart some form of π-facial discrimination towards the resultant aldol adduct. When solely the ketone or aldehyde possesses stereochemical influence during the aldol transition state predicting the final aldol stereochemistry is generally straightforward. Above discussion primarily focused on ketone enolate geometry controlling the stereochemical outcome of the resulting aldol adduct. Aldehydes with chirality primarily at the α-position (β, γ positions more isolated from aldol reaction site) can also be used to
impart some selectivity on the product when combined with achiral ketones. This selectivity can also be predicted as α-methyl aldehydes reactivity is based on the Felkin-Anh model.\textsuperscript{114-116}

1.3.6 Felkin-Anh Model

The Felkin-Anh model\textsuperscript{114-116} was designed to predict the preferred addition of a nucleophile (the enolate) to the most sterically favoured face of the electrophilic carbonyl species (the aldehyde). Through the use of Newman projections (Figure 1.22) and by considering the Burgi-Dunitz trajectory (~107°) for nucleophilic attack of the carbonyl group, it is possible to anticipate the favoured stereochemical outcome but not the overall stereoselectivity of the following aldol addition. The final selectivity can also be affected by several contributing factors including: steric s, electronic s and chelation interactions.

\[ 	ext{Felkin Preference} \]

\[ 	ext{Anti-Felkin Preference} \]

\[ R_1\text{O}R_2\text{OLi} + H\text{O}\text{R}_1\text{OH}R_2 \rightarrow R_1\text{O}R_2\text{OLi} + H\text{O}\text{R}_1\text{OH}R_2 \]

\[ \text{Figure 1.22: The competing Felkin and anti-Felkin preferences of chiral α-methyl aldehydes 76} \]

In general, though it is usually noted that (E)-enolates 75 react with α-methyl aldehydes 76 following the Felkin-Anh model rules to produce Felkin products 77, whereas (Z)-enolates go against this trend and prefer anti-Felkin approach of the aldehyde 76 to give the corresponding anti-Felkin products 78. The use of α-methyl aldehydes 76 alone in aldol reactions to influence the stereochemical outcome is not recommended as this generally leads to low diastereoselectivity ratios, and hence should be incorporated with substrate, reagent and auxiliary control to achieve maximum selectivity results. The chiral aldehyde approach should not be solely relied upon for achieving stereocontrol, however the π-facial preference of the aldehyde must be considered when reacted with a chiral enolate. This process is commonly referred to as a double stereodifferentiation aldol.
1.3.7 Use of Chiral Auxiliaries

Another form of achieving enolate asymmetry can be introduced through the use of a chiral auxiliary. Chiral auxiliaries are thought to be relatively similar to that of substrate controlling ketones in that the asymmetry is usually located at the α-carbon to achieve maximum stereoselectivity. These chiral auxiliaries though are different to the extent that this chirality component is not present in the final product and is eventually removed after the desired stereoselectivity has been achieved. In some instances, like Evan’s oxazolidinone \(79-81\) and thiazolidine thione \(82\) auxiliaries on removal can be recovered, purified and eventually be reused to install further stereocentres towards the final compound. Some of the most prevalent α-chiral auxiliaries still in use today (Figure 1.23) are the already mentioned Evans’ oxazolidinone \(79-81\) and thiazolidine thione \(82\) auxiliaries,\(^{103,104}\) Paterson’s lactate derived ketone \(83-84\) auxiliaries,\(^{117,118}\) while Masamune’s\(^{119}\) and Heathcock’s\(^{120}\) original chiral based silyl ketones \(85-86\) have to a large extent been superseded by those mentioned above.

![Figure 1.23: α-chiral auxiliaries used in asymmetric aldol reactions](image-url)

The Evans’ \(N\)-acetyl-oxazolidinone (79, ent-79) and \(N\)-acetyl-thiazolidine thione (82, ent-82) auxiliaries (Figure 1.23) can be synthesised readily in three linear synthetic steps from the
commercially available amino acids using a reduction, cyclisation and acylation reaction pathway.\textsuperscript{103,104} These auxiliaries have been widely used in organic synthesis for \textit{syn}-aldol carbon-carbon bond forming reactions. In Chapter Two the thiazolidine thione auxiliary \textsuperscript{82} was used to selectively produce the \textit{syn}-stereoisomer to allow for easier stereochemical assignment of future products and to facilitate the final cyclisation synthetic step as an effective leaving group. The attractiveness of all the Evan’s auxiliaries’ stems from the ability to install highly selective motifs and the capacity for them to be removed using a variety of conditions depending on particular substrate stability. Weinreb amides are regularly adopted by synthetic chemists towards the synthesis of natural products\textsuperscript{121,122} in the preparation of intermediate ketone and aldehyde fragments. For example (Figure 1.24) use of Weinreb’s salt to displace the auxiliary \textsuperscript{87} to give amide \textsuperscript{88}, which in turn can reacted using a variety of nucleophilic reagents including Grignards, hydrides and alkyllithiums to give ketones \textsuperscript{89}.\textsuperscript{123} The auxiliary \textsuperscript{87} can also be effectively reduced using DIBALH or LiBH\textsubscript{4} to the corresponding alcohol \textsuperscript{90}.\textsuperscript{123} oxidation to the aldehyde \textsuperscript{91} can then continue chain elongation through further aldol couplings.

Similarly Paterson’s lactate derived ketones (\textsuperscript{83}, ent-\textsuperscript{83}) (Figure 1.23) are also easily synthesised in two linear steps from commercially available (S)-ethyl lactate (\textsuperscript{98}) or (R)-isobutyl lactate (\textsuperscript{99}).\textsuperscript{117,124} Interestingly, the ketone enolate geometry can be altered by simple exchange of the amine base used in conjunction with the coordinating Lewis acid. It has been extensively shown that the retrospective enolates of these lactate derived ketones react very well with substituted aldehydes to

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Versatility of Evans’ oxazolidinone auxiliary}
\end{figure}
form anti-anti adducts and anti-syn adducts. Although the stereochemical functionality of these auxiliaries cannot be recovered or reused for synthetic purposes, the versatility with which the product can be manipulated into useful reaction intermediates makes them an appealing synthon for construction of polyketide natural products. As shown in Figure 1.25 and in Chapter Four, once the lactate derived ketone 83 undergoes the diastereoselective aldol reaction to produce adduct 92 the stereocentre can be removed in one of two possible ways. Either the benzoyl ester can be reductively cleaved with SmI$_2$ to give ethyl ketone 93, or a two step procedure involving the reduction of the benzoate with LiBH$_4$, followed by the oxidation of the resultant diol 94 with NaIO$_4$ affords the corresponding aldehyde 95.

![Figure 1.25: Versatility of Paterson’s lactate derived ketone 83 auxiliary](image-url)
1.4 Natural Product Targets for Total Synthesis

In this chapter, sections have been attributed to introducing the rise and search for biologically active polyketide natural products and their biosynthetic pathways. The section has also provided a review of current acylation and aldol reactions and their fundamental use in the assembly of such complex molecules. This complexity and biological activity makes polyketide natural products appealing synthetic targets for research and development of new scientific methodologies. The main aims for the total synthesis of polyketide natural products and indeed this research are: Synthesise sufficient material for thorough biological testing (preserve natural source), implement a successful asymmetric approach to allow for complete structural elucidation and stereochemical assignment of the target compounds, and finally to develop novel methodologies to advance synthetic organic chemistry towards obtaining newly discovered natural product targets. The discussion below will introduce the two natural product synthesis targets of this research, and the remaining chapters will detail the results obtained from the synthetic studies conducted. In addition to this, the use of the common Swern oxidation procedure on β-hydroxy carbonyl substrates will also be discussed.

Chapter two will present the studies directed towards the total synthesis of the intriguing polyketide natural product CR377 (9) isolated from the *Fusarium* sp. by Brady et al. The synthetic strategy was designed to produce both the (S,S) and (R,S) stereoisomers, as shown below. The relative stereochemistry of the natural product would be determined by literature NMR comparison, while the absolute stereochemistry would be confirmed by comparison of CR377’s (9) reported optical rotation of [α]_D

\[^{25}\text{D}\] +21.8° (c 1.0, CH₂Cl₂). The main synthetic attempts (Figure 1.26) involved both a cyclic and acyclic approach towards generating this novel unsaturated tricarbonyl structural system. As CR377 (9) is the only identified polyketide to possess this unsaturated tricarbonylmethane system, and with its known antifungal biological activity made CR377 (9) an interesting target compound.
Chapter three will introduce the Swern oxidation reaction and its constant use towards achieving total synthesis of natural products. It will discuss an interesting product observed during the reaction of an unsaturated β-hydroxy carbonyl derivative using the generic Swern oxidation procedure. The unexpected reaction product was determined through the synthesis and characterisation of a model substrate derivative.

Chapter four will outline the retro-Claisen approach to the total synthesis of dolabiferol (10) (Figure 1.27), a marine polypropionate isolated from the *Dolabifera dolabrifera* species. Dolabiferol (10) is an unusual polyketide natural product as it possesses a non-contiguous carbon backbone. This total synthesis follows a pseudo-biomimetic pathway in that a protected linear precursor is formed through the successful aldol coupling of an aldehyde and ketone. Selective deprotection/cyclisation modes, and the proposed retro-Claisen rearrangement of hemiacetal was utilised to afford the natural product (10). Substrate control was achieved using Paterson’s lactate derived (R)-ketone to generate all but the C₆ stereogenic centres present in dolabiferol (10), whose adjacent methyl and oxygen substituents possess two symmetrical anti-structural moieties.
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**Figure 1.27**: Total synthesis of dolabriferol (10) following a pseudo biomimetic approach
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Chapter Two
Synthetic Studies towards Polyketide Natural Product CR377

This chapter discusses the synthetic strategies that have been attempted towards the first total synthesis of polyketide natural product CR377 (9). The synthesis strategies focused on the formation of a linear precursor 114, an acyclic precursor 127 and a cyclic precursor 204. Both the acyclic 127 and cyclic 204 precursors were to be formed through the common synthesis of β-keto ester 128. This β-keto ester 128 was formed in two linear steps from aldehyde 131, which was formed in five linear steps from ethyl-(S)-lactate (132). Ethyl-(S)-lactate (132), isobutyl-(R)-lactate (138) and (S)-2-methyl butyryl chloride (120) were to be employed as the chiral building blocks for the determination of CR377’s (9) absolute stereochemistry due to their commercial availability.

2.1 Discovery of CR377

2.1.1 Isolation and Characterisation

In 2000, Brady and Clardy\(^1\) isolated an endophytic fungus from a moss fern of the *Fusarium* Species, (Figure 2.1) as it displayed potent activity towards a commonly known fungal pathogen *Candida albicans*
Synthetic Studies towards CR377

in an agar plug screen. The compound responsible for the observed antifungal activity in the agar plug screen was isolated from the interior of a surface-sterilized piece of Selaginella pallescens stem tissue, and purified by normal phase chromatography methods.

Figure 2.1: Moss fern of the Fusarium species

The compound responsible for the antifungal activity was named CR377 (9) and its skeletal structure was proposed based on extensive NMR and HRFABMS analysis, along with comparison to known natural products podoblastin A² (96), alternaric acid³⁵ (97) and dehydroacetic acid⁶ (98) (Figure 2.2). From ¹H-¹H and ¹H-¹³C experiments, it was rationalised the structure contained three methyl groups, one exocyclic double bond, one methylene, two methines and a strongly deshielded exchangeable proton. The ¹³C NMR spectrum also suggested the presence of an additional double bond and two carbonyl groups, a ketone at δ 211.8 and an ester at δ 163.5.

Figure 2.2: The proposed structure of CR377 (9) and known tricarbonyl natural products podoblastin A (96), dehydroacetic acid (98) and alternaric acid (97) used for structural determination.
Synthetic Studies towards CR377

Analysis of the \(^1\text{H}-\text{H}\) relay experiments (Figure 2.3) revealed three two-carbon spin systems. Two of those systems C\(_9\) to C\(_{12}\) and C\(_{10}\) to C\(_{11}\) are linked through a HMBC correlation from the C\(_{12}\) methyl to the methylene protons at C\(_{10}\). The additional HMBC correlation from the C\(_8\) carbonyl to the C\(_{12}\) methyl protons confirms partial structure 1. The third two-carbon spin system C\(_5\) to C\(_6\) is involved in additional long range correlations that define partial structure 2. The C\(_5\)-C\(_6\) spin system is adjacent to the C\(_2\)-C\(_7\) exocyclic methylene as shown by HMBC correlations between C\(_4\) to C\(_6\) and C\(_7\) to C\(_5\). The C\(_2\) to C\(_3\) enolic structure was proposed based on long range coupling from C\(_2\) and C\(_3\) to the highly deshielded exchangeable proton at \(\delta\) 17.89. This feature was believed to be linked to the exocyclic double bond as HMBC showed correlations between C\(_4\) to H\(_3\) (enolic hydrogen) and the H\(_7\) methylene protons to C\(_3\). The correlation between the C\(_4\) ester and the H\(_5\) methine proton but not the H\(_6\) methyl suggests that partial structure 2 is completed through linking the C\(_4\) ester to the C\(_5\) through the ester oxygen.

![Partial Structures](image)

Figure 2.3: Partial CR377 (9) structures based on extensive 2D-NMR analysis

Structural determination of CR377 (9) was also aided by the use of HRFABMS (High Resolution Fast Atom Bombardment Mass Spectrometry), which is a relatively low fragmentation soft ionisation technique producing mainly intact protonated molecules (M+H) and deprotonated molecules (M-H). This technique is similar to that of electron ionisation (EI) and matrix-assisted laser desorption/ionisation (MALDI) mass spectrometry. The HRFABMS indicated the structure possessed a molecular formula of C\(_{12}\)H\(_{16}\)O\(_4\), as HRMS-FAB (M+H) (m/z) calculated for C\(_{12}\)H\(_{17}\)O\(_4\) was 225.1127, and found 225.1125.

The above partial structures 1 and 2 contained all the atoms predicted in the molecular formula by HRFABMS. The molecular formula C\(_{12}\)H\(_{16}\)O\(_4\) has an unsaturated index of five, and as such one unsaturation must be incorporated into the final structure. As no additional atoms can be used this
claim can only be achieved by closure of the lactone ring and joining the two partial structures together to give CR377 (9), a 2-methylbutyraldehyde-substituted α-pyrene. The presence of this tricarbonyl moiety within the proposed final CR377 (9) structure was well supported through comparison of $^1$H and $^{13}$C spectral data with known natural product Podoblastin A (96) (Figure 2.4).

![Figure 2.4: Comparison of selected CR377 (9) and podoblastin A (96) $^1$H and $^{13}$C NMR resonances](image)

Structural elucidation of the recently identified and reported fujikurins A-D, $^7$ (9, 99-101) (Figure 2.5) isolated from the PKS-19 gene cluster within Fusarium fujikuroi showed that the spectroscopic data acquired for fujikurin A (9) was identical to that previously reported for the bioactive natural product CR377 (9).$^1$ Besides fujikurin A (9), the fujikurins B-D (99-101) have not been previously described before and represent new natural products with interesting and unique structural properties. Fujikurin B (99) could be formed by the addition of water across the double bond of fujikurin A (9), leading to the proposed structure that contains the 1,3-oxygenation pattern typical of polyketides.$^8$ Based on the spectra obtained and the reduced chromatographic separation between Fujikurins C (100) and D (101), it was proposed that these new compounds are stereoisomers. The PKS-19 gene cluster is understood to be a highly reducing PKS domain, and due to the structural similarity, it is plausible that through PKS reduction these novel natural products are all directly related.
Synthetic Studies towards CR377

![Chemical structures of Fujikurins A, B, C, and D]

*Figure 2.5: Recently identified and reported Fujikurins A-D (9, 99-101) isolated from Fusarium fujikuroi*

### 2.1.2 Biological Activity

When antifungal activity levels were compared with nystatin, a known commonly used polyene antifungal agent, it was observed that CR377 (9) displayed slightly more potent antifungal activity towards two strains of the *Candida albicans* fungus.\(^1\) *Candida albicans* is the most frequently isolated fungal pathogen in humans and is present amongst the digestive, respiratory and urogenital tracts.\(^9\) The degeneration of this parasite from unicellular to multicellular form can occur in immunosuppressed individuals, which can result in serious candidiasis. On infection, *Candida albicans* will shift from unicellular (yeast) to an invasive multicellular (hyphae, pseudohyphae) form where the overgrowth will then begin to attack the human body.\(^10\) Candidiasis manifestations may be acute, subacute or chronic to episodic. Involvement may be localised to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs, and the gastrointestinal tract, or become systemic as in septicemia, endocarditis and meningitis. Unless the patient is receiving aggressive cancer treatment, severely immunosuppressed or undergoing transplant therapy most candidiasis infections will remain superficial and respond readily to the appropriate treatment.\(^10\)

Currently nystatin,\(^9\) amphotericin B,\(^11\) caspofungin\(^12\) and fluconazole\(^13\) are the most commonly used synthetic drugs used to treat candidiasis. Nystatin binds to ergosterol, a major component of the fungal cell membrane. When the polyene antifungal is in high concentration it forms pores in the fungal membrane which results in leakage of potassium and subsequently causes death of the cell.\(^14\) As these fungal based infections continue to develop resistance to these currently supplied medications,\(^15\) the search for new potent antifungal agents constantly remains a high priority. The need for new novel
Synthetic Studies towards CR377

antifungal agents has resulted, and hence the total synthesis of CR377 (9) would provide synthetic material to aid in the use and development of new antifungal agents. Synthesis of this structurally unique polyketide natural product would also provide a pathway towards the development of new novel antifungal analogue based drugs.

2.1.3 Synthesis Aims

Applying the CR377’s (9) skeletal numbering system employed by Brady and Clardy, the relative and absolute stereochemistry of the natural product was not established at the C5 and C9 positions, and hence there exist four possible stereoisomers of the natural product (Figure 2.6). The aims of this research were to determine CR377’s (9) relative and absolute stereochemistry, as well as provide sufficient synthetic material for further biological testing. While the different enantiomers of CR377 (9) may have different biological activity, it was initially decided to attempt the synthesis of one stereoisomer from each enantiomeric pair to ascertain both the relative and absolute stereochemistry of CR377 (9). Due to the commercial availability of building blocks ethyl-(S)-lactate, isobutyl-(R)-lactate and (S)-2-methyl butyryl chloride the (S,S) and (R,S) stereoisomers would be targeted to confirm CR377’s (9) absolute stereochemistry.

Figure 2.6: The four possible stereoisomers of CR377 (9)
Synthetic Studies towards CR377

It has been reported that carolic acid\textsuperscript{16,17} (102) and agglomerin A\textsuperscript{18} (103) (Figure 2.7) both exhibit antibiotic activity and structurally possess five-membered α-furanone ring systems that include an exocyclic double bond. Apart from the sole discovery of CR377 (9) there currently have been no other reports of six-membered α-pyrone systems that possess this exocyclic methylene functionality. Therefore the complete synthesis of CR377 (9) would be highly valuable alone in developing new methodology for the formation of these substituted ring systems.

![Figure 2.7: CR377 (9) and similar five-membered α-furanone systems carolic acid (102) and agglomerin A (103)](image)

2.1.4 Retrosynthetic Analysis

A significant structural feature of CR377 (9) is the tricarbonylmethane system and all synthetic strategies towards this natural product need to address the synthesis of this structural motif. The ring system is composed of three carbonyls that are all directly attached to the same methine carbon. This functionality is interesting as all known compounds (including CR377) that possess this interesting tricarbonylmethane system exist completely as the enol tautomer with the enolic hydroxyl \(^1\)H NMR signal present at chemical shifts greater than \(\delta\) 10. Retrosynthetic analysis of the predicted skeletal structure of CR377 (9) reveals several possible synthetic disconnections that could be attempted to achieve the first total synthesis (Figure 2.8). The pathways (A, C-D) towards the natural product CR377 (9) involve the formation of the distinctive tricarbonylmethane ring system as the final synthetic transformation, whereas pathway B proposes the lactonisation of the preformed carbonyl system as the final step.
The following section discussions detail the synthetic attempts towards CR377 (9) based on the retrosynthetic disconnections that target the direct precursors outlined for pathways A, B and C. Pathway A involves disconnection of the tricarbonylmethane ring system to give a linear polyketide precursor 104 that could be formed by coupling of the appropriate acid and alcohol fragments through an esterification reaction. The linear precursor 104 could then undergo a Dieckmann reaction to form the natural product (9). Pathway B involves the disconnection of the lactone ring to furnish a preformed tricarbonyl precursor 105. This tricarbonyl precursor 105 can be formed through two independent approaches that both involve the acylation of a β-keto ester substrate 106/107 with the corresponding acyl halide 108/109. Selective removal of the alcohol protecting group from the tricarbonyl precursor 105 would then allow lactonisation to form the pyrone ring system of CR377 (9). Pathway C requires disconnection of the tricarbonylmethane system to produce an unsaturated lactone 110 and a 2-methylbutyryl acyl group 111. The unsaturated lactone 110 could be formed through lactonisation of a deprotected linear β-keto ester 112. Direct carbon acylation of the lactone 110 with the 2-methylbutyryl group 111, or by acylation on oxygen followed by a rearrangement would afford CR377 (9). Pathway D is similar to pathway A in that formation of the natural product (9) would result from a 1,3-dicarbonyl intramolecular nucleophilic acylation of an alternate linear precursor 113. Due to time constraints and the complications to be discussed associated with pathway A, it was thought that investigation towards CR377 (9) through pathway D would prove as equally difficult, and hence was not explored.
2.2 Intramolecular Cyclisation Studies towards CR377

2.2.1 Novel Cyclisation Approach

The initial synthetic method (Pathway A) was designed to create a linear polyketide 114 product that under a base induced intramolecular cyclisation would form the tricarbonylmethane system of CR377 (9) (Figure 2.9). The linear precursor 114 could be formed through the coupling of alcohol 115 and acid 116 fragments. A stereoselective Bayliss-Hillman reaction between ethyl acrylate (117) and acetaldehyde (118) could be employed to produce the required pure alcohol 115 fragment. The acid 116 fragment could be acquired through the acylation of ethyl acetate (119) with (S)-2-methylbutyryl chloride (120), followed by hydrolysis of the ethyl ester 121. This synthesis strategy was initially considered an attractive pathway towards the formation of the tricarbonylmethane system, as it was believed the final intramolecular cyclisation of the linear precursor 114 product to CR377 (9) would be an efficient and rapid process.
2.2.2 Intramolecular Cyclisation Model Studies

Dieckmann reactions have been reported for the synthesis of unsaturated five-membered ring systems, but this proposed intramolecular cyclisation reaction to form the desired six-membered ring system is unprecedented. The potential to develop new methodology towards the synthesis of such ring systems meant that this novel cyclisation approach would be attempted. In order to test this intramolecular cyclisation strategy towards CR377 (9) a model system 122 was developed (Figure 2.10) which omitted the exocyclic methylene and the stereocentre present of the acyl sidechain for simplicity. The acyl-dihydropyrone 122 model system was to be accessed through the formation of a linear precursor 123, followed by the proposed base induced intramolecular cyclisation. The linear precursor 123 was to be formed through a base catalysed esterification between alcohol 124 and acid 125 fragments. These two fragments could be both readily derived from ethyl acetoacetate (126) following selective reduction and hydrolysis procedures.

Figure 2.9: Retrosynthesis of CR377 (9) using an intramolecular cyclisation approach
Beginning with synthesis of β-hydroxy ester 124, this was to be achieved by the selective reduction of the ketone of ethyl acetoacetate (126) (Scheme 2.1) following a modified procedure from Onaran et al.\textsuperscript{20} To a solution of ethyl acetoacetate (126) in ethanol at -10°C was added sodium borohydride for 30 minutes. The mixture was carefully quenched by the addition of a saturated ammonium chloride solution and following extraction and purification by column chromatography the β-hydroxy ester 124 was obtained as a racemate in 86% yield.

Following a procedure from Grayson and coworkers,\textsuperscript{21} the β-keto acid 125 was formed by the hydrolysis of the ethyl ester in ethyl acetoacetate (126) (Scheme 2.1). Ethyl acetoacetate (126) was dissolved in THF and H\textsubscript{2}O, the mixture was cooled to 0°C and sodium hydroxide was added slowly, and then it was warmed to ambient temperature for four hours. The reaction mixture was kept basic and washed with ethyl acetate to remove unwanted organic material. The aqueous solution was then acidified and allowed the now soluble β-keto acid 125 to be extracted and was obtained in 70% yield.

The coupling of β-hydroxy ester 124 and β-keto acid 125 fragments to attain the linear precursor product 123 was achieved by following a Steglich esterification, reported by Steglich et al.\textsuperscript{22} (Scheme 2.1). β-keto acid 125 and DMAP were combined and added to a stirring solution of β-hydroxy ester 124 in CH\textsubscript{2}Cl\textsubscript{2} at 0°C. DCC was added at 0°C and the reaction was stirred for 30 minutes before being warmed to room temperature overnight. The dicyclohexylurea by-product was removed by filtration and purification by column chromatography of the remaining residue afforded the diester 123 in 75% yield. The addition of DMAP is crucial to the success of this coupling as the alcohol addition to the O-acylisoura intermediate can be slow and can lead to the formation of N-acylurea by-products. As DMAP is a
Synthetic Studies towards CR377

stronger nucleophile than the alcohol it reacts with the O-acylisourea intermediate to form an activated amide, which cannot form intramolecular side products but does react rapidly with alcohols.\textsuperscript{22}

![Chemical structure](image)

Reagents and Conditions: a. \(\text{NaBH}_4\) (1.5eq), EtOH, -10°C, 30 minutes. b. \(\text{NaOH}\) (1.6eq), THF/H\(\text{H}_2\text{O}\), RT, 4 hours. c. DCC (2.4eq), DMAP (1.5eq), CH\(\text{Cl}_2\), 0°C for 15 minutes, then 15 hours RT.

Scheme 2.1: Synthesis of the \(\beta\)-hydroxy ester 124, \(\beta\)-keto acid 125 and their coupling to give diester 123

With the linear polyketide precursor 123 in hand, various endeavors (Table 2.1) were made to synthesise the CR377 model system 122 directly using an intramolecular cyclisation method. Initial attempts involved the use of DBU, a strong non-nucleophilic base, sufficiently able to remove the highly acidic \(\alpha\)-protons of the \(\beta\)-keto ester 123 to invoke cyclisation. The reaction was conducted in deuterated chloroform to allow for continual \(^1\text{H}\) NMR monitoring, and to ensure that cyclisation would preferably proceed via \(C\)-alkylation. Treatment of the linear precursor 123 with DBU was monitored over six hours by \(^1\text{H}\) NMR spectroscopy; however no cyclised product was produced with only starting material retrieved. As an alternative, sodium hydride and sodium ethoxide each were employed to initiate cyclisation, however the same result was obtained as above.
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<table>
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<th>Base</th>
<th>Solvent</th>
<th>Equivalents</th>
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<td>6</td>
<td>NR</td>
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<td>NR</td>
</tr>
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</tr>
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<td>iPrMgCl</td>
<td>THF</td>
<td>1</td>
<td>6</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Table 2.1: Attempts made towards the deprotonation and intramolecular cyclisation of diester 123*

Isopropylmagnesium chloride was also employed, as it was believed deprotonation and the corresponding chelation of the magnesium to the diester 123 dicarbonyl framework would ensure if cyclisation was to proceed then it would be by the desired pathway (Figure 2.11). Unfortunately, like the reagents employed above this approach was also unsuccessful in the formation of the desired pyrone 122 moiety.

![Proposed cyclisation using iPrMgCl deprotonation/chelation approach](image)

*Figure 2.11: Proposed cyclisation using iPrMgCl deprotonation/chelation approach*

This observed lack of reactivity of the linear polyketide 123 is likely to be due to complexities in enolisation, intramolecular cyclisation on the electrophilic ester carbonyl, or the ethoxide’s leaving group ability. The difficulty with this approach moving forward was the ability to generate a suitable leaving group, and then to produce the dicarbonyl anion without simply just reacting with the newly formed leaving group. It was indicated through a simultaneous acyclic investigation towards CR377 (9) (discussed below) that this novel linear cyclisation approach was also going to encounter significant difficulties when the exocyclic methylene and the sidechain α-stereocentre were introduced into the synthesis, and hence this synthetic approach towards CR377 (9) was abandoned.
2.3 Acyclic Lactonisation Approach towards CR377

2.3.1 Acyclic Lactonisation Retrosynthesis

This approach (Figure 2.12) involves the final step in the formation of CR377 (9) to be lactonisation of the completely formed protected acyclic tricarbonylmethane precursor 127 (pathway B). This tricarbonylmethane system is proposed to be formed through acylation of β-keto ester 128 with (S)-2-methyl butyryl chloride (120). The preparation of β-keto ester 128 was to be achieved through the oxidation of the β-hydroxy ester 129, the product of an aldol reaction between t-butyl acetate (130) and aldehyde 131. The aldehyde 131 was to be produced in five linear synthetic steps from ethyl-(S)-lactate (132), which provides the alcohol stereocentre. The sequence involves the protection of the secondary alcohol of ethyl-(S)-lactate (132) as the PMB-ether 133, displacement of the ethoxide with dibromomethane would give the brominated ketone 134. Acetate addition by $S_n2$ displacement of the bromine would afford the ester 135, followed by a Wittig reaction to convert ketone into the alkene 136 intermediate. Mild alkaline hydrolysis of the acetate 136 produces the unsaturated alcohol 137 and following oxidation affords the desired aldehyde 131. The aldehyde (ent-131) enantiomer was then to be produced using the same synthetic steps beginning with isobutyl-(R)-lactate (138) to facilitate the opposite stereochemistry at the alcohol stereocentre.
2.3.2 Acyclic Lactonisation Model Studies

To determine the potential success of this synthetic approach a simple model system 139 was developed (Figure 2.13). This model system 139 omitted the stereocentre on the propyl ketone side chain and the exocyclic methylene. This simplifies the synthesis of the fragments significantly, but still enables the testing for the formation of the tricarbonyl system by acylation, and also allows the final lactonisation to be investigated. The acylated precursor 140 could be simply be prepared by a dianion aldol between the commercially available t-butyl acetoacetate (141) and acetaldehyde (142). This aldol adduct 143 was to be protected as the TBS-ether 144 and following acylation with butyryl chloride (145) would afford the acylated precursor 140. Removal of the silyl protecting group and cyclisation should produce the intended model system 139.
Following a modified procedure from Yamaguchi et al., the t-butyl acetoacetate (141) dianion was formed through the addition of sodium hydride followed by n-BuLi. The dianion mixture was cooled to -78°C and acetaldehyde (142) in THF was added via cannula and allowed to stir for a further two hours at this temperature. Selectivity for this reaction was not required but the product of this reaction is known to undergo elimination into conjugation on warming, so this reaction mixture was maintained at low temperature primarily to avoid formation of the dehydrated side-product. For the same reason the reaction mixture was not subjected to column chromatography, and the protection of the resultant aldol adduct 143 was carried out on unpurified concentrated organic extracts following 1H NMR analysis.

It was initially proposed to protect this model aldol adduct 143 as the p-methoxy benzyl ether to best imitate that of the designed synthesis approach towards CR377 (9), however attempts employing sodium hydride and PMB-Cl or PMB-imidate and CSA proved unsuccessful. It was believed that the basic and acidic solutions required for PMB-ether protection most likely promoted the formation of the above predicted dehydration product. Adjustment to the use of a TBS-protecting group was thought to be easier to install and serve an equal purpose. Using a procedure from Corey and coworkers, the protection of the crude alcohol 143 as the TBS-ether was achieved in CH₂Cl₂ at -78°C using 2,6-lutidine following by addition of TBSOTf. The reaction mixture was stirred for 2 hours, warmed to room temperature and following purification gave the TBS-protected aldol adduct 144 in 85% yield over two steps (Scheme 2.2).
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Reagents and Conditions: a. NaH (4.0eq), THF, 0°C, 20 minutes, then n-BuLi (1.0eq), -10°C, 10 minutes, then acetaldehyde (141) (10.0eq) at -78°C, 45 minutes. b. TBSOTf (1.5eq), CH2Cl2, 2,6-lutidine (2.0eq), -78°C, 2 hours.

Scheme 2.2: Formation and TBS-protection of the dianion aldol adduct 143

Successful acquisition of the TBS-protected β-keto ester 144 meant attention could be now focused on constructing a similar tricarbonylmethane system and the completing the final lactonisation to achieve the designed acyl dihydropyrone 139 model system. Rathke and Cowan had reported a procedure for the single step acylation of β-keto esters and diesters.27 The procedure uses metal complexation to enhance the acidity of the methylene protons, such that tertiary amine bases can deprotonate the complexed dicarbonyl to allow nucleophilic acylation of the acyl halide. To test this procedure it was decided to replicate their acylation of ethyl acetoacetate (126) with butyryl chloride (145) (Scheme 2.3). Magesium chloride was added to a solution of ethyl acetoacetate (126) in CH2Cl2 at 0°C to facilitate the complexation. The magnesium complexed ethyl acetoacetate (126) was deprotonated with pyridine, and butyryl chloride (145) was then added dropwise, the reaction mixture was warmed to ambient temperature for one hour. Analysis of the purified product revealed the desired tricarbonyl adduct 146 had formed in 64% yield, confirmed by the presence of the characteristic enol resonance at δ 17.8 and the three carbonyl signals at δ 198, δ 195, and δ 167.

Reagents and Conditions: a. MgCl2 (1.7eq), pyridine (2.0eq), CH2Cl2, 0°C, then 1 hour at RT.

Scheme 2.3: Acylation of ethyl acetoacetate (126) with butyryl chloride (145)
The success of this test acylation confirmed that viability of implementing this approach towards installing the tricarbonylmethane system in CR377 (9). Application of this procedure was successful in achieving the acylation of TBS-protected β-keto ester 144 with butyryl chloride (145) to give the acyclic tricarbonyl model precursor compound 140 only in situ as the reaction mixture was quenched with 6 N HCl. Unfortunately, the addition of HCl completely cleaved the TBS-protecting group, and as a result facilitated lactonisation to produce the model pyrone 139 in only 15% yield. Although this result was encouraging, the desired model acyl pyrone 139 was isolated in poor yield and as such the conditions were modified to improve the yield in preparation for the synthesis towards the natural product CR377 (9). The acylation procedure was repeated and instead the reaction mixture was quenched by the addition of a saturated CuSO₄ solution. The aqueous CuSO₄ solution also served to remove the excess pyridine from the organic extracts and following purification the tricarbonyl model precursor 140 was obtained in 66% yield (Scheme 2.4). This product was again confirmed by the enol resonance at δ 17.4 and the three carbonyl signals at δ 197, δ 194, and δ 166. Selective deprotection of the TBS-ether was undertaken using HF/pyridine in buffered pyridine followed by addition of TFA in methylene chloride at room temperature for 24 hours. This achieved the same acyl pyrone model system 139 in 31% yield over two synthetic steps. The yield although moderate demonstrated the potential for this synthetic approach to be adapted towards the natural product (9).

**Reagents and Conditions:**

- **a.** MgCl₂ (1.7eq), pyridine (2.0eq), CH₂Cl₂, 0°C, then 1 hour at RT.
- **b.** HF/Pyr/Pyr (1.0eq), THF, RT, 24 hours, then TFA (0.1eq), CH₂Cl₂, RT, 24 hours.

**Scheme 2.4:** Acylation and lactonisation to give the acyl-dihydropyrene 139 model system.
2.3.3 Acquisition of Aldehyde 131

The success of the synthesis of the above designed model system 139 confirmed the potential of this acyclic lactonisation approach to be applied towards the synthesis of natural product CR377 (9) (Figure 2.11). Due to the commercial availability of chemicals ethyl-(S)-lactate (132) and (S)-2-methyl butyryl chloride (120), these materials would be used to target the (S,S)-stereoisomer of CR377 (9). Initial synthetic studies though focused on the synthesis of unsaturated aldehyde 131, as a robust and efficient synthesis of this fragment from ethyl-(S)-lactate (132) was believed to be fundamental in achieving total synthesis of CR377 (9). Similarly this synthetic sequence would also have to be performed using isobutyl-(R)-lactate (138) as the stereochemically pure material to produce the (R,S)-stereoisomer to conclusively determine the absolute stereochemistry of the natural product (9).

Protection of ethyl-(S)-lactate (132) as the PMB-ether 133 was made with the anticipation that this protecting group would be robust enough to endure all the proposed synthetic steps and be straightforwardly cleaved at the final stage, allowing lactonisation to form the natural product (9). Protection of ethyl-(S)-lactate (132) as the PMB-ether 133 firstly required the synthesis of PMB-imidate 147 from PMB-alcohol 148 (Scheme 2.5).

Synthesis of PMB-imidate 147 followed a method outlined by Patil,28 which was also utilised in the synthesis of benzyl imidate (Chapter four, Scheme 4.1). This new procedure is applicable to a broad spectrum of benzylic alcohols and avoids the tedious washing and handling sodium hydride that is required of the traditional method.29,30 As shown in Scheme 2.5, treatment of p-methoxybenzyl alcohol (148) with aqueous KOH and phase-transfer catalyst tetrabutylammonium hydrogen sulphate, followed by the addition of trichloroacetonitrile afforded PMB-imidate 147 in 94% yield after purification by Kugelrohr distillation.
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Reagents and Conditions: a. 50% KOH, CH₂Cl₂, (n-Bu)₄NH, HSO₄ (cat.), 0°C, Cl₃CC≡N (1.2eq), 2 hours at RT.

Scheme 2.5: Synthesis of PMB-imidate (147) from PMB-alcohol (148)

The newly acquired PMB-imidate 147 was used immediately to protect ethyl-(S)-lactate (132) as the PMB-ether 133 by following a procedure reported by Yu et al.,³¹,³² where PMB-imidate 147 and CSA was added to a solution of ethyl-(S)-lactate (132) in CH₂Cl₂ at room temperature. The reaction mixture was stirred for four days at room temperature where extra PMB-imidate 147 and CSA were added as considered appropriate by TLC analysis. Concentration of the reaction mixture allowed hexane trituration to remove the trichloroacetamide by-product, and following extensive chromatography due to the presence of a compound with a similar Rf, the desired PMB-lactate 133 was achieved in 71% yield.

The next four linear reaction steps were achieved following methodology published from Kaluza et al.¹³ The PMB-lactate 133 was homologated to the bromomethylketone 134 in 79% by reacting methylene bromide with methyl lithium at -78°C. The addition of the dibromomethyl lithium anion to the ester followed by an extra equivalent of methyl lithium facilitates rapid metal-halogen exchange and loss of ethoxide to produce the monobromoketone lithium enolate intermediate which is protected from further nucleophilic alkylation. The bromomethylketone 134 is formed by trapping the monobromoketone lithium enolate intermediate with a protic source like acetic acid.³⁴ SN₂ displacement of the bromine to form the acetate ester 135 was achieved in 80% yield by dissolving the brominated ketone 134 in DMF and addition of sodium acetate for four hours at room temperature. Synthesis of the acetate 135 added in the required oxygen functionality but also served to protect it during the following Wittig reaction. The triphenylphosphonium salt 149 required for the following Witting reaction was synthesised in 83% from triphenylphosphine and methyl iodide at room temperature for four days.³⁵ The ester 135 was then converted to the alkene intermediate 136 by treatment of the triphenylphosphoniummethyl iodide salt (149) with n-BuLi forming the required ylide. The
Synthetic Studies towards CR377

Triphenylphosphine oxide by-product was removed by filtration through celite and the remaining filtrate residue was concentrated and dissolved in methanol. A catalytic amount of potassium carbonate was added and the reaction was stirred for three hours to effect the mild alkaline hydrolysis of the acetate to give the unsaturated primary alcohol \( {137} \) in 77% yield over two steps. The primary alcohol \( {137} \) was then converted to the desired aldehyde \( {131} \) as required, and was achieved in 94% yield using Dess-Martin periodinane (150) in \( \text{CH}_2\text{Cl}_2 \) at room temperature for one hour. This simple synthesis of aldehyde \( {131} \) was achieved in 33% overall yield from ethyl-(S)-lactate \( {132} \) in five linear steps (Scheme 2.6) and provided a building block for a number of synthetic approaches to CR377 (9).

\[
\begin{align*}
{132} & \xrightarrow{\text{a.} \ 71\%} {133} & \xrightarrow{\text{b.} \ 79\%} {134} \\
& \xrightarrow{\text{c.} \ 80\%} {135} & \xrightarrow{\text{d.} \ 77\%} {136} \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad
signals at δ 9.86, δ 7.82, δ 6.99 and δ 3.86 correspond to anisaldehyde, an oxidative cleavage by-product of the PMB-group during reaction with Dess-Martin periodinane (150). Analysis of the $^{13}$C NMR spectrum (Figure 2.15) shows the 11 unique carbon resonances. Most notable is the aldehyde carbonyl resonance at δ 193.6 and the six sp$^2$ hybridised carbons between δ 159.0-113.6.

*Figure 2.14: The $^1$H NMR spectrum of aldehyde 131 in CDCl$_3$*
Dess-Martin periodinane (150) was synthesised according to the two step reaction procedures shown in Scheme 2.7. The intermediate iodoxybenzoic acid (151) was formed by treatment of iodobenzoic acid (152) with potassium bromate and sulfuric acid in accordance with the original procedure reported by Dess and Martin.\textsuperscript{37,38} Acetylation of the iodoxybenzoic acid (151) with a catalytic amount of \(\text{p-TsOH}\) and acetic anhydride gave the Dess-Martin periodinane (DMP) (150) reagent in excellent yield on a 50-gram scale. This procedure developed by Ireland \textit{et al}\textsuperscript{39} was designed to reduce the irregular behavior seen in other reported Dess-Martin acetylations.\textsuperscript{40,41}

\[\begin{array}{c}
\text{PMBO} \quad \cdot \quad \text{CO} \\
\text{I} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{AcO} \\
\text{AcO} \\
\text{AcO} \\
\end{array}\]

\textbf{Reagents and Conditions:} \textit{a.} KBrO\textsubscript{3} (1.3eq), H\textsubscript{2}SO\textsubscript{4} (0.7M, 1.6eq), 70°C for 4 hours; \textit{b.} \text{p-TsOH} (cat.), Ac\textsubscript{2}O, 80°C for 2 hours.

\textit{Scheme 2.7: Synthesis of Dess-Martin periodinane (150)}
2.3.4 Synthesis of β-Keto Ester 128

Acquisition of the unsaturated aldehyde 131 in excellent overall yield then allowed the focus of the synthetic strategy to be shifted towards construction of the unsaturated β-keto ester 128, which could then be acylated to form the planned tricarbonyl acyclic precursor 127. The dicarbonyl compound 128 was to be formed through an aldol coupling of the newly synthesised aldehyde 131 with t-butyl acetate (130). The resultant alcohol 129 could then be oxidised immediately forming the required unsaturated β-keto ester 128 product. The aldol coupling of the unsaturated aldehyde 131 and t-butyl acetate (130) (Scheme 2.8) followed a method adapted from Bulger et al,42 where t-butyl acetate (130) was added dropwise to a solution of LiHMDS in THF at -78°C. After 30 minutes the aldehyde 131 was added as a solution in THF via cannula and the reaction mixture was maintained at -78°C for a further 30 minutes before being warmed to 0°C for another two hours. Purification of the concentrated organic extracts gave the acetate-aldol adduct 129 in 95% yield as a mixture of diastereomers. Use of an achiral auxiliary in t-butyl acetate (130) meant that the aldol product 129 was observed as a 50/50 mixture of diastereoisomers as the facial preference was determined solely by the aldehyde 131. As the facial preference of the aldehyde 131 was only influenced by its own β-stereocentre, which as seen in transitions states T10 and T11, is relatively remote and hence does not favour a particular diastereomeric product (Scheme 2.8). This lithium aldol reaction was nonselective towards the production of a particular diastereomer, however both diastereomers can be combined for the subsequent oxidation step of the secondary alcohol 129, which negates the need for a stereoselective aldol reaction.
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\[
\text{PMBO} \rightarrow \text{131} + \text{130} \xrightarrow{\text{a. 95\%}} \text{129}
\]

**Reagents and Conditions:** a. LiHMDS (1.7eq), THF, t-butyl acetate (130) (1.7eq), -78°C, 30 minutes, warmed to 0°C for 2 hours.

**Scheme 2.8:** Lithium hexamethyldisilazane aldol of t-butyl acetate (130) and aldehyde 131

The oxidation of aldol adduct 129 to the β-keto ester 128 (Scheme 2.9) was initially conducted under the identical Swern oxidation conditions as those employed by Bulger and coworkers due to their substrate similarity. This oxidation attempt only produced an intriguing reaction product that was not the desired product (the chemistry occurring in this oxidation reaction is discussed in detail in Chapter 3). The Swern oxidation of β-hydroxy ester 129 was once again repeated but unfortunately this attempt also produced the same unknown reaction product. For the purposes of this synthesis our attention turned to the previously used Dess-Martin periodinane (150) to affect this oxidation. The secondary alcohol 129 was dissolved in CH2Cl2 and H2O, then DMP was added and the mixture was stirred at room temperature for three hours to give the β-keto ester 128 in a modest 30% yield. Even though oxidation of β-hydroxy ester 129 to the dicarbonyl 128 was successful it still required improvement to be a viable synthetic approach towards the natural product CR377 (9). Another reagent for the conversion of secondary alcohols to ketones is pyridinium chlorochromate (PCC). This reagent though is unpopular for this functional group transformation due to the reagents’ toxicity, tedious workup procedures and other mild oxidation techniques. As the other mild oxidation practices detailed above had proved unsuccessful, PCC (153) appeared to be a practical pathway moving forward. Synthesis of PCC (153) was achieved in 80% yield following a procedure detailed by Corey and Suggs, where a solution of pyridine hydrochloride was added to CrO3 at ambient temperature for 30 minutes. With the newly synthesised PCC (153) in hand, following a method detailed by Kamimura et al, β-hydroxy ester 129 was dissolved in CH2Cl2, and at room temperature equal amounts of PCC (153) and
celite solid support\textsuperscript{67} were added. The dark reaction mixture was stirred for 4 hours and following filtration and purification produced the desired β-keto ester \textbf{128} in an acceptable 75\% yield.

\textbf{Scheme 2.9: Swern, DMP and PCC oxidation attempts of 8-hydroxy ester 129}

**2.3.5 Studies towards the Acyclic Tricarbonyl Precursor 127**

To attempt the acylation of β-keto ester \textbf{128} to form the acyclic tricarbonyl precursor \textbf{127} first required the synthesis of (S)-2-methylbutyryl chloride \textbf{(120)} acylating agent from the commercially available (S)-2-methylbutanol \textbf{(154)} (Scheme 2.10). Conversion of this enantiomerically pure alcohol \textbf{154} to the analogous carboxylic acid \textbf{155} was achieved using Jones oxidation\textsuperscript{48} without causing epimerisation of the α-methyl substituent.\textsuperscript{49} The alcohol \textbf{154} was dissolved in acetone and at 0°C was added to a premixed solution of CrO\textsubscript{3}/H\textsubscript{2}SO\textsubscript{4}/H\textsubscript{2}O dropwise until the mixture maintained a distinctive orange. The mixture was quenched with ethanol until the solution turned a deep green colour, and following purification by distillation gave the optically pure acid \textbf{155} in 85\% yield. Conversion of the acid \textbf{155} to the acyl halide \textbf{120} was achieved in 86\% excellent yield by dissolving the acid \textbf{155} in thionyl chloride.\textsuperscript{50} The mixture was heated at 50°C for 2 hours to effect the thionyl chloride 1,2-addition/1,2-elimination reaction of the acid \textbf{155}. Distillation was again used to purify the reaction mixture by removing the excess thionyl chloride (bp. 78°C) to obtain the (S)-2-methylbutyryl chloride \textbf{(120)} product (bp. 115°C).\textsuperscript{51}
Synthetic Studies towards CR377

![Chemical Structure](image)

**Reagents and Conditions:**

a. CrO$_3$ (0.1M), H$_2$SO$_4$, acetone, H$_2$O, 0°C for 30 minutes, then EtOH.

b. SOCl$_2$ (3.0eq), 50°C, 2 hours.

**Scheme 2.10: Preparation of (S)-2-methylbutyryl chloride (120) from (S)-2-methylbutanol (154)**

With the enantiomerically pure acid chloride 120 in hand, attention turned to implementation of the acylation procedure reported by Rathke and Cowan$^{27}$ used in Schemes 2.3 and 2.4 for the single step construction of tricarbonylmethane systems. Addition of magnesium chloride followed by pyridine to a cooled solution of unsaturated β-keto ester 128 in dichloromethane should have formed the desired complexed enolate. The dropwise addition of the acid chloride 120 to the reaction mixture was monitored by TLC over a four hour period. TLC analysis highlighted that an extra product had formed in addition to that of the starting β-keto ester 128 starting material. Analysis of $^1$H NMR spectrum of the crude reaction material indicated the presence of signals attributed to the two key synthesised reagents, but confirmed that no desired acylation of β-keto ester 128 had occurred due to absence of the products’ characteristic enol tautomer signal around δ 17, as observed for the previous model tricarbonyl systems $^{139}$ and $^{147}$. Purification of the organic extracts confirmed the above prediction and only succeeded in the recovery of the β-keto ester 128. A second acylation attempt utilising iPrMgCl Grignard reagent at low temperature to form the identical magnesium complexed dicarbonyl enolate was employed. Addition of the (S)-2-methyl butyryl chloride (120) was allowed to stir at -78°C for two hours, then the reaction mixture was warmed to room temperature for a further 15 hours. The additional reaction time at room temperature was implemented as the previous synthetic attempt yielded no acylated product 127 after four hours. This increased reaction period was also unsuccessful in the formation of the desired acylated product 127 with β-keto ester 128 recovered as the sole product following purification. This acylation attempt was repeated, and the warmed reaction mixture was further heated to reflux for two hours, this though leads to the reduced recovery of the β-keto ester 128 starting material. To exclude the possibility that the above methodologies were failing to produce the required enolate a third acylation attempt was investigated with the addition of t-BuLi to a solution of β-keto ester 128 in THF at -78°C. This acylation attempt was also unsuccessful in the formation of the
acyclic tricarbonyl precursor 127, and as a result this synthetic approach required further revision in order to achieve the desired acyclic precursor 127 product.

![Reagents and Conditions](image)

**Reagents and Conditions:**

- **a.** MgCl₂ (1.7eq), pyridine (2.0eq), CH₂Cl₂, 0°C, then 1 hour at RT.
- **b.** iPrMgCl (1.2eq), THF, -78°C, 2 hours, then 15 hours RT.
- **c.** t-BuLi (1.0eq), THF, -78°C, 2 hours, then 2 hours RT.

**Scheme 2.11:** Acylation attempts of acid chloride 120 with β-keto ester 128 to achieve the acyclic precursor 127

The resonance contributors and tautomerisation of β-keto ester 128 was believed to be the reason acylation at the α-carbon of this β-keto ester 128 product proved unattainable using a variety of reagent conditions. As a result, based on studies conducted by Zhang and coworkers it was decided to revise this acyclic approach and target this identical tricarbonyl precursor 127 through the synthesis of the alternate β-keto ester 156 and acyl halide 157 (Figure 2.16). This new combination should alleviate the problems encountered above in attempting to acylate the original unsaturated β-keto ester 128, as incorporating the challenging conjugated alkene functionality was to be attached on the more reactive acid chloride substrate.

![Figure 2.16](image)

**Figure 2.16:** Revised retrosynthesis towards the acyclic tricarbonyl precursor 127
To test this new approach firstly, methacryloyl chloride (158) was synthesised directly from methacrylic acid (159) in 72% yield using oxalyl chloride and a catalytic amount of DMF (Scheme 2.12). From the conditions used above, it was decided that isopropyl magnesium chloride was the key reagent for this acylation reaction, as it could be simultaneously used to deprotonate and chelate the β-keto ester. Due to commercial availability of ethyl acetoacetate (126) and t-butyl acetoacetate (141) both were reacted with methacryloyl chloride (158) to access this acylation approach towards synthesis of unsaturated model acyclic tricarbonyl precursors 160 and 161 (Scheme 2.12). Both ethyl acetoacetate (126) and t-butyl acetoacetate (141) were exposed to iPrMgCl for 30 minutes at -78°C, followed by the dropwise addition of methacryloyl chloride (158). The reactions were stirred for two hours at -78°C, and then warmed to room temperature for a further 30 minutes. In both cases the desired tricarbonyl model systems 160 and 161 were produced in encouraging 65% and 71% yields, respectively.

Reagents and Conditions: a. (COCl)$_2$ (1.1eq), CH$_2$Cl$_2$, DMF, 0°C then 40°C for 3 hours. b. iPrMgCl (1.2eq), THF, methacryloyl chloride (158) (1.0eq), -78°C, 2 hours.

Scheme 2.12: Preparation of methacryloyl chloride (158) and acylation of β-keto esters (126) and (141)

The success of the above methacryloyl chloride (158) acylations of ethyl acetoacetate (126) and t-butyl acetoacetate (141) to give the corresponding tricarbonyl model systems 160 and 161 led to the design and synthesis of the alternate β-keto ester 157 (Scheme 2.13). Oxidation of (S)-2-methyl butanol (154) to (S)-2-methyl butyraldehyde (162) was achieved in 90% yield under general Swern oxidation conditions. Applying the aldol methodology as used above (Scheme 2.8), the lithium enolate of t-butyl acetate (130) was generated using LiHMDS at -78°C. The newly formed aldehyde 162 was added via cannula and the resulting reaction mixture was stirred for 2 hours to give the acetate aldol adduct 163 in
76% yield. The aldol adduct 163 was dissolved in CH₂Cl₂ and oxidised to the planned β-keto ester 156 in 82% using PCC (153) and celite, at room temperature for 4 hours.

![Chemical structure of reactions](image)

**Reagents and Conditions:** a. DMSO (3.0eq), (COCl)₂ (1.5eq), CH₂Cl₂, NEt₃ (6.0eq), -78°C, 2 hours. b. LiHMDS (1.1eq), THF, t-butyl acetate (130) (1.1eq), -78°C, 30 minutes, warmed to 0°C for 2 hours. c. PCC (2.0eq), CH₂Cl₂, celite, 4 hours RT.

**Scheme 2.13:** The three step synthesis of β-keto ester 156 from (S)-2-methylbutanol (154)

With the β-keto ester 156 in hand, and an excess amount of methacryloyl chloride (158) it became apparent in addition to the model systems 160 and 161 synthesised above (Scheme 2.12) to look into the acylation of β-keto ester 156 with methacryloyl chloride (158) (Scheme 2.14). Aside from targeting the actual acyclic tricarbonyl precursor 127, this investigation would provide the best representation towards the likelihood of success for this revised acylation approach. In an identical manner to that detailed above β-keto ester 156 was dissolved in THF and reacted with 1.2 equivalents of iPrMgCl for 30 minutes at -78°C. Methacryloyl chloride (158) was added dropwise and the reaction mixture was stirred for two hours at -78°C, before being warmed to ambient temperature for a further 30 minutes. This internally developed methodology also produced the desired tricarbonyl model system 164 in 73% yield, emphasising the potential for this synthetic approach towards the natural product (9).

![Chemical structure of reactions](image)

**Reagents and Conditions:** a. iPrMgCl (1.2eq), THF, methacryloyl chloride (158) (1.0eq), -78°C, 2 hours.

**Scheme 2.14:** Acylation of β-keto ester 156 with methacryloyl chloride (158)
The successful synthesis of the above tricarbonyl model systems (160, 161 and 164) and the formation of β-keto ester 156 from the aldol addition between (S)-2-methyl butyraldehyde (162) and t-buty1 acetate (130), followed by PCC oxidation signified the potential of this alternative acylation approach towards the natural product (9). As a result, focus now turned towards obtaining the PMB-protected acyl chloride 165 required for the acylation reaction with β-keto ester 156 to form the acyclic tricarbonyl precursor 127. With a sound methodology for the synthesis of aldehyde 131 (Scheme 2.6), it seemed appropriate to extend that approach towards the formation of the desired acid chloride 165 through the preparation of unsaturated acid 166 (Scheme 2.15). Although Jones oxidation was successfully employed above for the direct conversion of (S)-2-methyl butanol (154) to the (S)-2-methyl butyric acid (155), it was believed these harsh reaction conditions would cause decomposition of the PMB-ether functionality. As a result, following a procedure detailed by Jeffery et al55 the aldehyde 131 would be further oxidised to the carboxylic acid 166 using Pinnick oxidation conditions. The aldehyde 131 was dissolved in t-BuOH and H2O at room temperature, 2-methylbut-2-ene, followed by NaClO2 and NaH2PO4 were added together and the reaction was stirred for 2 hours. The mixture was then diluted with CH2Cl2/H2O (2:1) and acidified by the addition of TFA to give the unsaturated acid 166 following column chromatography in an excellent 90% yield. Conversion of the acid 166 to the acyl chloride 165 was attempted using both thionyl chloride50 and oxalyl chloride53 methods as previously used above, however both cases failed to produce the desired transformation. During this time it was discovered that Ghosez et al56 had developed a α-chloroenamine for the formation of acyl halides under mild conditions. It was also noted that Jimenez and coworkers57 had successfully used Ghosez’s reagent during their total synthesis of dictyostatin analogues for the conversion of an allylic acid into the corresponding acyl halide. Application of that procedure saw PMB-acid 166 converted into acid chloride 165 as required by dissolving acid 166 in CH2Cl2 at ambient temperature followed by the dropwise addition of the α-chloroenamine reagent.
Reagents and Conditions: a. NaClO₂ (5.0 eq), NaH₂PO₄ (4.0 eq), t-BuOH, 2-methylbut-2-ene, H₂O, RT for 2 hours, acidified with TFA. b. 1-Chloro-N,N-2-trimethyl-1-propenylamine (1.0 eq), CH₂Cl₂, RT for 3 hours.

Scheme 2.15: Preparation of PMB-acid chloride 165 from unsaturated aldehyde 131

The newly prepared acyl chloride 165 was concentrated, redissolved in dry THF and added via cannula to the simultaneous deprotonation and chelation of β-keto ester 156 at -78°C with ³PrMgCl (Scheme 2.16). The reaction mixture was stirred for 2 hours before being warmed to 0°C for a further 30 minutes. Analysis of the crude reaction mixture by ¹H NMR straight away revealed the absence of the vinylic and tricarbonyl enol signals as seen in the previous model systems. Purification of the mixture by column chromatography followed by extensive NMR characterisation identified this unknown reaction product to be γ-pyrone 167. Mechanistically this γ-pyrone product 167 is believed to have formed through an intramolecular enol conjugate addition⁵⁸,⁵⁹ of the desired acyclic precursor 130. Although unfortunate the acquisition and identification of this acylation by-product 167 did confirm that Ghosez’s reagent had successfully converted the acid 166 into the acyl halide 165 fragment. This confirmation then allowed future syntheses of this acyl halide 165 to be characterised by NMR spectroscopy prior to use.

Reagents and Conditions: a. ³PrMgCl (1.2 eq), THF, acid chloride 165 (1.0 eq) -78°C, 2 hours, then 0°C for 30 minutes.

Scheme 2.16: Acylation of β-keto ester 156 and intramolecular conjugate addition to give γ-pyrone 167
This identified product probed the reanalysis of the above model systems (160, 161 and 164) to determine if this process had also occurred over time as this by-product was not observed for either model system during first analysis. Reanalysis of the above model systems (160, 161 and 164) indicated that small amount of the respective acyclic tricarbonyl systems had also undertaken the same intramolecular enol conjugate addition (Scheme 2.17) to give pyrones (168, 169, and 170).

\[
\begin{align*}
R_1 &= \text{CH}_3, R_2 = \text{CH}_2\text{CH}_3 \\
R_1 &= \text{CH}_3, R_2 = \text{C(\text{CH}_3)}_3 \\
R_1 &= \text{CH(\text{CH}_3)CH}_2\text{CH}_3, R_2 = \text{C(\text{CH}_3)}_3
\end{align*}
\]

Scheme 2.17: Intramolecular conjugate addition products 168, 169, and 170 isolated from the acyclic tricarbonyl model systems 160, 161 and 164

2.3.6 Synthesis of a Protected Acyclic Precursor 172

The above reaction conditions undoubtedly formed the desired model acyclic precursors (160, 161 and 164), the isolation of the corresponding pyrones (168, 169, and 170) following purification highlighted though the need for a revised approach towards the preparation of an acyclic precursor product. It was proposed that rather than an immediate oxidation of the aldol product 163 to the following β-keto ester 156, the aldol product 163 was to be protected to avoid the formation of this intramolecular conjugate addition product 167. To assist product assignment N-acetyl thiazolidine thione (82) was used as the auxiliary to provide a stereochemically pure acetate aldol product 171. Successful acylation of the bis-protected acetate aldol product 171 would produce a protected acyclic precursor 172 and following selective deprotection and lactonisation would form the γ-pyrone moiety. Removal of the final protecting group and oxidation of the resultant alcohol would afford the natural product CR377 (9) (Figure 2.16).
Excellent stereoselectivities have been observed for acetate aldol condensations using 1,3-oxazolidine-2-thiones and 1,3-thiozolidine-2-thiones.\textsuperscript{60,61} The synthesis of these auxiliaries is less tedious than that of oxazolidinone and has been shown to produce significantly better diastereoselectivity results in these acetate aldol condensations. Recent advances in aldol methodology have indicated that Nagao’s auxiliary is highly compatible with titanium chloride enolates,\textsuperscript{62-65} and when combined with unsaturated aldehydes produce an elevated diastereoselectivity between products than the similar tin triflate based aldols. This is thought to be due to sulfurs’ known higher affinity towards titanium,\textsuperscript{66} thus creating a more rigid favourable transition state compared to the oxazolidinone equivalent. These listed advantages led to the synthesis of the 1,3-thiazolidine thione auxiliary 82 (Scheme 2.18) for the use in the following acetate aldol condensation to generate a single β-hydroxy diastereomer.\textsuperscript{67}

The borane reduction of (S)-phenylalanine (173) to (S)-phenylalanol (174) was achieved in 92% following a procedure detailed by Evans et al.\textsuperscript{67} Nagao’s auxiliary 175 was then obtained in 84% yield as white needles using a procedure from Delaunay et al,\textsuperscript{68} in which (S)-phenylalanol (174) was refluxed with KOH and CS\textsubscript{2} for 16 hours. Nagao’s auxiliary 175 was acylated using a modified method from Yadav et al,\textsuperscript{69} where thiazolidine thione 175 was reacted with n-BuLi and acetyl chloride (22) at -78°C for 1 hour, then a further 30 minutes at room temperature. Purification by column chromatography gave the N-acetyl thiazolidine thione auxiliary (82) in 94% yield as a yellow powder.
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![Chemical structures](image)

**Reagents and Conditions:**

a. BF₃·OEt₂ (1.0eq), BH₃·SMe₂ (1.1eq), THF, reflux for 8 hours, then NaOH/THF/H₂O, reflux for a further 15 hours.  
b. KOH (1M), CS₂ (5.0eq), reflux for 15 hours.  
c. n-BuLi (1.0eq), THF, -78°C, acetyl chloride (22) (1.2eq), 1 hour, then RT for 30 minutes.

**Scheme 2.18:** Three step synthesis of (S)-N-acetyl thiazolidine thione (82) from (S)-phenylalanine (173)

The determination of the stereochemical outcome for these Evans’ based acetate auxiliary aldols has been rationalised by consideration of the competing chair transition states (Scheme 2.19). Transition state TS12 illustrates the additional sulfur coordination with the titanium enolate, and also shows the steric benzyl group of the auxiliary facing away from the centre of the transition state. These two facts have been proposed for this transition state being the preferred pathway leading to the most thermodynamically stable syn-acetate product 176. As can be seen from TS13, the large benzyl group still is directed away from the centre of the transition state preventing any significant unfavourable steric interactions, but the stabilising coordination of the auxiliary sulfur to the titanium enolate is absent. The preference for either the syn or anti-aldol adducts 176 and 177 can be altered by changing the stoichiometry, the Lewis acid and or the amine base. In this case, though where the resultant alcohol stereocentre would eventually be oxidised at the final stage of the synthesis, the preference for a particular stereochemistry was not required, however formation of a sole diastereomer was desired for the structural determination of future synthesis targets. Modification of a procedure by Crimmins et al was utilised for the formation of the sole syn-syn aldol adduct 176 (Scheme 2.19), where the acetate auxiliary 82 was complexed with TiCl₄ for 30 minutes at -40°C. A slight excess of iPr₂NEt was added dropwise and stirring continued for an additional hour to ensure complete enolisation of the auxiliary, which was confirmed by the characteristic homogeneous dark red solution. The mixture was cooled to -78°C and aldehyde 131 in CH₂Cl₂ was added via cannula and the reaction was stirred for a further two hours to give the combined acetate-aldol products 176 and 177 in 85% yield. Separation of the diastereomers by column chromatography was achieved to give the major syn-acetate aldol product 176 in 78% yield and the minor anti-aldol product 177 in 7% yield.
Reagents and Conditions: a. TiCl₄ (1.5 eq), iPr₂NEt (1.90 eq), CH₂Cl₂, -40°C, for 30 minutes, then aldehyde 131, -78°C for 2 hours.

Scheme 2.19: Selective syn-acetate aldol reaction with aldehyde 131 and (S)-N-acetyl-thiazolidine thione (82)

With the syn-syn β-hydroxy amide 176 in hand, attention turned towards protection of the secondary alcohol 176 to test the success of the following acylation procedure (Scheme 2.20). For simplicity it was decided to protect the β-hydroxy amide 176 as the corresponding TBS-ether 178, which was achieved in 92% overall yield by the addition of TBSOTf and 2,6-lutidine in CH₂Cl₂ at -78°C for 3 hours. For the corresponding acylation; t-BuLi was selected due to its strong non-nucleophilic base character to deprotonate the bis-protected amide 178. Adaption of a procedure used by Burgos et al., amide 178 was dissolved in THF and t-BuLi was added dropwise at -78°C and the mixture stirred for 15 minutes. (S)-2-methylbutyryl chloride (120) was added and the reaction mixture was stirred for a further two hours then warmed to 0°C for a further 30 minutes. Purification of the reaction mixture revealed that no acylation product 179 formed and only led to the recovery of the bis-protected amide 178.
Reagents and Conditions: a. TBSOTf (1.5eq), 2,6-lutidine (2.0eq), CH$_2$Cl$_2$, -78°C for 3 hours. b. t-BuLi (1.0eq), THF, (S)-2-methyl butyryl chloride (120) (1.5eq), -78°C for 2 hours. c. DDQ (1.2eq), CH$_2$Cl$_2$, H$_2$O, RT for 2 hours.

Scheme 2.20: Acylation attempts on synthesis products bis-protected amide 178 and PMP-acetal 180 with (S)-2-methylbutyryl chloride (120)

Although the acylation of amide 178 was unsuccessful; it was proposed that the protection of the acetate aldol product 176 as the TBS-ether would have considerably obstructed the reaction site towards acylation. As opposed to introducing extra steric factors with the installation of a new protecting group, it was decided to form the p-methoxybenzylidine acetal 180. The acetate-aldol 176 adduct was converted to the PMP-acetal 180 in 85% yield under the normal PMB-ether cleavage conditions, as following oxidation with DDQ in CH$_2$Cl$_2$ at room temperature the adjacent alcohol quenches the intermediate benzylic cation. The identical t-BuLi acylation procedure used above was applied directly to the newly constructed PMP-acetal 180, however no acylation product 181 was formed, and purification of this reaction mixture only afforded PMP-acetal 180 reagent.

An Acylation attempt on the protected aldol adducts 178 and 180 in each case only led to the recovery of starting material. From these results, it was unclear as to whether the t-BuLi was actively deprotonating the amide or if the reaction site was now too sterically hindered to allow the proposed acylation to proceed. As some acylation success was had when the acyl halide 165 contained the α-methylene-β-protected hydroxyl functionality, the preparation of the alternate protected thiazolidine
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Thione aldol adduct 182 appeared a viable pathway forward. Application of the above successful titanium tetrachloride mediated aldol as reported by Crimmins et al70 was again applied towards thiazolidinone thione 82 and (S)-2-methylbutanal (162) (Scheme 2.21) to achieve the syn-anti-acetate-aldol product 182 in 80% yield. From the competing transition states TS14 and TS15, it is evidently clear that TS14 again is preferential due to the additional sulfur coordination to the titanium enolate. The slightly reduced diastereoselectivity is attributed to the α-chiral aldehyde 162 imparting a small diastereomic transition state preference towards the minor anti-syn acetate-aldol Felkin product 183.

Reagents and Conditions: TiCl₄ (1.5eq), iPr₂NEt (1.90eq), CH₂Cl₂, -40°C, for 30 minutes, then (S)-2-methyl-aldehyde (162), -78°C for 2 hours.

Scheme 2.21: Selective syn-aldol reaction with (S)-2-methylbutanal (162) and (S)-N-acetyl-thiazolidinone (82)

Protection of the new acetate aldol product 182 would similarly avoid the previously seen intramolecular cyclisation by removing the active enol functionality. Construction of this acetate-aldol product 182 would also eliminate the potential competing cyclisation mode once the PMB-ether was selectively cleaved. Although this cyclisation mode had not been encountered during previous studies, the ability to form exclusively the desired γ-pyrone through selective deprotection and controlled cyclisation pathways is a powerful synthesis tool for the modern day chemist. Synthesis of the γ-pyrone followed by removal of the newly installed silyl protecting group and correction of oxidation state would afford the natural product CR377 (9).
Employing the identical reaction conditions as described above (Scheme 2.20) the syn-aldol adduct 182 was protected as the corresponding TBS-ether 184 in 93% yield. If this substrate was at all susceptible to undertake acylation, use of the smallest acyl halide available in acetyl chloride (22) would best determine the potential for this synthetic pathway (Scheme 2.22). As such, TBS-ether 184 was dissolved in THF and t-BuLi was added dropwise at -78°C. The reaction mixture was stirred for 15 minutes, then acetyl chloride (22) was added dropwise and the mixture stirred for a further two hours. Purification and analysis of this reaction mixture once again only reproduced the TBS-ether 184 with no acylated product 185 observed.

The thiazolidine thione auxiliary 82 was an exceptional choice for producing a sole diastereomer for both acetal aldol reactions above, which were readily protected in excellent yields. The subsequent acylation attempts using t-BuLi to effectively deprotonate the amide followed by the addition of synthesised acid chloride 165, (S)-2-methylbutyryl chloride (120), and or the commercially available acetyl chloride (22) were unable to produce the targeted products. It was concluded from these results that use of the Evans auxiliary 82 although excellent in achieving stereoselectivity may have contributed further steric bulk to the reaction site, and hence was reasoned an unsuitable auxiliary for this synthetic approach towards achieving a protected acyclic precursor. Alteration of the thiazolidine thione auxiliary 82 to the Weinreb amide 186 would not provide the exceptional stereoselectivity seen previously for the respective aldol but would reduce the steric interactions surrounding the reaction site for the proposed acylation reaction (Scheme 2.23).
Weinreb amide 186 was synthesised by modification of a procedure by Crossman et al., where ethyl acetate (119) was added to a solution of N,O-dimethylhydroxylamine in THF and Et₂O. This mixture was cooled to -20°C and isopropyl magnesium chloride was slowly added to maintain this temperature for 30 minutes, the mixture was then warmed to 0°C for a further 30 minutes. An aqueous quench followed by organic extraction and purification by column chromatography gave the N-methoxy-N-methylacetamide (186) in 86% yield. β-hydroxy amide 187 was synthesised in 76% as a mixture of diastereoisomers by following the same LiHMDS aldol methodology as seen previously in Scheme 2.8. Protection of the alcohol 187 as the corresponding TBS-ether 188 was achieved in 94% yield after addition of imidazole and TBS-Cl to a solution of the alcohol 187 in DMF at room temperature for 15 hours.77,78 Acylation of this silyl-protected amide 187 with acetyl chloride (22) using t-BuLi to generate the required enolate unfortunately though was not successful in producing the desired product 189.

Reagents and Conditions: a. MeONH(Me).HCl (2.50eq), Et₂O, THF, iPrMgCl (5.0eq), -20°C for 30 minutes, then 0°C for 1 hour. b. LiHMDS (1.1eq), THF, aldehyde 162 (1.2eq), -78°C, 30 minutes, warmed to 0°C for 2 hours. c. TBS-Cl (1.1eq), imidazole (2.0eq), DMF, RT for 15 hours. d. t-BuLi (1.0eq), THF, acetyl chloride (22) (1.5eq), -78°C for 2 hours.

Scheme 2.23: Synthesis of TBS-protected β-hydroxy amide 188 and acylation attempt with acetyl chloride (22)

The acidity (pKₐ) of tertiary amides is relatively low for the preparation of enolates in comparison to that of ketones and esters due to the increased resonance stabilisation created by nitrogen’s extra π-donar capabilities.79 As the β-hydroxy ester product 163 had been previously synthesised above (Scheme 2.13), it was decided that this substrate would be adapted as a final attempt for this protected acylation approach towards the total synthesis of CR377 (9) (Scheme 2.24).
Protection of the acetate-alcohol product 163 as the TBS-ether was achieved following addition of imidazole and TBS-Cl to a room temperature solution of alcohol 163 in DMF. The reaction mixture was stirred overnight for 15 hours, then purified by column chromatography to give the TBS-protected aldol adduct 190 in 88% yield. As above, acetyl chloride (22) was chosen to determine whether acylation of this silyl protected adduct 190 to form an acyclic precursor 191 was in fact a viable approach. Similar to above, the TBS-protected product 190 was dissolved in THF and t-BuLi was added dropwise at -78°C for 15 minutes. Acetyl chloride (22) was slowly added and the reaction mixture stirred for an additional two hours at this temperature. Analysis of the remaining concentrated residue revealed that only β-TBS-protected ester 190 starting material was observed, ultimately proving that further modification in the auxiliary or alteration of the β-hydroxy protecting group for this revised acyclic synthetic approach was not practical.

Reagents and Conditions: a. TBS-Cl (1.1eq), imidazole (2.0eq), DMF, RT for 15 hours. b. t-BuLi (1.0eq), THF, acetyl chloride (22) (1.5eq), -78°C for 2 hours.

Scheme 2.24: Synthesis of TBS-protected β-hydroxy ester 190 and the acylation attempt with acetyl chloride (22)

The inability to affect acylation after the successful protection of the secondary alcohol using a range of auxiliaries indicated that although this synthetic approach had merit the results concluded that this was not a practical way forward towards accessing the natural product (9). The above studies concluded that preparation of a tricarbonyl acyclic precursor or a masked acyclic precursor was not a viable synthetic approach towards CR377 (9) and investigation towards an alternative synthesis was required.
2.4 Acyl Rearrangement Approach towards CR377

2.4.1 Oxygen to Carbon Acyl Rearrangements

As introduced above another obvious synthetic pathway towards the natural product CR377 (9) is formation of the unsaturated pyrone system followed by incorporation of the acyl 2-methylbutanone functionality (Pathway C). Direct acylation on carbon of cyclic pyrone ring systems is known to be quite a difficult process, and in most cases requires the use of an acyl transfer catalyst. This catalyst allows the initial oxygen acylated product to be slowly converted to the more thermodynamically stable product. For aromatic phenolic esters this process is referred to as the Fries-rearrangement, which employs a Lewis acid as the acyl transfer catalyst to generate the hydroxyl aryl ketone product (Figure 2.17).\(^{80}\) The rearrangement of the acyl group to either the ortho or para position on the aromatic ring can be achieved selectively by alteration of the temperature, reaction solvent or the Lewis acid catalyst.

![Figure 2.17: Fries-Rearrangement of aromatic phenolic esters with AlCl₃](image)

The accepted intermolecular mechanism for the Fries-rearrangement\(^{81,82}\) initially involves coordination of the Lewis acid (AlCl₃) to the more electron rich carbonyl oxygen on the acyl group. This interaction polarises the bond between the phenolic oxygen and the acyl group which allows the Lewis acid to rearrange to the phenolic oxygen. This rearrangement produces an acylium carbocation which can then react at either the ortho or para positions on the aromatic ring through electrophilic aromatic substitution. Formation of the ortho product (reaction pathway 1) requires the use of high temperature
and or non-polar solvent. The para-product (reaction pathway 2) forms at low temperatures and is also favoured by addition of polar solvents. For aromatic substrates where either the ortho or para position on the ring is already substituted the Fries-rearrangement will proceed to the next available free position.

Even though CR377’s (9) proposed structure is not an aromatic system the proposal of conducting an acyl-type rearrangement from a diester precursor to give the final tricarbonyl product has literature precedent.\textsuperscript{83,84} Tabuchi and coworkers\textsuperscript{85} work initially showed that DCC and DMAP could be used to effectively conduct Fries-type rearrangements on pyrone substrates. In 1994,\textsuperscript{4,86} studies toward the synthesis of alternaric acid (98) involved the development of a model system (Figure 2.18) in which β-keto lactone 192 was coupled with propionic acid in the presence of DCC and DMAP at room temperature for four days. This method successfully produced the diester 193 instantly, while the following Fries-rearrangement to the desired C-acylation product 194 was produced on exposure to silica gel, confirmed by the presence of the enol hydroxyl signal at δ 17.9 in the \textsuperscript{1}H NMR spectrum.

![Figure 2.18: Propionic acid acylation of pyrone 192 and rearrangement of diester 193](image)

Miyakado and coworkers\textsuperscript{2,87} illustrated that Podoblastin A, B and C (96, 195 and 196) could also be synthesised using a Fries-type rearrangement of the enol-acyl group towards the adjacent carbon to produce the tricarbonyl moiety (Figure 2.19). The conversion of the pyrone to each of the final tricarbonyl systems was achieved using a two step reaction process of acylation on oxygen followed by rearrangement to carbon. Each diester was afforded by the reaction of lactone with DBU and the appropriate acyl halide. The diesters were isolated prior to the addition of DMAP in refluxing toluene to effect the acyl rearrangement. This acyl rearrangement procedure was efficient in synthesising Podoblastin A, B and C (96, 195 and 196) natural products in respectable yields of 75%, 73% and 67%.
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Podoblastin A 96  \( R_1 = CH_3(CH_2)_{10} \)  \( R_2 = n\text{-Pr} \)  \( R_3 = H \)
Podoblastin B 195  \( R_1 = CH_2=CH(CH_2)_9 \)  \( R_2 = n\text{-Pr} \)  \( R_3 = H \)
Podoblastin C 196  \( R_1 = CH_3(CH_2)_{12} \)  \( R_2 = n\text{-Pr} \)  \( R_3 = H \)

Figure 2.19: Synthesis of Podoblastin A, B and C (96, 195 and 196) using an O- to C-acyl rearrangement approach

2.4.2 Acyl Rearrangement Model Studies

The success of these two studies to generate their respective tricarbonylmethane moieties following a Fries-type rearrangement approach indicated the ability for this synthetic pathway to be adapted towards the first total synthesis of CR377 (9). To further assess this rearrangement approach towards the natural product (9) it was decided to form a simplified pyrone 192, and to test the acyl rearrangement on CR377’s actual side chain. Synthesis of the model system pyrone 192 (Scheme 2.25) began with the formation of the t-butyl acetoacetate (141) dianion with acetaldehyde (142) as described above in Scheme 2.2.23 The unpurified acetate aldol product 143 was dissolved in CH₂Cl₂ and TFA was added dropwise at 0°C. The reaction mixture was warmed to room temperature where stirring continued for a further 15 hours to affect the lactonisation.86 As the lactone 192 was extremely water soluble, the acidic solution was concentrated in vacuo and loaded directly onto silica gel to furnish the model pyrone 192 in 81% yield over two steps as a white powder.

Scheme 2.25: Synthesis of model racemic lactone 192

Reagents and Conditions: a. NaH (4.0eq), THF, 0°C, 20 minutes, then n-BuLi (1.0eq), -10°C, 10 minutes, then acetaldehyde (142) at -78°C, 45 minutes. b. TFA (1.1eq), CH₂Cl₂, 0°C, RT for 15 hours.
With the synthesised lactone 192 in hand, attention turned towards achieving the desired acyl migration. It was decided to employ the two step procedure developed by Miyakado et al.\(^{87}\) as outlined above, as this evidently produced the best overall yield for this required transformation over a reduced timeframe. To internally assess this two-step synthetic acyl rearrangement approach it was elected to firstly employ butyryl chloride (145) as the acyl substrate to simplify the NMR characterisation of both the diester 197 and tricarbonyl 198 products. Following the procedures outlined by Miyakado and coworkers,\(^{87}\) butyryl chloride (145) was added dropwise to a mixture of lactone 192 and DBU in toluene at 0°C. The mixture was stirred for two hours at 0°C, and then quenched with a pH 7 buffered solution. The mixture was extracted with toluene to give the model diester 197 compound following purification by column chromatography in a respectable 72% yield. To effect the Fries-type rearrangement, diester 197 was dissolved in toluene and a small amount of DMAP was added. The solution was heated to 85°C for 15 hours, then cooled to room temperature and the toluene was concentrated \textit{in vacuo}. NMR analysis of the purified residue confirmed that the thermodynamically favourable acyl rearrangement had taken place to produce the tricarbonyl model system 198 in 66% yield (Scheme 2.26).

\[\begin{align*}
\text{O} & \text{O} & \text{Cl} & \text{O} & \text{O} \\
\begin{array}{ccc}
\text{192} & + & \text{145} \\
\end{array} & \xrightarrow{\text{a.}} & \text{O} & \text{O} & \text{O} & \text{Cl} & \text{O} & \text{O} \\
\begin{array}{ccc}
\text{197} \\
\end{array} & \xrightarrow{\text{b.}} & \text{O} & \text{O} & \text{O} & \text{OH} & \text{O} & \text{O} & \text{OH} & \text{O} \\
\begin{array}{ccc}
\text{198} \\
\end{array}
\end{align*}\]

\[\begin{align*}
\text{O} & \text{O} & \text{Cl} & \text{O} & \text{O} \\
\begin{array}{ccc}
\text{192} & + & \text{199} \\
\end{array} & \xrightarrow{\text{a.}} & \text{O} & \text{O} & \text{O} & \text{Cl} & \text{O} & \text{O} \\
\begin{array}{ccc}
\text{200} \\
\end{array} & \xrightarrow{\text{b.}} & \text{OH} & \text{O} & \text{O} & \text{OH} & \text{O} & \text{O} & \text{OH} & \text{O} \\
\begin{array}{ccc}
\text{201} \\
\end{array}
\end{align*}\]

**Reagents and Conditions:** a. DBU (1.1eq), toluene, 0°C for 2 hours. b. DMAP (0.05eq), toluene, 85°C for 15 hours.

*Scheme 2.26: Acylation/rearrangement synthesis of model tricarbonyl systems 198 and 201*
Analysis of the $^1$H NMR spectrum (Figure 2.20) shows the presence of the newly formed tricarbonyl enol peak at $\delta$ 17.9. As this product only contains one chiral centre the signal at $\delta$ 16.1 is attributed to the presence of one of the two other possible enol tautomeric structures. This feature is also easily recognisable at the sole stereocentre with both the methylene multiplet and methyl doublet signals displaying an additional resonance. The absence of the vinylic proton resonance at $\delta$ 5.90 from the diester 197 precursor material also confirms the success of the acyl rearrangement. Inspection of the $^{13}$C spectrum (Figure 2.21) shows the correct number of chemically unique resonances. The three signals at $\delta$ 204.4, $\delta$ 194.9, and $\delta$ 164.2 represent the three carbonyl functionalities that form the tricarbonyl system. The signal at $\delta$ 102.9 is also indicative of the highly deshielded methine carbon between the three carbonyls.

*Figure 2.20: The $^1$H NMR spectrum of model tricarbonyl system 198 in CDCl$_3$*
These two synthetic transformations were repeated by substituting butyryl chloride (145) for racemic 2-methylbutyryl chloride (199) to evaluate the success of the acyl rearrangement when there is substitution present at the α-position, (Scheme 2.26) as this is currently unprecedented. Apart from the exocyclic methylene, the addition of this racemic stereocentre would make this model system structurally identical to CR377 (9), and would provide insight into the ability to distinguish between CR377’s (9) diastereomers using NMR spectroscopy. The O-acylation product 200 was afforded in an identical manner to that detailed above, where racemic 2-methylbutyryl chloride (199) was added dropwise to a mixture of lactone 192 and DBU in toluene. The mixture was stirred at 0°C for two hours and following extraction and purification the diester 200 was achieved in 84% yield. The diester 200 was dissolved in toluene and a catalytic amount of DMAP was added, the mixture was heated to 85°C for 15 hours which facilitated the Fries-type rearrangement to the corresponding tricarbonyl model system 201 as mixture of inseparable diastereomers in 70% yield.
As can be seen from the analysis of the $^1$H and $^{13}$C NMR spectrums (Figures 2.22 and 2.23) for model system 201, the occurrence of two resonances for each chemically unique signal indicates the expected presence of diastereomers. Due to the similarity between the two model systems 198 and 201 the resonances and chemical shift values encountered in both the $^1$H and $^{13}$C NMR spectrums are comparable. The signals at δ 18.1 in the $^1$H NMR represents the enol proton that corresponds with the formation of the tricarbonyl system 201 through the successful acyl rearrangement of the diester 200. The presence of this signal also corresponds to the absence of vinylic proton that is present in the diester 200 starting material at δ 5.88. The $^{13}$C NMR displays the correct number of unique carbon environments including the three carbonyl environments at δ 208, δ 195, δ 164 and the methine carbon resonance at δ 102.

*Figure 2.22: The $^1$H NMR spectrum of model tricarbonyl system 201 in CDCl$_3$*
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2.4.3 Acquisition of Unsaturated Lactone 202

The overall success of the two acyl rearrangements from the diesters 197 and 200 towards their respective tricarbonyl methane model systems 198 and 201 strongly indicated that this synthetic approach presented a promising pathway towards achieving the first total synthesis of CR377 (9). To employ this approach towards achieving CR377 (9) one must first construct the required unsaturated lactone 202 fragment. Previous synthetic attempts outlined the successful synthesis of unsaturated β-keto ester 128, which following cleavage of the protecting group would furnish alcohol 203. Acid catalysed cyclisation of alcohol 203 would then afford this desired lactone 202 (Figure 2.24).

Figure 2.23: The $^{13}$C NMR spectrum of model tricarbonyl system 201 in CDCl$_3$

Figure 2.24: Retrosynthesis of lactone 202 from unsaturated β-keto ester 128
With the β-keto ester 128 in hand, the methodology described above in Scheme 2.20 would be followed to cleave the PMB ether under mild conditions. As such, DDQ was added to a solution of PMB-ether 128 in CH$_2$Cl$_2$ and H$_2$O at 0°C. The mixture was warmed to room temperature for two hours which effectively cleaved the PMB-ether to give the secondary alcohol 203. The alcohol 203 was obtained in 91% yield following purification by column chromatography to remove the anisaldehyde by-product from the concentrated reaction mixture. The alcohol 203 was dissolved in CH$_2$Cl$_2$ at 0°C, TFA was added dropwise and the solution was warmed to ambient temperature for 15 hours to facilitate the simultaneous cleavage of the t-butyl auxiliary and lactonisation to produce the targeted unsaturated lactone 202 in 86% yield (Scheme 2.27).

- **Reagents and Conditions:**
  - a. DDQ (1.2eq), CH$_2$Cl$_2$, H$_2$O, 0°C then RT for 2 hours.
  - b. TFA (1.1eq), CH$_2$Cl$_2$, 0°C, RT for 15 hours.

**Scheme 2.27: Two step synthesis of lactone (202) from β-keto ester (128)**

Looking at the $^1$H NMR spectrum (Figure 2.25) the unsaturated pyrone 202 in CDCl$_3$ is represented as approximately a 1:1 mixture of ketone and enol tautomers. The signals that aren’t involved in the tautomerisation process between the ketone and enol forms are represented twice. The diastereotopic methylene and the enol vinylic proton resonances are displayed between δ 6.42 and δ 5.36. The ketone tautomers’ methylene protons between to the carbonyl groups appear as two doublets at δ 3.75 and δ 3.57. Finally the two methine quartets at δ 5.28 and δ 5.12 couple to their respective methyl doublets at δ 1.66 and δ 1.57. Unfortunately, the enol proton that corresponds to the vinylic proton at δ 5.94 is significantly downfield and was not captured during analysis.

Analysis of the $^{13}$C spectrum (Figure 2.26) once again shows the impact of tautomeric structures. This pyrone 202 contains seven unique carbons environments; however examination of the $^{13}$C spectrum displays 14 individual resonances. Due to the free tautomerisation between the ketone and enol forms in CDCl$_3$ solvent the pyrone 202 displays duplicate resonances for each unique carbon. As a result, there
are four signals attributed to carbonyls, five to sp$^2$ hybridised, two methine, one methylene and two methyl carbons. Although this unsaturated pyrone 202 was still relatively easy to characterise, the use of deuterated methanol or benzene could have been used to isolate a single preferred tautomer during the NMR acquisition.\textsuperscript{88}

\textbf{Figure 2.25:} The $^1$H NMR of unsaturated lactone (202) in CDCl$_3$
2.4.4 Attempted Acyl Rearrangement of Diester 204

The successful acquisition of the unsaturated pyrone 202 was achieved through an additional two linear steps including deprotection and cyclisation from β-keto ester 128. Successful synthesis of the required unsaturated pyrone 202 meant attention would be turned towards employing the acyl rearrangement methodology from the above model systems 198 and 201 towards achieving total synthesis of the natural product CR377 (9). The reaction conditions employed towards the formation of the above tricarbonyl model systems 198 and 201 would be applied directly to the newly synthesised pyrone 202 (Scheme 2.28). Firstly, formation of diester 204 through O-acylation of the lactone 202 proceeded in a respectable 77% yield following reaction with DBU and (S)-2-methylbutyryl chloride (120) in toluene at 0°C for two hours. To affect the oxygen to carbon acyl rearrangement, diester 204 was dissolved in toluene and a catalytic amount of DMAP was added before being heated to 85°C of 15 hours as done previously for the construction of model systems 198 and 201. ¹H NMR analysis of the unpurified organic extracts instantly revealed the absence of both the exocyclic methylene proton signals and the vinylic proton present in the diester 204 precursor product. The ¹H spectra did show the presence of the signals
attributed to the 2-methylbutyric acid (155) side-chain indicating that prior to quenching the reaction mixture the acyl transfer catalyst DMAP had formed the desired 2-methylbutyryl pyridinium species. Several attempts in altering the concentration of the DMAP catalyst and reaction temperature still produced identical results as those encountered originally. Determination of the decomposed product or products was unsuccessful, but it is thought that these conditions may have promoted a series of decarbonylation, decarboxylation or rearrangement reactions of the unsaturated lactone 202.

\[
\begin{align*}
\text{202} & \xrightarrow{\text{a. 77\%}} \text{204} & \xrightarrow{\text{b.}} \text{9} \\
\end{align*}
\]

**Reagents and Conditions:** a. DBU (1.1eq), toluene, (S)-2-methylbutryrl chloride (120) (1.1eq), 0°C for 2 hours. b. DMAP (0.05eq), toluene, 85°C for 15 hours.

**Scheme 2.28:** Synthesis of diester (204) from lactone (202) and attempted acyl rearrangement to form CR377 (9)

At the same time as the stereochemical investigation towards affecting the acyl rearrangement towards the natural product CR377 (9) was a simultaneous effort towards producing the required unsaturated lactone 202 precursor more efficiently. Due to time constraints and a simultaneous synthesis towards marine polypropionate dolabriferol (10) (Chapter four), it was decided to target CR377 (9) as a mixture of diastereomers. It was believed the successful design and complete synthesis of CR377 (9) as a mixture of diastereomers outweighed the additional aim of determining the absolute configuration of the natural product.

### 2.4.5 Synthesis of Racemic Lactone 214

To further explore this acyl rearrangement synthetic approach towards CR377 (9) the required unsaturated pyrone 202 needed to be produced more efficiently as the racemate than the opposed nine step linear sequence using commercially available ethyl-(S)-lactate (132) to install the preferred
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The stereochemistry of the pyrone 202. Fortunately this proposal was considered probable through the use of Bayliss-Hillman methodology, followed by simple functional group manipulation for the swift construction of the main unsaturated aldehyde 213 fragment.

The Bayliss-Hillman reaction (Figure 2.27) involves the use of a tertiary amine 204 or phosphine catalysed coupling of an aldehyde 205 with an α,β-unsaturated carbonyl compound 206. Michael addition of the amine 204 or phosphine catalyst to the acrylate 206 activates the 2-position towards nucleophilic attack of the aldehyde 205 by way of an aldol-type mechanism to give the intermediate zwitterion 207. The subsequent proton shift and release of the base catalyst by β-elimination leads to the formation of the Bayliss-Hillman reaction product 208. This reaction is among one of the most useful carbon-carbon bond forming reactions for current synthetic chemists due to the structural motif that is present in numerous natural products like CR377 (9) of biological and medicinal interest.90,91

![Figure 2.27: The proposed Bayliss-Hillman reaction mechanism](image)

In 2001, Yu and coworkers92 reported the efficient use of the Bayliss-Hillman reaction for the preparation of a 3-hydroxy-2-methylenepropionate substrates using a stoichiometric amount of base catalyst and an aqueous medium. Using a modified procedure, acetaldehyde (142) was added to a premixed solution of methyl acrylate (209) and DABCO (204) in dioxane/H2O (1:1) at room temperature for one hour. The reaction mixture was monitored by TLC analysis and confirmed complete after 48 hours at ambient temperature. The mixture was extracted with ether and the combined organic extracts were washed with further aliquots of water to separate the dioxane prior to concentration in vacuo. The
remaining residue was purified by column chromatography to give the racemic 3-hydroxy-2-methylene butyric acid methyl ester (210) adduct in 70% yield as clear oil. Use of the identical procedure for the PMB protection of ethyl-(S)-lactate (132) (Scheme 2.6) was directly applied to the newly synthesised β-hydroxy methyl ester 210,\textsuperscript{31,32} such that PMB-imidate 147 and CSA was added at room temperature to a solution of alcohol 210 in \( \text{CH}_2\text{Cl}_2 \). The reaction mixture was stirred for four days at this temperature, monitored using TLC analysis, and further aliquots of PMB-imidate 147 and acid catalyst were added as reasoned appropriate. Workup and purification of the concentrated organic extracts gave the PMB-methyl ester 211 in 65% yield, as colourless clear oil. The protected methyl ester 211 was then reduced to the alcohol 212 in 76% yield using DIBALH for three hours at -78°C.\textsuperscript{93} The alcohol 212 was then oxidised under Swern conditions to the desired racemic key aldehyde 213 fragment in 33% overall yield in four linear steps. This racemic aldehyde 213 fragment was then converted into the lactone 214 in four additional linear steps following an identical aldol, oxidation, deprotection and lactonisation sequence as previously detailed. Due to the chemical and physical properties of enantiomers the primary alcohol 212 through to the unsaturated lactone 214 produced identical NMR spectra to that obtained for the enantiomerically pure material. The success of the Bayliss-Hillman reaction pathway towards producing racemic aldehyde 213 then facilitated the swift conversion to the required lactone 214 precursor product (Scheme 2.29).

\[ \begin{align*}
142 & \xrightarrow{a.} 70\% \quad 210 & \xrightarrow{b.} 65\% \quad 211 \\
& \quad \text{PMBO} \quad & \quad \text{PMBO}
\end{align*} \]

\[ \begin{align*}
210 & \xrightarrow{c.} 76\% \quad 212 & \xrightarrow{d.} 96\% \quad 213 \\
& \text{4 steps} \quad & \quad 214
\end{align*} \]

**Reagents and Conditions:**

<table>
<thead>
<tr>
<th>Step</th>
<th>Reagent(s)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Methyl acrylate (209) (3.0eq), DABCO (1.0eq), dioxane, ( \text{H}_2\text{O} ), RT</td>
<td>for 48 hours.</td>
</tr>
<tr>
<td>b</td>
<td>PMB-imidate 147 (1.0eq), ( \text{CH}_2\text{Cl}_2 ), CSA (0.1eq), RT</td>
<td>for 4 days.</td>
</tr>
<tr>
<td>c</td>
<td>DIBALH (3.0eq), ( \text{CH}_2\text{Cl}_2 ), -78°C for 3 hours then 0°C for 1 hour</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>DMSO (3.0eq), ( \text{(COCl)}_2 ) (1.5eq), ( \text{CH}_2\text{Cl}_2 ), ( \text{NET}_3 ) (6.0eq), -78°C, 2 hours.</td>
<td></td>
</tr>
</tbody>
</table>

**Scheme 2.29:** Synthesis of racemic lactone (214) through Bayliss-Hillman methodology
Although the aldehyde 213 was produced in an overall excellent yield of 33% the time taken for the Bayliss Hillman reaction and the subsequent PMB-protection of the resultant secondary alcohol was considered almost analogous to that required for the production of the stereochemically pure material. As a result, use of the Bayliss-Hillman reaction pathway to directly install the α-methylene-β-hydroxy carbonyl species was a significantly easier process than the one undertaken towards achieving stereochemically pure material. Substitution of the PMB-ether for a TBS-ether would afford a considerable amount of time through an increased protection reaction rate due to oxygen’s higher affinity for silicon as opposed to carbon. The TBS-ether would also be able to endure the equivalent reaction conditions towards the synthesis of racemic pyrone 214 precursor material. Synthesis of the TBS-protected aldehyde 215 (Scheme 2.30) began with an identical Bayliss-Hillman reaction of methyl acrylate (209) and acetaldehyde (142) to produce the α-methylene-β-hydroxymethyl ester (210). The alcohol 210 was then protected as the proposed TBS-ether 216 in 94% yield by addition of imidazole and TBS-Cl in one portion to a solution of the alcohol 210 dissolved in DMF..94 The next two synthetic steps were analogous to that conducted above for the conversion of the PMB-methyl ester 211 to the corresponding aldehyde 213. As such, the TBS-protected methyl ester 216 was reduced using DIBALH to the primary alcohol 21793 and oxidised to the aldehyde 218 under Swern conditions.95

Conversion of the TBS-aldehyde 218 into the racemic pyrone 214 (Scheme 2.31) followed an analogous series of functional group transformations as seen previously that included; aldol, oxidation, deprotection and cyclisation. To start with TBS-aldehyde 218 was added to a solution of LiHMDS and t-butyl acetate (130) at -78°C for 30 minutes, then warmed to 0°C for two hours to give the acetate-aldol product 219 in 83% yield. The acetate-aldol adduct 219 was dissolved in CH₂Cl₂, PCC and celite were
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added in one portion at room temperature. The dark reaction mixture was stirred at room temperature for 4 hours to affect the oxidation to β-keto ester 220 in 88% yield. Adaption of a procedure by Clarke et al., β-keto ester 220 was then dissolved in CH₂CN and CH₂Cl₂, and at 0°C aqueous HF was added for 2 hours. These acidic conditions effectively cleaved the TBS protecting group and the t-butyl ester causing the free alcohol to cyclise onto the carboxylic acid, and following dehydration afforded the racemic lactone 214 in 27% yield over seven linear steps.

Reagents and Conditions:

- **a.** LiHMDS (1.1eq), THF, t-butyl acetate (130) (1.1eq), aldehyde 218 (0.90eq) -78°C, 30 minutes, warmed to 0°C for 2 hours.
- **b.** PCC (2.0eq), CH₂Cl₂, celite, RT, 4 hours.
- **c.** 40% HFₐq, CH₂Cl₂, CH₃CN, 0°C for 2 hours.

Scheme 2.31: Synthesis of the racemic lactone 214 from TBS-aldehyde 218

2.4.6 Acyl Migration and Direct Acylation attempts towards Racemic CR377

The success of forming this racemic pyrone 214 both efficiently and quantitatively then allowed further investigation for the inclusion of 2-methylbutyryl acyl sidechain to the pyrone 214 substrate. Following on from the partial success of the acyl rearrangement approach towards CR377 (9) a variety of reagents and conditions were employed to affect the final oxygen to carbon migration (Scheme 2.32). To test these alternate acyl migration catalysts firstly, the racemic diester 221 precursor was synthesised in 80% yield by addition of DBU and 2-methylbutyryl chloride (199) to a solution of pyrone 214 in toluene at 0°C for 2 hours. Extension to the studies conducted in Scheme 2.28, it was decided to firstly employ pyrrolidinopyridine (PPY), a derivative of DMAP, due to its similar success in acyl rearrangements. Similar to the methodology conducted above, a catalytic amount of PPY was added to a solution of racemic diester 221 in toluene. The reaction mixture was heated to 85°C for six hours, and then concentrated in vacuo to determine if some desired acyl rearrangement had occurred. Purification of the concentrated
reaction mixture by column chromatography just produced similar unidentifiable products as those encountered in previous studies, suggesting these pyridine based catalysts and the reaction conditions were unsuitable to affect the required acyl transformation. Lewis acids are known to promote acyl migration in the Fries rearrangement; it was decided to investigate two known reagents in boron trifluorodiethyl etherate (BF$_3$.OEt$_2$)$^{97}$ and aluminium chloride (AlCl$_3$).$^{98}$ Addition of five equivalents of BF$_3$.OEt$_2$ to diester 221 was heated to 85°C for six hours. Analysis of the unpurified organic extracts revealed that the diester 221 had completely decomposed, and that no desired tricarbonyl product (CR377) had formed under these reaction conditions. Alternatively to effect the desired acyl migration; AlCl$_3$ was added to a solution of the racemic diester 221 in CH$_2$Cl$_2$ at room temperature, the mixture was heated to reflux for an equivalent six hours. Following workup and extraction NMR analysis indicated that only some decomposition had occurred but following purification of the mixture the diester 221 was recovered in 90% yield.

Scheme 2.32: Acyl rearrangement catalysts used to effect the O- to C-acyl migration

As documented above, use of a range of tertiary amines and Lewis acid acyl transfer rearrangements for the oxygen to carbon migration approach unfortunately either led only to the recovery of diester 221 or decomposition products. Moving away from this acyl migration approach, as a final investigation it was decided to try to induce the required acylation directly on to carbon by means of Mukaiyama conditions$^{99-101}$ or enamine chemistry$^{102-104}$ (Scheme 2.33). Attempted synthesis of the TMS-enol ether 222 followed a modified procedure outlined for the preparation of the diester 221, where DBU and TMS-Cl were added to a solution of lactone 214 in CH$_2$Cl$_2$ at 0°C for two hours. Following this, the
mixture was cooled to -78°C and TiCl₄ and 2-methylbutyryl chloride (199) were added simultaneously. This mixture was stirred for a further two hours at -78°C, then warmed to ambient temperature for another two hours. Analysis of the crude ¹H NMR mixture just revealed the racemic lactone 214 starting material suggesting that either the TMS-enol ether 222 did not form under these conditions or was unsuccessful in reaction with the acyl halide 199. If the TMS-enol ether 222 had formed using these reaction conditions, an aqueous quench on workup would have hydrolysed the TMS-enol ether 222 back to give the racemic pyrone 214 as observed during NMR analysis.

Reagents and Conditions: a. TMS-Cl (1.0eq), DBU (1.0eq), CH₂Cl₂, 0°C, 2 hours. b. TiCl₄ (1.0eq), 2-methylbutyryl chloride (199) (1.2eq), CH₂Cl₂, -78°C for 2 hours, RT for 2 hours. c. Morpholine (1.30eq), toluene, p-TSOH (0.05eq), 115°C for 6 hours. d. NEt₃ (1.0eq), 2-methylbutyryl chloride (199) (1.2eq), CHCl₃, 60°C for 4 hours, 6M HCl for 4 hours.

Scheme 2.33: Direct Acylation attempts of lactone 214 using Mukaiyama conditions and enamine chemistry

Enamines are commonly formed through an acid catalysed condensation of carbonyls with secondary amines, and their performance as a source of excellent carbon-based nucleophiles can be explained by consideration of their resonance contributors. Similar to enamine alkylation, enamines can also undergo acylation to form carbon-carbon bonds resulting in the corresponding 1,3-dicarbonyl products. Morpholine enamines of cyclic ketones have been shown to react favourably with acyl halides to form the equivalent dicarbonyl moieties. Although there are no documented reports for enamine formation of cyclic β-keto lactones, it was envisioned that successful formation of enamine 223 followed by in situ addition of 2-methylbutyryl chloride (199) and final hydrolysis of the enamine 223 to achieve
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CR377 (9) outweighed the lack of literature precedent. Adaption of a procedure by Schobert et al.,\textsuperscript{107} β-keto lactone 214 was dissolved in toluene and morpholine, and a catalytic amount of \textit{p}-TsOH was added. The reaction mixture was heated to reflux for six hours, in which time the elimination of \textit{H}_2\textit{O} had ceased indicating reaction completion. NMR analysis of unpurified extracts revealed the possible success of enamine formation and hence was immediately dissolved in dry chloroform. Triethylamine and the 2-methylbutyryl chloride (199) were added and the reaction mixture was heated to 60°C for four hours. HCl solution (6 \textit{N}) was then added, and refluxing continued for a further four hours to facilitate the cleavage of the enamine reinstalling the ketone functionality in the prospect of obtaining CR377 (9) directly following the desired acylation. Following this procedure, unfortunately no desired CR377 (9) product or the lactone 214 precursor were detected suggesting that decomposition of the β-keto lactone 214 or the corresponding enamine 223 intermediate occurred during the above detailed reaction conditions.

As several different reagents and conditions along with additional methodologies had been attempted to install the required acyl sidechain onto the unsaturated pyrone 214, without further advancement on the initial DMAP catalysed acyl rearrangement procedure. The remaining time available with a simultaneous investigation directed towards the total synthesis of dolabriferol (10) (Chapter four) meant that further revisions towards the synthesis of CR377 (9) by protection of the exocyclic methylene functionality could not be investigated but should provide the framework for the first successful total synthesis of CR377 (9).

2.5 Future Directions towards CR377 and Related Products

2.5.1 Protection of the Exocyclic Double Bond

As detailed above the most successful approach towards polyketide natural product CR377 (9) was utilising an acylation/rearrangement process similar to that employed towards the synthesis of Podoblastin A (96). The formation of cyclic pyranone 192 from \textit{t}-butylacetoacetate (141) in two linear steps was successfully converted into model systems 198 and 201 employing an acylation reaction on oxygen, followed by rearrangement to carbon using DMAP as an acyl transfer catalyst (Figure 2.28).
This process towards CR377 (9) though was complicated by the addition of the exocyclic conjugated alkene in the pyranone structure (Figure 2.27). Moving forward, it is believed that protection of this exocyclic alkene through conjugate addition of thiophenol\textsuperscript{108,109} will facilitate the acylation and rearrangement pathway. Oxidation of the thiophenol to the sulfoxide\textsuperscript{110} should then allow elimination to reform the alkene by thermolysis\textsuperscript{111} and afford the natural product CR377 (9) (Figure 2.29).

As shown in Schemes 2.30 and 2.31 the racemic unsaturated lactone 214 can be formed in seven linear steps from methyl acrylate (209). Michael addition of thiophenol to the pyrone 214 would serve to protect the alkene functionality and hence remove the perceived conjugation problems as seen above. Protection of the exocyclic methylene would assist the analogous pyrone 224 in the acylation and rearrangement approach for the formation of the tricarbonylmethane system, which was successfully completed for model systems 198 and 201. Oxidative removal of the thiophenol protecting group should then allow restoration of the exocyclic alkene, and thus, complete the first total synthesis of polyketide natural product CR377 (9).
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Similarly if, conjugate addition of the unsaturated pyrone 224 proves difficult then this thiophenol protection of the double bond can be successfully achieved on linear β-keto ester 220. This alternative approach (Figure 2.30) is similar to that employed in Chapter three in synthesis of a nitroaniline derivative. With the thiophenol addition product 225 in hand, removal of the TBS ether with HF and subsequent acid catalysed cyclisation and dehydration should give the identical thiophenol protected pyrone 226. From this point the synthesis follows the analogous acylation, rearrangement and oxidation reactions described above to give the natural product CR377 (9).

2.5.2 Revised Synthetic Approach towards CR377 and Related Products

If the protection of the exocyclic double bond of pyrone 224 or the acyclic β-keto ester 225 as the thiophenol continues to still prove problematic towards the total synthesis of CR377 (9), then the installation of this unique functionality will require a complete revised synthetic approach.

The recent isolation and structural elucidation of new novel polyketide natural products Fujikurin B, C and D (99, 100 and 101) also creates an opportunity to further extend the studies conducted towards
the total synthesis of CR377 (9) to achieve the synthesis of these related natural products. A revised approach towards CR377 (9) detailed in Figure 2.31 could be employed to produce all four related natural products.

The synthetic approach initially couples ethyl acetoacetate (126) and formaldehyde (227) together in an aldol condensation reaction to produce the mono-methylenehydroxyethylacetoacetate product (228). Protection of the aldol product 228 as the t-butyldiphenylsilyl-ether (TBDPS) 229 would be ideal as a robust stability is required at this position as this protection is carried throughout the modified synthesis. Although robust, TBDPS-ethers can be cleaved under mild conditions making them valuable protecting groups for total synthesis strategies. Although the aldol condensation of 1,3-dicarbonyls with formaldehyde are known, there have only been a handful of documented reports of the subsequent hydroxyl protection as a silyl-ether. This is most likely due to the stability of the aldol product 228 as slightly acidic or basic reaction conditions could promote formation of the Knoevenagel condensation product. Following successful TBDPS-ether protection, the ketone component would be selectively reduced with Ru-BINAP\textsuperscript{113,114} to give the β-hydroxy ester 230, and then subsequently be protected as the PMB-ether 231. Reduction of the ester 231 to the primary alcohol 232 would be achieved with DIBALH, followed by oxidation to the corresponding aldehyde 233 using Dess-Martin periodinane.

With the protected aldehyde 233 in hand, synthetic progression towards the natural product CR377 (9) follows a similar reaction pathway to that discussed above, in that aldehyde 233 is reacted with t-butyl acetate (130) in a LiHMDS aldol. The aldol adduct 234 is oxidised with PCC to form the β-keto ester 235. Selective removal of the PMB-ether over the TBDPS-ether would be achieved using DDQ and the free secondary alcohol 236 would be cyclised with TFA to form the TBDPS-ether pyrone 237. Addition of DBU and 2-methyl butyryl chloride (199) would form diester 238, followed by acyl transfer using DMAP to generate the silyl protected tricarbonylmethane product 239. Cleavage of the TBDPS-ether with HF would then afford Fujikurin B (99). Addition of NaHCO\textsubscript{3} should facilitate dehydration by elimination forming the unique conjugated exocyclic double bond, and as a result complete the first total synthesis of CR377 (9). Hydrogenation of the CR377’s (9) exocyclic double bond using palladium on carbon and an excess of hydrogen gas would then afford the predicted stereoisomers Fujikurin C and D (100 and 101), respectively.
Figure 2.31: Revised synthetic approach towards CR377 (9) and related fujikurin natural products

Although this revised approach is virtually untested, the innovation of this synthetic pathway is in the installation of the protected methylene hydroxyl to masquerade as the conjugated exocyclic double bond. The proposed aldol condensation reaction between the ethyl acetoacetate (126) and formaldehyde (227) has precedent and creates this desired functionality immediately. Therefore the potential success of this proposed synthetic strategy or variant thereof could be determined almost immediately, and as such is definitely worth investigation.
2.6 Conclusion:

The studies described above detail several explored synthetic strategies towards the polyketide natural product CR377 (9). The devised strategies fell short of their ultimate goal; however the simplified model compounds 139, 198 and 201 to test the proposed synthetic pathways proved successful. Adaption of these methods towards the natural product by inclusion of the exocyclic double bond unfortunately proved difficult to implement with several issues encountered. The acyclic pathway was successful in the formation of the desired linear tricarbonyl system, unfortunately though the same acylation conditions also allowed further reaction by intramolecular cyclisation to produce saturated pyrone 167. The cyclic pathway was successful in the formation of diester 204 as a direct precursor to CR377 (9) as a single stereoisomer in 14% overall yield from ethyl-(S)-lactate (11 linear steps). Although acyl rearrangement to achieve the natural product was ultimately unsuccessful, the loss of the vinylic protons in the process as indicated by $^1$H NMR emphasised the requirement for the exocyclic alkene to be protected. Further investigation into alternative acyl rearrangement catalysts or by undertaking one of the listed methodologies above should allow rearrangement of the 2-methyl butyryl acylium ion to the desired position. Following acyl migration, reformation of the conjugated alkene would then afford the first total synthesis of CR377 (9).

This work also highlighted that simplified model systems can be an effective tool for the current synthetic chemist to test devised approaches. The model systems developed for both the acyclic and cyclic synthetic strategies were successful indicating their potential towards adjustment to the real system. The inclusion of the unique exocyclic alkene however though led to an intramolecular conjugate addition in the acyclic approach, and in the cyclic approach this extra conjugation functionality was believed to impact on the final acyl rearrangement. Although the synthesis of these model systems indicated their potential to be used towards the natural product CR377 (9), omission of the unique alkene functionality emphasised the importance of designing representative systems. This may have indicated the problems associated with this functionality earlier allowing sufficient time to correct the synthetic strategy to that proposed above, and as such, the first total synthesis of CR377 (9) may have been completed.
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Synthetic Studies towards CR377


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Synthetic Studies towards CR377


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Chapter Three

Swern Oxidation and Electrophilic Chlorination

This chapter describes the Swern oxidation of structurally diverse β-acyl or β-keto alcohols employing the oxalyl chloride-DMSO protocol, which unexpectedly gave rise to products resulting from electrophilic chlorination. The initial α,α-dichlorinated product 242 arose during total synthesis attempts towards CR377 (9), where β-hydroxy ester 129 was to be oxidised to the β-keto ester. Swern oxidation conditions with model compound 243 gave the analogous dichlorinated compound 252. Conversion of 252 to the m-nitroaniline solid derivative 253 which was suitable for single crystal X-ray analysis confirmed the structures of the unexpected oxidation products.

3.1 Swern Oxidation

3.1.1 Swern Oxidation and its use in Organic Synthesis

The Swern oxidation is an extremely mild and often highly efficient method for the conversion of primary and secondary alcohols to their corresponding aldehyde or ketone derivatives.1-6 The Swern oxidation is currently used extensively in synthetic chemistry due to its mild character and ability to be conducted in the presence of sensitive functional groups like: epoxides,7 aziridines,8 thioacetals,9 p-methoxybenzyl ethers and p-methoxybenzylidene acetals.10-12 Some advantages of the Swern
oxidation are that it does not over oxidise primary alcohols to carboxylic acids and also avoids the use of alternative chromium based techniques like Jones and PCC oxidation.\(^8,13,14\)

The Swern oxidation is most commonly conducted by activation of DMSO (3.0eq) with oxalyl chloride (1.5eq) in methylene chloride for 20 minutes at low temperature (-78°C). A solution of alcohol in CH\(_2\)Cl\(_2\) is added to the DMSO/(COCl\(_2\)) mixture for 30 minutes followed by the addition of a tertiary amine base (6.0eq). The mixture is generally kept at -78°C for two hours and then allowed to reach room temperature which facilitates the oxidation to create the corresponding carbonyl derivative (Figure 3.1).\(^15,16\) Temperature control is important in the Swern oxidation to avoid the formation of unwanted \(\alpha\)-epimerisation\(^17\) or \(\beta\)-elimination\(^18\) side-products and intermediate decompositions.\(^15\)

![Figure 3.1: Outline for the generic Swern oxidation](image)

The generally accepted mechanism for the oxidation of alcohols to carbonyl compounds via the Swern oxidation is as follows: At -78°C, oxalyl chloride is added to a mixture of DMSO in dichloromethane to activate the DMSO. This intermediate undergoes decomposition with elimination of CO\(_2\) and CO to afford the dimethylchlorosulfonyl ion. Addition of the alcohol then results in reaction with the dimethylchlorosulfonyl ion to form the alkoxysulfonium ion. Deprotonation of this intermediate gives a sulfur ylide, which undergoes intramolecular deprotonation via a five-membered ring transition state and fragmentation to yield the oxidised product and dimethyl sulfide, as shown in Figure 3.2.\(^15,16\)
3.1.2 Discovery of an Interesting Unknown Product

During attempts towards the total synthesis of polyketide natural product CR377 (9) (discussed in Chapter 2) the oxidation of β-hydroxy ester 129 to the corresponding β-keto ester 128 was attempted (Scheme 3.1). Swern oxidation was chosen to complete this transformation after Bulger and co-workers\(^\text{19}\) reported the successful oxidation of their methacrolein and t-butylacetate aldol product. When the standard Swern oxidation conditions (detailed above) were applied to this β-hydroxy ester 129 product, the main isolated material was not the predicted β-keto ester 128 product.

Reagents and Conditions: a. DMSO (3.0eq), (COCl)\(_2\) (1.5eq), CH\(_2\)Cl\(_2\), NEt\(_3\) (6.0eq), -78°C, 2 hours.

Scheme 3.1: Swern oxidation of β-hydroxy ester 129 to β-keto ester 128
A similar result had been encountered previously within the Perkins’ research group during the initial studies towards CR377 (9). These studies employed the standard Swern oxidation procedure to oxidise β-hydroxy amide 240 to the analogous unsaturated β-keto amide compound 241 (Figure 3.3). This substrate contained the Evans’ thiazolidine thione auxiliary, which had been used to produce a single stereoisomer in a preceding titanium chloride mediated aldol reaction. The NMR data showed distinct variations or absence of signals in several areas for the anticipated oxidation product, such that the product was determined not to be the expected product 241. It was initially suspected that the failure of the oxidation reaction was associated with the presence of sulfur functionality within the auxiliary. This unknown product was not able to be identified in that study, and when analogous results were obtained with the oxidation of our β-hydroxy ester 129 it was decided to investigate the failure of Swern oxidation on these substrates.

In the initial study, this interesting unknown product was thought to have primarily formed as part of an intramolecular cyclisation or rearrangement involving the thiazolidinone auxiliary and the alkene. This appears now not the case as the attempted Swern oxidation of the unsaturated β-hydroxy ester 129 with a tertiary butoxy group in place of the thiazolidine thione auxiliary again failed to produce the expected β-ketoester 128, instead giving the unknown product 242. It was identified from the $^1$H NMR and $^{13}$C NMR spectra that the methylene protons and the corresponding carbon signal anticipated for the ketone tautomer of the expected product were not present, and equally these proton and carbon signals anticipated for the potential enol tautomer were absent (Scheme 3.2).
Swern Oxidation of β-Hydroxy Carbonyl Compounds

Reagents and Conditions: a. DMSO (3.0eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6.0eq), -78°C, 2 hours.

Scheme 3.2: Swern Oxidation of β-hydroxy ester 129 indicating the NMR inconsistencies observed for the unknown product 242

The β-hydroxy ester 129 used for this reaction was a diastereomeric mixture (80:20) at the CHOH position, which was not separated as this stereocentre was to be removed in the oxidation step, but this slightly complicates the NMR of this compound. The $^1$H and $^{13}$C NMR spectra of the β-hydroxy ester 129 (Figures 3.4 and 3.5) in CDCl$_3$ show signals that could be assigned to the major isomer such as the hydroxyl proton at δ 3.45 and the corresponding CHOH proton signal at δ 4.62. The diastereotopic protons between the hydroxyl and carbonyl at δ 2.54-2.68 were observed to couple with the methylene CHOH proton at δ 4.62, and the vinylic protons for the major isomer are also present at δ 5.24 and δ 5.32, respectively.
Swern Oxidation of β-Hydroxy Carbonyl Compounds

Figure 3.4: The $^1$H NMR spectrum for β-hydroxy ester 129 in CDCl$_3$

Figure 3.5: The $^{13}$C NMR spectrum for β-hydroxy ester 129 in CDCl$_3$
This required oxidative conversion to \(\beta\)-keto ester 128 eventually proceeded in excellent yield of 85\% by reacting two equivalents of PCC, in methylene chloride at room temperature for four hours with \(\beta\)-hydroxy ester 129 (Scheme 3.3).\(^\text{21}\) Celite was added to the reaction mixture to uptake the known PCC reaction residue by-products allowing separation by filtration from the keto-ester 128 product prior to purification by column chromatography.

Reagents and Conditions: a. PCC (2.0eq), CH\(_2\)Cl\(_2\), celite, RT for 4 hours.

Scheme 3.3: Successful oxidation of \(\beta\)-hydroxy ester 129 using PCC

The NMR spectra of the oxidised \(\beta\)-keto ester 128 product shown in Figures 3.6 and 3.7, the absence of the \(\text{CHOH}\) hydrogen signal is immediately apparent. The diastereotopic methylene (\(\text{CH}_2\)) protons have been shifted downfield to \(\delta 3.65\) as a result of the oxidised hydroxyl moiety and now appear as doublet of doublets. Their integration shows the predominance of the \(\beta\)-keto tautomer of 128. The vinylic protons have also been shifted downfield to \(\delta 6.15\) and \(\delta 6.23\) due to the deshielding nature of the newly present carbonyl. In CDCl\(_3\), it can also been seen that the ketone tautomer is predominately favoured with a minor amount of enol tautomer present. The signals present at \(\delta 12.35\) and \(\delta 6.00\) are indicative of enol and vinylic protons. The singlet at \(\delta 5.28\) is due to methylene chloride residual solvent. The main difference between the two carbon spectrums is the resonance at \(\delta 193\) indicative of the newly oxidised ketone carbon, followed by the apparent loss of a C-OH signal in the \(\delta 60\)-80 region.
Figure 3.6: The $^1$H NMR spectrum of $\beta$-keto ester 128 in CDCl$_3$.

Figure 3.7: The $^{13}$C NMR spectrum of $\beta$-keto ester 128 in CDCl$_3$. 
3.2 Swern Oxidation of a Model β-Hydroxy Ester

3.2.1 Synthesis of the Model β-Hydroxy Ester 243

As Swern oxidation attempts on two related substrates had not given the desired product an
decision was made to ascertain the structures of the unknown products and propose a
mechanism for their formation. It was decided to prepare a simple model β-hydroxy ester 243 using
aldol methodology to imitate the functionality present in β-hydroxy ester 129 for the subsequent
Swern oxidation (Scheme 3.4). This was achieved following the identical procedure\textsuperscript{22} used in Scheme
2.8 (Chapter 2), t-butyl acetate (130) was added to a solution lithium hexamethyldisilylazide in THF
at -78°C for 15 minutes, followed by the dropwise addition of methacrolein (244) in THF. The
mixture was allowed to stir for two hours at -78°C, before being warmed to ambient temperature
and quenched with an ammonium chloride solution to produce the desired β-hydroxy ester 243
adduct in an excellent 88% yield.

\[
\begin{align*}
\text{Reagents and Conditions: a. LiHMDS (1.2eq), THF, -78°C, 2 hours, then warmed to RT.}
\end{align*}
\]

\textit{Scheme 3.4: Aldol synthesis of model β-hydroxy ester 243}

3.2.2 Swern Oxidation of β-Hydroxy Ester 243

With the model β-hydroxy ester 243 in hand, attention turned towards replicating the above Swern
oxidation procedure to determine if it gives the expected product or the anomalous product 245
(Scheme 3.5). The model β-hydroxy ester 243 was added to a premixed solution of DMSO and oxalyl
chloride in CH\textsubscript{2}Cl\textsubscript{2} at -78°C. The mixture was stirred for 30 minutes to ensure complete formation of
the alkoxy sulfonium ion intermediate, triethylamine was added and the resulting mixture stirred at
-78°C for a further two hours. The reaction mixture was warmed to room temperature and quenched
by the addition of ammonium chloride, extracted and purified by column chromatography to give a
product that was isolated in 82% yield. This product again lacked a signal that could be assigned to
the expected methylene between the two carbonyls and thus appeared to be the analogous product
245 to that obtained in the other system.
Reagents and Conditions: a. DMSO (3.0eq), (COCl)₂ (1.5eq), CH₂Cl₂, NEt₃ (6.0eq), -78°C, 2 hours.

Scheme 3.5: Swern oxidation of model β-hydroxy ester 243

Analysis of the purified NMR spectra (Figures 3.8 and 3.9) highlighted that this unknown product 245 appeared as the main isolated product of this reaction. The spectra again highlighted the disappearance of the methylene proton signals between the two carbonyls along with the absence of the enol tautomer’s vinyl and hydroxy signals common to this oxidised structural motif. The singlet at δ 5.28 is due to methylene chloride residual solvent. Analysis of the ¹³C NMR spectrum also indicated that the carbon associated with these methylene protons also appeared to be absent. The major carbon signals present were attributed to the remaining vinyl methylene, vinyl methyl and the t-butyl methyl substituents. The two small signals present at δ 82 and δ 53 were attributed to minor impurities.
Swern Oxidation of β-Hydroxy Carbonyl Compounds

Figure 3.8: The $^1$H NMR spectrum of unknown model oxidised product 245 in CDCl$_3$

Figure 3.9: The $^{13}$C NMR spectrum of unknown model oxidised product 245 in CDCl$_3$
3.2.3 Synthesis of a Solid Derivative

As a significant quantity of this model unknown product 245 was synthesised through the two step procedure it was decided to prepare a solid derivative of this unknown compound suitable for single crystal X-ray diffraction. This type of structural determination was targeted as the common spectroscopic techniques used to identify unknown synthetic compounds (NMR, MS and IR) continued to be inconclusive.

Analysis of the carbon spectrum of unknown model compound 245 indicated that the oxidation from the secondary alcohol to the ketone functionality had occurred due to the signal present at δ 184. With this in mind, the first approach to derivatisation was to employ dinitrophenylhydrazine (246) (Brady’s Reagent) to convert the ketone functionality into the analogous dinitrophenylhydrazone 247 (Scheme 3.6). This reaction proceeds as a condensation reaction between the hydrazine and ketone in an acidic alcohol medium. Following a procedure adapted from Zubarev et al. the unknown oxidation product 245 was dissolved in ethanol and was added to a premade solution of 2,4-dinitrophenylhydrazine (246), ethanol and H₂SO₄ at room temperature. The reaction mixture was refluxed for one hour, cooled and the precipitate filtered and recrystallised from ethyl acetate. This process though only led to recovery of the 2,4-dinitrophenylhydrazine (246) reagent.

![Scheme 3.6: Attempted synthesis of the predicted dinitrophenylhydrazone 247 derivative](image)

**Reagents and conditions:** a. Dinitrophenylhydrazine (246) (1.3eq), EtOH, H₂SO₄ (3 drops), reflux for 1 hour.

Unfortunately the attempts made towards this synthetic conversion proved unsuccessful. The uncertainty surrounding the unknown oxidised product’s 245 structure was considered the main factor for this ineffective synthetic derivatisation, as the isolatable residue from the concentrated filtrate was believed to be the result of decomposition.
Conjugation problems encountered during synthetic attempts towards polyketide natural product CR377 (9) led to the idea of synthesising a conjugate addition derivative product that would be suitable for single crystal X-ray analysis.

From spectroscopic analysis, it was believed that the unknown oxidation product 245 possessed an α,β-unsaturated carbonyl functionality, which through resonance stabilisation could promote 1,4-conjugate addition over 1,2-direct addition. Although there are numerous potential nucleophiles that will naturally display 1,4-conjugate addition properties, initially phthalimide (248) and m-nitroaniline (249) were selected as these compounds generally produce isolatable solid crystalline products.

Conjugate addition has been a forefront of organic chemistry for the construction of carbon-carbon bonds for over a century, but the use of nitrogen based nucleophiles for this process has become evident only recently. Prior to this most of the documented literature for aza-michael addition was dedicated to the development of β-amino acids. Lithium amides, universally known as strong bases have been recently recognised as suitable nucleophiles for aza-michael additions.

Following the procedure outlined by Hawkins’ et al., the conjugate addition of phthalimide (248) was attempted first (Scheme 3.7). Phthalimide (248) was dissolved in THF at -78°C, then dropwise addition of n-butyl lithium (1.5M) was utilised to create a nucleophilic anion. Addition of the unknown product 245 in THF was added at -78°C, stirred for one hour and warmed to room temperature over the following two hours. Unfortunately, this failed to afford any phthalimide conjugate addition product 250. Due to the known resonance stabilisation of phthalimide (248) it was decided that the corresponding deprotonated imide in this particular case was not reactive enough to achieve the desired 1,4-addition product 250.

These results led to the use of m-nitroaniline (249) as the nucleophilic source to produce a suitable solid derivative (Scheme 3.7). Analogous to the procedure described above, m-nitroaniline (249) was dissolved in THF at -78°C, and n-BuLi was added dropwise. Addition of the unknown oxidised product 245 in THF was added at -78°C, stirred for one hour and warmed to room temperature over the next two hours. TLC analysis of the reaction mixture confirmed that the unknown oxidised product 245...
had been consumed. On workup, concentration of the organic extracts yielded clumps of orange crystalline material. Analysis of this material using $^1$H NMR spectroscopy (shown in Figure 3.10) showed that 1,4-conjugate addition of $m$-nitroaniline (249) to the unknown product 245 had occurred through the disappearance of the vinylic and vinyl methyl proton signals. The presence of the aromatic aniline signals at $\delta$ 6.87-7.52, the amine signal at $\delta$ 4.45, the methyl doublet at $\delta$ 1.37 and the new coupled protons at $\delta$ 3.32 and $\delta$ 3.60, respectively were also consistent with the desired $m$-nitroaniline conjugate addition product 251. The $^{13}$C spectrum (Figure 3.11) also still displays both the carbonyl signals at $\delta$ 197 and $\delta$ 161, and only the six $sp^2$ carbons obtained from the aniline addition also confirm the loss of the unsaturated methylene functionality.

![Diagrams showing the reaction and product structures](image)

**Reagents and Conditions:**

- **a.** phthalimide (248) (1.0eq), $n$-BuLi (1.0eq), THF, -78°C, 1 hours, then warmed to RT.
- **b.** $m$-nitroaniline (249) (1.0eq), $n$-BuLi (1.0eq), THF, -78°C, 1 hours, then warmed to RT.

**Scheme 3.7:** Synthesis of a $m$-nitroaniline conjugate addition derivative 251 and attempted synthesis of a phthalimide derivative 250
Swern Oxidation of β-Hydroxy Carbonyl Compounds

Figure 3.10: The $^1$H NMR spectrum of m-nitroaniline conjugate addition product 251 in CDCl$_3$

Figure 3.11: The $^{13}$C NMR spectrum of m-nitroaniline conjugate addition product 251 in CDCl$_3$
Recrystallisation of the crude orange material mixture from hot ethyl acetate produced several large orange crystals appropriate for single crystal X-ray analysis. Two-dimensional diffraction patterns of electron density gathered from the unknown molecular crystal was able to confirm that in fact the m-nitroaniline (249) 1,4-conjugate addition had occurred. The X-ray data calculated the molecular formula to be C₁₆H₂₀Cl₂N₂O₅ and after a series of reflection acquisitions predicted the unknown model product 245 to be that of the α,α-dichlorinated product 252 (Scheme 3.8). This product is believed to be formed by double electrophilic addition of chlorine from excess chlorodimethylsulfonium cation. The excess chlorodimethylsulfonium cation is produced from the extra equivalents of DMSO and oxalyl chloride used in generic Swern oxidation procedures to ensure reaction completion. The m-nitroaniline solid derivative confirmation of the dichlorinated over addition product 253 showed that the signal present at δ 82 (also present in Figure 3.9) was attributed to the dichloromethylene carbon and not just a small product impurity as considered previously.

Reagents and Conditions:  

a. DMSO (3.0eq), (COCl)₂ (1.5eq), CH₂Cl₂, NEt₃ (6.0eq), -78°C, 2 hours.  
b. m-nitroaniline (249) (1.0eq), n-BuLi (1.5M, 1.0eq), -78°C, 1 hour, warmed to room temperature.

Scheme 3.8: Confirmation of the unknown oxidation product by X-ray diffraction

There have been a few reports for the observation of chlorinated products as a result of using the Swern oxidation for particular substrates (Figure 3.12).²⁹⁻⁻³¹ Smith and Leenay²⁹ showed during their synthesis attempts towards dendrobine (254) and paspaline (255) that by using an excess of oxalyl chloride and dimethyl sulfoxide, chlorination at the α-position of ketones is likely when a high
Swern Oxidation of β-Hydroxy Carbonyl Compounds

proportion of enol form is present. Both Yang et al\textsuperscript{30} and Feldman et al\textsuperscript{31} in their syntheses of dragmacidin D (256) and vindoline (257), respectively described that the 3-indole position can be easily chlorinated by nucleophilic attack of the dimethylchlorosulfonium ion during Swern oxidations. To the best of our knowledge, this is the first reported discovery of Swern oxidation producing an electrophilic α,α-dichlorination product 252 of an unsaturated 1,3-dicarbonyl system.

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{Swern} \quad \text{Cl} \quad \text{HO}_2\text{O} \\
\text{OH} & \quad \text{Swern} \quad \text{Cl} \quad \text{O} \\
\text{OH} & \quad \text{Swern} \quad \text{Cl} \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{Swern} \quad \text{Cl} \\
\end{align*}
\]

Figure 3.12: Reported electrophilic chlorinations during Swern oxidations approaches towards natural products dendrobine (254), paspaline (255), dragmacidin D (256) and vindoline (257)
3.3 Investigation of Electrophilic Dichlorination of β-Hydroxy Carbonyl Compounds

3.3.1 Nucleophilic and Electrophilic Chlorination

Chlorinated by-products can result from oxidations using DMSO with oxalyl chloride, N-chlorosuccinimide or other chlorine containing DMSO-based oxidants by both nucleophilic\textsuperscript{32,33} and or electrophilic\textsuperscript{29-31} pathways. Typically in the former chloride anions react using an $S_N2$ type nucleophile displacement to form either acyl or alkyl chlorides. In well developed synthetic procedures like the Swern oxidation where allylic alcohols are reacted with DMSO/NCS or DMSO/(COCl)$_2$ reagents, electrophilic chlorination from excess chlorodimethylsulfonium cation can lead to the recovery of a variety of chlorinated side products. Electrophilic chlorine (Cl$^+$) in the form of the chlorodimethylsulfonium cation is generated from DMSO-(COCl)$_2$ as well as dimethyl sulfide and chlorine, and gives a variety of possible chlorination reactions. Electrophilic chlorination reactions include: addition at the $\alpha$-position of ketones,\textsuperscript{29,34,35} electrophilic aromatic substitution of phenols\textsuperscript{36} and other electron-rich aromatics, such as phenyl ethers,\textsuperscript{37} anilines and indoles\textsuperscript{30,31} (Figure 3.13).

![Figure 3.13: Known electrophilic chlorine addition reactions](image-url)
3.3.2 Keto-Enol Tautomerisation

A carbonyl containing compound can exist in either the enol form or as the more thermodynamically stable ketone. The enol and ketone forms are tautomers of each other, and their interconversion is facilitated by the movement of an α-hydrogen and bonding electrons, as shown in Figure 3.14.\(^{38,39}\)

![Figure 3.14: The tautomerism between ketone and enol tautomers](image1)

The mechanism for this interconversion between the tautomers is shown in Figure 3.15. The tautomerisation between ketone and enol isomers does occur normally in neutral conditions, but is catalysed in the presence of acidic or basic media.\(^{40}\) Under acidic conditions protonation of the carbonyl oxygen is followed by loss of a α-hydrogen, alternatively basic removal of the α-hydrogen generates the resonance stabilised oxygen centered anion which abstracts a proton, giving the enol in each case.

![Figure 3.15: Interconversion between ketone and enol tautomers in acidic and basic conditions](image2)
Normally, the keto-enol tautomerisation is thermodynamically controlled, and at ambient temperature usually favours the formation of the ketone. There are several factors that will shift the chemical equilibrium in favour of the enol form. As the name suggests the factors that stabilise both alkenes and alcohols (enol) like aromaticity, hydrogen bonding, conjugation, substitution and non-polar solvent also favour the formation of the enol tautomer.\textsuperscript{38,39}

### 3.3.3 Proposed Mechanism for the Electrophilic Dichlorination Product

This intriguing dichlorination product 252 is believed to be formed from the original Swern oxidation desired β-keto ester 258 product. It appears that β-keto ester 258 rapidly tautomerises to its enol form under the reaction conditions and continues to react further with additional equivalents of electrophilic chlorine obtained from the dimethylsulfonium chloride ion complex (Figure 3.16).

Nucleophilic addition of the electron rich enol double bond to the dimethylsulfonium chloride complex results in electrophilic chlorination at the α-position between the carbonyl groups. With the extra equivalents of DMSO and oxalyl chloride used in the normal Swern oxidation reaction this initial process can occur a second time to create the dichlorinated compound 252. As a result, this process releases a further two equivalents of the characteristic odour dimethyl sulfur, a known by-product of Swern oxidation.

\[ \text{253} \rightarrow \text{258} \rightarrow \text{252} \]

\[ \text{2 x S}^{-} + \text{252} \rightarrow \text{253} + \text{2 x S}^{2-} \]

*Figure 3.16: Proposed mechanism for the formation of the oxidised dichlorinated product 252*
Intriguingly, this proposed formation of the α,α-dichlorinated product 252 requires at least three equivalents of the dimethylsulfoxonium chloride ion complex, one for the initial Swern oxidation and a further two for the electrophilic chlorination.

The previously reported electrophilic chlorinations (Figure 3.12) were the result of using a significant excess of DMSO and oxalyl chloride reagents supporting the above proposed mechanism. The Swern oxidation attempts of β-hydroxy esters 129 and 243 gave both the dichlorinated products 242 and 252 in excellent yields even though the attempts were conducted using only 3 equivalents of DMSO and only 1.5 equivalents of oxalyl chloride. These equivalents would imply there should be insufficient electrophilic chlorine to facilitate the formation of these α,α-dichlorinated products in excellent yields, and as a result the above proposed mechanism for the formation of these dichlorinated products still requires further investigation.

3.3.4 Synthesis of an Array of β-Hydroxy Carbonyl Compounds

This electrophilic dichlorination discovery though prompted an investigation towards synthesising a series of β-hydroxy carbonyl compounds (shown in Table 3.1) to determine the required functionality for this unusual reactivity. Four β-hydroxy esters (259-262) and one β-hydroxy ketone 263 were synthesised (Table 3.1) employing the lithium hexamethyldisilazide aldol procedure as described above41 (Scheme 3.4). The lithium enolates of t-butyl acetate (130), ethyl acetate (119) and pinacolone (264) were coupled with a small range of available aldehydes including: isobutyraldehyde (265), propionaldehyde (266), benzaldehyde (267) and methacrolein (244). From Table 3.1, it can be seen that all five lithium hexamethyldisilazide aldol additions proceeded in excellent yields (80-95%). These five synthesised substrates were also designed to determine the influence that conjugation, ester functionality and carbonyl substitution had on isolation of the electrophilic dichlorination product during the following identical Swern oxidation procedure.
3.3.5 Electrophilic Dichlorination of the Synthesised β-Hydroxy Carbonyl Compounds

With each newly synthesised β-hydroxy carbonyl compound 259-263 in hand; the electrophilic dichlorination over-addition product could be investigated. Each newly constructed aldol product (259-263) was subjected to an identical Swern oxidation procedure where oxalyl chloride (2 M in CH₂Cl₂) was added dropwise to a mixture of dimethyl sulfoxide in methylene chloride at -78°C. This mixture is stirred for 20 minutes to ensure complete formation of the activated sulfonium complex. The secondary alcohol, dissolved in methylene chloride is added via cannula at -78°C and the reaction mixture is stirred at this temperature for a further 30 minutes to obtain the alkoxy sulfonium intermediate. Triethylamine is then added at -78°C and the reaction mixture was stirred for two hours, and then warmed to ambient temperature. After the addition of the triethylamine the formation of the α,α-dichlorinated product was monitored at regular hourly intervals through TLC analysis. The mixture was quenched with a saturated ammonium chloride solution, and the aqueous layer extracted with three aliquots of methylene chloride. The organic extracts were concentrated in vacuo and the oil residue purified by column chromatography to give the following dichlorinated products 268-272 in moderate to excellent yields (Table 3.2).
<table>
<thead>
<tr>
<th>Aldol Product</th>
<th>Reagents</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="259" /></td>
<td>DMSO (3eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6eq), -78°C to RT, 12hrs</td>
<td><img src="image" alt="268" /></td>
<td>70</td>
</tr>
<tr>
<td><img src="image" alt="260" /></td>
<td>DMSO (3eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6eq), -78°C to RT, 15hrs</td>
<td><img src="image" alt="269" /></td>
<td>78</td>
</tr>
<tr>
<td><img src="image" alt="261" /></td>
<td>DMSO (3eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6eq), -78°C to RT, 2hrs</td>
<td><img src="image" alt="270" /></td>
<td>85</td>
</tr>
<tr>
<td><img src="image" alt="262" /></td>
<td>DMSO (3eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6eq), -78°C to RT, 2hrs</td>
<td><img src="image" alt="271" /></td>
<td>89</td>
</tr>
<tr>
<td><img src="image" alt="263" /></td>
<td>DMSO (3eq), (COCl)$_2$ (1.5eq), CH$_2$Cl$_2$, NEt$_3$ (6eq), -78°C to RT, 6hrs</td>
<td><img src="image" alt="272" /></td>
<td>45</td>
</tr>
</tbody>
</table>

*Table 3.2: Swern oxidation of α-diketone adducts 259-263 to produce the oxidised dichlorinated products 268-272*

From Table 3.2, Swern oxidation followed by electrophilic chlorination proceeded for each of the β-hydroxy carbonyl substrates 259-263. Each of the β-hydroxy carbonyl substrates 259-263 when exposed to the Swern oxidation procedure produced moderate to excellent yields of the corresponding dichlorinated products 268-272.

In the case of β-hydroxy ketone 263, it was less successful in producing the analogous dichlorinated product 272 (45%), with a minor product isolated in 25% yield determined to be the monochlorinated product 273. This is believed to be attributed to the increased stability created by the extra delocalisation of electrons throughout the diketone moiety compared to the β-ketoester functionality.

It was also noted that the unsaturated β-hydroxy esters 243, 261 and 262 gave their respective electrophilic chlorination products 252, 270 and 271 in excellent yields within the normal Swern oxidation reaction timeframe of one to three hours. The saturated isobutyl and propyl β-hydroxy...
esters 259-260 although still achieved good yields for their respective dichlorinated products 268-269, the reaction required between 10-15 hours at room temperature to reach completion. Therefore the additional alkenyl or aromatic conjugation properties contribute to the actual Swern oxidation product to equilibrate more towards the enol tautomer, which then readily undergoes electrophilic chlorination.

In the cases where the Swern oxidation product is an alkyl dicarbonyl species it predominately remains as the ketone tautomer due to its increased thermodynamic stability. As these substrates do not possess any extra conjugation properties to assist the interconversion between the tautomers, the dichloroination of the saturated β-keto esters requires extra time to go to completion.

From our results there was no observable difference in the electrophilic chlorination of conjugated substrates containing either t-butyl esters (243 and 261) or the ethyl ester derivative 262, as the dichlorinated products were achieved within 1-2 hours following the addition of triethylamine. Theory would suggest that the t-butyl ester substrates (243 and 261) would provide extra steric hindrance of the electrophilic chlorination reaction site reducing the reaction rate of the addition process.

Further work could include the application of an identical Swern oxidation procedure to a synthesised unsaturated β-hydroxy ethyl ketone aldol substrate 274 from methyl ethyl ketone (275) and methacrolein (244) (Scheme 3.9). This would then allow for the comparison with the above β-hydroxy pinacolone product 263. The predicted extended timeframe that is required for this dichlorination addition due to the stability of 1,3-diketones could be used to determine a reaction rate comparison between ethyl ketones and t-butyl ketones. Although based on the comparative results observed between the t-butyl esters (252 and 270) and ethyl ester 271 dichlorination of an unsaturated ethyl diketone derivative 276 is predicted to require a similar reaction time, indicating that steric influence in this dichloroination process is negligible.
3.4 Conclusion

The initial unknown oxidation product as a result of the Swern oxidation of β-hydroxy ester compound 129 led to the development of a model substrate 243, which when reacted under Swern oxidation conditions produced an analogous result. As common spectroscopic techniques proved inconclusive in determining the unknown products structure, a solid derivative was prepared exploiting the predicted conjugate addition reaction preference for this compound. The synthetic m-nitroaniline derivative 251 was examined using X-ray crystallography and confirmed the unidentified oxidation product to be the α,α-dichlorinated-β-keto ester 253. This product is proposed to result from the electrophilic dichlorination of the desired β-keto ester with the dimethylsulfonium chloride complex, but still requires further investigation.

As a result, future Swern oxidations of conjugated β-hydroxy carbonyl motifs should be completed employing an alternative dimethyl sulfoxide activating agent to oxalyl chloride. Potential alternative activation agents that predate the use of oxalyl chloride include: dicyclohexylcarbodiimide (DCC), acetic anhydrides, sulfur trioxide pyridine complex (SO₃.Py) and phosphorus pentoxide. The use of these reagents to create the corresponding active dimethylsulfonium ion should facilitate the analogous oxidation of the secondary alcohol. As demonstrated above, oxidation of these structural motifs also proceed in moderate to excellent yield at room temperature utilising pyridinium chlorochromate (PCC) as the oxidation source.
Further investigation into the formation of this dichlorinated compound was trialled with the successful synthesis of another five similar β-hydroxy carbonyl substrates 259-263. These compounds were all exposed to the same Swern oxidation conditions as used previously to determine the influence that conjugation, ester functionality and carbonyl derivative had on isolation of the corresponding electrophilic dichlorination products 268-272. From the results obtained, it was concluded that both conjugation and carbonyl derivative were the important factors in obtaining the dichlorinated compound, whereas changing the ester functionality from a tertiary butyl group to an ethyl group provided no overall observable effect on the isolation of the dichlorinated product.
3.5 References

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(2) T. Tidwell Synthesis 1990, 2, 857.
(4) K. Omura; D. Swern Tetrahedron 1978, 34, 1651.
(23) S. S. Kadam; S. T. Tambe; N. D. Grampurohit; D. D. Gaikwad IJRPC 2012, 2, 1086.
Swern Oxidation of β-Hydroxy Carbonyl Compounds


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This chapter describes the total synthesis of marine polypropionate dolabriferol (10) employing a retro-Claisen rearrangement to construct dolabriferol’s (10) unique non-contiguous backbone. Key moments of this total synthesis include; the synthesis of linear precursor 398 from the two key aldehyde 377 and ketone 363 fragments, and the fragmentation of trioxaadamantane 403 following a retro-Claisen pathway to produce the direct acyclic ester precursor 405. Benzyl lactate ketone 82 was used in three separate anti-aldol reactions to construct the C₄-C₆ and C₁₀-C₁₃ stereochemical arrays.

4.1 Isolation and Characterisation of Dolabriferol

4.1.1 Isolation of Dolabriferol from Dolabrifera dolabrifera

*Dolabrifera dolabrifera* is a species of sea hare that belongs to the Dolabriferidae family of marine gastropods. This species is commonly found around the world in warm tropical to sub-tropical waters.¹ This sea hare is distinguished from the other members of the aplysia genus due to the
parapodia closely appressed to the body and two small apertures on the posterior portion. The rhinophores and cephalic tentacles are small and it is variously mottled in brown, red and olive green (Figure 4.1). This sea hare is sometimes termed the ‘warty seacat’ and although often described as smooth, it would seem that this species is covered in lower tubercles which bear retractile single or compound papillae, and moves with a distinctive leech-like crawl.

In 1996, Ciavatta et al\textsuperscript{2} performed the first chemical study conducted on a gastropod mollusc belonging to the Dolabriferidae family, which ultimately led to the isolation of dolabriferol (10).\textsuperscript{3,4} *Dolabrifera dolabrifera* specimens that were collected off the coast of Cuba (11 specimens), yielded 7.5mg of dolabriferol (10) as the main metabolite from the diethyl ether soluble fraction of the acetone extracts (0.7mg/specimen). This compound was interesting as it was shown to be present by TLC analysis in the acetone extracts of the dissected parapodia and hepatopancreas of a sole specimen, but absent in the digestive glands. This result implies that dolabriferol (10) is produced for an environmental advantage and is not obtained by the organism through algal feeding or symbiotic creation. As marine polypropionate natural products represent a rich source of bioactive compounds, it is unfortunate that Ciavatta and coworkers\textsuperscript{2} did not report the presence of any biological activity associated with dolabriferol (10) upon isolation and structural elucidation.
4.1.2 Structural Determination of Dolabriferol

The structure of dolabriferol (10) was determined by Ciavatta and co-workers through extensive NMR experiments and the relative stereochemistry of the compound was elucidated by single crystal x-ray analysis.² Dolabriferol (10) contains a highly substituted hemiketal coupled to a β-hydroxyketone via an unusual ester linkage. The presence of the non-contiguous carbon backbone assigns dolabriferol (10) to a group of similar related marine polypropionates that include: baconypyrones (A-D) (276-279),⁵ siserrone A (280)⁶ and micromelones A and B (281 and 282),⁷ whose absolute stereochemistry remains undefined (Figure 4.2).

![Chemical structures of dolabriferol, baconipyrones, siserrone A, and micromelones A and B](image)

**Figure 4.2: Dolabriferol (10) and other non-contiguous polypropionate natural products**

Despite the observations made by Ciavatta et al.,² which detail that dolabriferol (10) was found to be present in the extracts of the parapodia and hepatopancreas, but not in the digestive glands. It has been predicted that the ester linkage moiety present in dolabriferol (10) and compounds (276-282) is not the result of specific biodiversity, but the result of a thermodynamic cyclisation/fragmentation
cascade of an acyclic precursor either in the organism or upon extraction. The proposed formation of dolabriferol (10) is shown below in Figure 4.3 whereby a thermodynamic cyclisation of putative acyclic precursor 19 leads to intermediate hemiacetal 18 which undergoes a retro-Claisen rearrangement to give the ester 20. Hemiketalisation of ester 20 affords the natural product dolabriferol (10). A similar sequence of transformations can be used to explain the presence of the ester linkage in compounds (276-282).

![Proposed formation of dolabriferol (10) from a putative acyclic precursor](image)

**Figure 4.3: Proposed formation of dolabriferol (10) from a putative acyclic precursor**

### 4.2 Previous Synthetic Attempts towards Dolabriferol

#### 4.2.1 An Overview of the Literature

Since the isolation of dolabriferol (10) in 1996 by Ciavatta and coworkers there have been several synthetic attempts from research groups worldwide towards the total synthesis of this natural product. The first total synthesis by Vogel et al. was completed in 2010, which involved the development of α,β,γ-anti-anti stereotriads. This methodology was extended to develop suitable polypropionate subunits to be tethered via an esterification reaction. This method created for this reaction was of significant importance as prior to this publication the majority of other synthetic efforts directed towards dolabriferol (10) had also employed the coupling of an appropriate acid and alcohol fragment to access dolabriferol (10), which were all unsuccessful.
A Retro-Claisen Approach towards Dolabriferol

Aside from Vogel’s first total synthesis, and prior to the total synthesis of dolabriferol (10) reported by Currie et al in 2012 during our own studies, the most novel synthetic approach towards dolabriferol (10) was reported by Lister et al which details the formation of a protected acyclic precursor to dolabriferol (10) employing a retro-Claisen rearrangement approach to install the unusual ester linkage. The following sections detail the current synthetic developments that have been achieved towards the total synthesis of this natural product (10).

4.2.2 Goodman’s Computational Studies

In addition with the published synthetic efforts towards dolabriferol (10), Goodman et al has detailed a computational study of the reaction pathway towards dolabriferol (10) beginning with the proposed acyclic precursor compound.

The computational study used ROBIA, a reaction prediction program that was developed by Goodman and coworkers to assist organic chemists by creating potential reaction pathways and assessing the most favourable synthetic pathway. The program ROBIA was used to predict the low energy conformations of potential products as a result of a 3 step process of hemiketalisation, retro-aldol and hemiketalisation starting with the acyclic precursor (Figure 4.4).

The program predicted dolabriferol (10) as one of the potential outcome products. Although ROBIA also predicted 162 other potential reactant products, with many containing lower configurational energy levels. Goodman alleged that many of these potential structures could be omitted based on experimental evidence leaving dolabriferol (10) as the lowest energy product, although it is apparent many compounds can be constructed from this linear acyclic precursor.
A Retro-Claisen Approach towards Dolabriferol

Figure 4.4: Goodman’s three step ROBIA calculation results from putative acyclic precursor
A Retro-Claisen Approach towards Dolabriferol

4.2.3 Dias’ Studies towards Direct Esterification

In 2003, Dias and co-workers\textsuperscript{13} published their attempt towards the synthesis of dolabriferol (10). Their strategy was based on a direct esterification reaction between lactol 283 and keto-acid 284 by employing intermediate amide 285 to access both key fragments. The desired amide 285 was synthesised directly from (S)-N-acyloxazolidinone 286\textsuperscript{14} via a 3-step process involving aldol addition, protection of resultant hydroxyl with TBS-ether followed by transamidation. The amide 285 undergoes an ethyl Grignard addition to give the corresponding ketone 287, which in turn is subjected to a selective anti-aldol addition followed by syn-reduction using zinc borohydride to produce the diol 288. The TBS-ether is removed followed by chemoselective Swern oxidation gave the desired lactol 283 fragment in 40% overall yield (Figure 4.5).\textsuperscript{13} This oxidation based strategy displayed the challenges faced of alternating oxidation states of the oxygen substituents in dolabriferol (10) to synthetic chemists.

The keto-acid 284 was formed by reduction and (E)-selective olefination of the common amide 285 to give the enoate 289. The enoate 289 underwent DIBALH reduction followed by epoxidation of the olefin to create the epoxide 290. Alkylation with methyl cuprate and resultant protection of the diol gave benzylidene 291. The target keto-acid 284\textsuperscript{13} was then formed over 3 steps involving TBS-ether cleavage, selective Swern oxidation to the intermediate aldehyde followed by further oxidation to the carboxylic acid fragment 284 (Figure 4.6). Discussion had with the Dias’ group\textsuperscript{15} revealed that
exhaustive attempts to couple intermediates 283 and 284 in an esterification reaction gave only decomposition products.

\[
\text{Figure 4.6: Dias' synthesis of acid 284 fragment}
\]

4.2.4 Chênevert’s Synthesis towards Direct Esterification

In 2003,\textsuperscript{16} Chênevert’s group published an enantioselective synthesis for the carboxylate portion of dolabriferol (10). Their convergent synthesis drew upon the inherent symmetry present in dolabriferol (10), in that diol 292\textsuperscript{17} could be employed to construct both the acid 293 and alcohol 294 fragments required for esterification (Figure 4.7).
The synthesis of the keto-acid 293 (Figure 4.8)\textsuperscript{16} fragment began with desymmetrisation of diol 292 with Candida rugosa lipase/vinyl acetate. Oxidation with Dess-Martin periodinane reagent furnished aldehyde 295. The aldehyde 295 then underwent selective ethyl Grignard addition to give a 6:1 ratio of separable alcohols 296-297. Double Swern oxidation gave an intermediate ketoaldehyde, which was then further oxidised with RuCl\textsubscript{3} to produce the target keto-acid 293 in 58% overall yield (5 Steps). The stereochemistry of diol 296 was confirmed through reaction with PDC, this resulted in a fast chemoselective oxidation of the primary alcohol 296 to the carboxylic acid derivative, which subsequently cyclised to produce known silyl protected lactone 298.
Recently in 2007, Chênevert and co-workers\textsuperscript{18} also reported the more complex enantioselective synthesis of the lactol 294 fragment for dolabriferol (10). As detailed above, this proposed synthetic strategy allowed both of the fragments to be constructed from the same symmetrical diol 292.

The synthesis of the lactol 294 moiety of dolabriferol (10) (Figure 4.9)\textsuperscript{18} also began with desymmetrisation of diol 292 to give acetate 299. This compound was TBS-deprotected and converted to the \( p \)-methoxybenzylidene acetal 300. Cleavage of the acetate gave alcohol, which was subsequently oxidised to aldehyde followed by alkylation with isopropyl magnesium bromide to give alcohol 301. This alcohol 301 was then oxidised to ketone 302, and then reduced back to the alcohol 303 to invert the stereochemistry at this position. The resulting alcohol 303 was protected as the TBS-ether and the \( p \)-methoxybenzylidene acetal was opened using DIBALH to give primary alcohol 304.

Conversion of this alcohol 304 into the protected alcohol moiety of dolabriferol (10) was achieved in four steps. Oxidation of alcohol 304 followed by ethyl magnesium bromide Grignard addition to the resulting aldehyde created a diastereomeric mixture of alcohols that were subsequently oxidised to
the corresponding ketone compound. The PMB-ether was cleaved using DDQ, and lastly the TBS protecting group was removed to produce the desired hemiacetal 294 in 14 linear steps (18% overall yield).

![Figure 4.9: Chênevert's synthesis of the lactol fragment 294](image)

The two key fragments were to be utilised in a direct esterification reaction to complete the total synthesis of dolabriferol (10). Since the publication of this lactol fragment 294 in 2007, there have been no new publications by the Chênevert research group regarding the total synthesis of dolabriferol (10), most likely confirming the results observed by Dias et al.

### 4.2.5 Vogel's Total Synthesis of Dolabriferol and Determination of Absolute Configuration

In 2010, Vogel and co-workers successfully completed their total synthesis of dolabriferol (10) and identified the natural product's absolute configuration. Their synthetic strategy involved a reaction cascade (oxyallylation of alkenes), which combines electron-rich dienes and (Z)-enoxy silanes through a SO\textsubscript{2} unppling. As a result, Vogel et al. have developed a one-pot synthesis for the construction of α,β,γ-syn-anti stereotriads. This methodology was then extended to (E)-enoxy silanes to produce α,β,γ-anti-anti stereotriads (Figure 4.10), which were used to develop efficient syntheses of polypropionate subunits of dolabriferol (10).
A Retro-Claisen Approach towards Dolabriferol

The reaction of diene 305 and (E)-silyl enol ether 306 with an excess of SO$_2$/toluene in the presence of (CF$_3$SO$_2$)$_2$NH, (Tf$_2$NH, 20 mol%) provided a mixture of silyl sulfonates, which were desulfinylated by $^3$PrOH/MeCN/K$_2$CO$_3$ in the presence of Pd(OAc)$_2$/PPh$_3$ (10 mol%). The resulting 3:1 mixture of stereotriads 307 and 308 (71% yield) were separated readily by flash chromatography on silica gel.

Ozonolysis of pure stereotriad 307 gave the carboxylic subunit 309 of dolabriferol (10) in 61% yield. Reduction of ketone 310 was achieved using Evans method of Bu$_3$SnH and Me$_3$AlCl to give the pure alcohol 311, which was converted to the ketone in 91% yield. Hydrogenolysis of the phenylethyl ether (H$_2$/Pd(OH)$_2$ in EtOAc) produced the hemiacetal subunit 312 in 72% yield (Figure 4.11). The structure of hemiacetal 312 was established by $^1$H and $^{13}$C NMR analysis and confirmed by single-crystal X-ray diffraction.

Figure 4.10: Vogel’s one-pot synthesis for the construction of $\alpha,\beta,\gamma$-anti-anti stereotriads 306 and 307

Figure 4.11: Preparation of the carboxylic 309 and hemiacetal 312 subunits
In order to reduce possible steric interference between these compounds, it was envisioned that the esterification of 309 with 312 would require a suitably protected acyclic precursor of the hemiacetal 312 (Figure 4.11). The enol acetate 310 was reduced to pure alcohol 311 in 89% yield. Protection as the allyl carbonate 313 (91% yield) followed by treatment with TiCl$_4$/CH$_2$Cl$_2$ provided 314 in 69% yield. Esterification between 309 and 314 using Paterson’s protocol$^{19}$ (2,4,6-trichlorobenzoylchloride, NEt$_3$, DMAP) gave a 9:1 mixture of the desired diastereoisomers 315 and a diastereoisomer resulting from the concurrent based-induced isomerization of 309. Selective removal of the acetyl group was realised by treatment of pure Bu$_3$SnOMe at 70°C followed by KF/H$_2$O workup. Subsequent treatment with TFA removed the phenylethyl ether giving ketone 316 in 96% yield. Final deprotection and formation of the cyclic acetal (Pd(OAc)$_2$, HNEt$_3$, TPPTS) gave dolabriferol (10) in 99% yield (Figure 4.12), the $^1$H and $^{13}$C NMR spectra of which were identical to those of the natural product. Furthermore, single-crystal X-ray analysis of the synthetic material confirmed its structure. As the absolute configurations of the starting dienes and the synthetic intermediates are known, this total synthesis of dolabriferol (10) established the absolute configuration to be (2R,3S,4S,5S,6S,2’R,3’R,4’S).

![Figure 4.12: Vogel’s total synthesis of dolabriferol (10)](image)
4.2.6 Lister’s Retro-Claisen Approach

Although the ester linkage is an obvious retrosynthetic disconnection within dolabriferol (10), prior to Vogel’s total synthesis in 2010\textsuperscript{8} it had been proven difficult to implement, hence in 2006 Lister et al\textsuperscript{10} chose a pseudo-biomimetic approach. This approach allowed the unique ester linkage to be formed through a retro-Claisen fragmentation of an intermediate acetal 317. This synthetic strategy employed lactate derived ketone ent-82 to install all but the C\textsubscript{6} stereocentre, which was accessed from the enantiomerically pure (R)-3-hydroxy-2-methyl ester (318).

Aldehyde 320 was prepared using a three step procedure that included benzyl protection of methyl ester 318, followed by reduction and oxidation. The main aldehyde 319 fragment was synthesised using a dicyclohexylborinate aldol with lactate derived ketone ent-82 and prepared aldehyde 320. The generated alcohol was protected with a TBS-ether and the benzoate functionality was cleaved. The C\textsubscript{3} position was reduced and protected as the PMB-ether, and then selective debenzylation followed by DMP oxidation furnished the required aldehyde 319 (Figure 4.13).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.13.png}
\caption{Lister’s synthesis of the main aldehyde fragment 319}
\end{figure}

Synthesis of the ketone 321 fragment (Figure 4.14) began with another dicyclohexylborinate aldol with lactate derivate ketone ent-82 and isobutyraldehyde (265). Protection of the resultant alcohol as the TBS-ether, reduction to the diol with lithium borohydride followed by oxidative cleavage gave aldehyde 322. This synthesised aldehyde 322 underwent another boron aldol with lactate derived
ketone ent-82, followed by protection of the free alcohol as the TES-ether and subsequent cleavage of the benzoate group gave the desired ketone 321.

![Figure 4.14: Lister’s synthesis of the main ketone fragment 321](image)

The two key aldol fragments were combined using a lithium-based aldol (LiHMDS) reaction. The C₃ oxidation state was altered to that of the natural product by PMB cleavage, followed by double Swern oxidation to give trione 323. Both the C₅ and C₁₁ silyl protecting groups were removed and upon extended exposure to DBU the retro-Claisen fragmentation was facilitated to furnish the protected acyclic precursor 324 to dolabriferol (10). Numerous attempts to remove the final TBS group proved unsuccessful, as it was noted that this remaining TBS-ether protecting group had already endured the conditions commonly used in the removal of silyl protecting groups on a sensitive system. Under harsh acidic conditions (30% aqueous HF in CH₃CN/CH₂Cl₂) it was noted that the TBS-silyl ether could be cleaved, however isolation of spiroacetal 325 led Lister and coworkers¹⁰ to conclude that an intramolecular Claisen reaction at the ester carbonyl had occurred to produce a putative unprotected linear precursor (identical to Goodman's)²⁰ which had cyclised to give a predicted low-energy spiroacetal 325 (Figure 4.15).
4.3 Attempts towards a Stereoselective Synthesis of Dolabriferol

4.3.1 Retrosynthetic Analysis of the Proposed Synthetic Strategy

This proposed synthetic approach towards dolabriferol (10) (Figure 4.16) is an expansion on the interesting studies conducted by Lister et al.,\textsuperscript{10} in that the unique ester moiety of dolabriferol (10) was to be constructed by means of a similar retro-Claisen rearrangement of an intermediate hemiacetal. This intermediate hemiacetal was to arise from a suitably protected acyclic precursor, which would be formed through the aldol coupling of an appropriate aldehyde and ketone fragment. The approaches pursued towards dolabriferol (10) presented herein intended to complete the total
synthesis of dolabriverol (10) and optimise the synthetic strategy providing a potential insight into the natural product’s biological origin.

The initial approach as shown retrosynthetically (Figure 4.16) involves opening of the hemiacetal ring in dolabriverol (10) to give the benzyl protected acyclic ester 326, whose formation was anticipated to result from a retro-Claisen rearrangement of hemiacetal 327. This hemiacetal 327 is a key intermediate in the total synthesis, as only this hemiacetal 327 would produce the desired ester 326 upon retro-Claisen fragmentation. This hemiacetal 327 is produced through a selective deprotection of the PMB-ether and cyclisation of the following free alcohol from hemiacetal 328. Hemiacetal 328 was to be formed from the aldol adduct 329 through cleavage of the silyl diether protecting group and double oxidation of the resulting cyclised product. Use of the silyl diether following cleavage should still allow a controlled cyclisation to proceed, which in turn is proposed to act as a protecting group of the C₅ alcohol allowing double oxidation of the remaining C₃ and C₇ hydroxyl groups to give hemiacetal 328. A retro-aldol bond disconnection of β-hydroxyketone 329 reveals β,γ-siloxyacetaldehyde 330 and bis-alkoxy ethyl ketone 331. The protecting groups for the linear precursor 329 were chosen to permit controlled cyclisation modes. Also evident along the linear carbon backbone of precursor 329 is the continuous anti-relationship between oxygen bearing and methyl bearing stereocentres.
4.3.2 Construction of the Key Aldehyde 330 Fragment

Aldehyde 330 was predicted to be available through several steps (Figure 4.17) after an initial titanium based syn-aldol coupling of synthesised ketone 332 (obtained from roche's ester in 3 linear steps) and propionaldehyde (266) followed by an anti-reduction of the ketone 333. Protection of the diol 334 as the silylene acetal 335, hydrogenation of the benzyl protecting group would afford the alcohol 336, which could be oxidised as required to the designed aldehyde 330.
A Retro-Claisen Approach towards Dolabrilferol

The initial stages of preparing aldehyde 330 focused on obtaining (S)-ketone 332, which was achieved through well-established synthetic chemistry steps (Scheme 4.1). Hydroxyl ester 337 was protected as the standard benzyl ether 338 by reaction with benzyl-acetimidate 339 in CH$_2$Cl$_2$ at room temperature with a catalytic amount of triflic acid (TfOH). The benzyl-acetimidate 339 used for this protection was readily prepared from benzyl alcohol (340) using potassium hydroxide and trichloroacetonitrile. The benzyl protected roche ester 338 was converted to the amide 341 under modified Weinreb conditions, followed by subsequent addition of ethyl magnesium bromide gave the desired ketone 332 in 79% yield over 3 steps. Conversion of the benzyl protected roche ester 338 to the Weinreb amide 341 before alteration to the desired ketone 332 fragment is essential as this overcomes the common problem of over-addition of Grignard and organolithium based reagents to carboxylic acid based derivatives.
**Reagents and Conditions:**

- **a.** 50% KOH aq Solution (w/w), CH₂Cl₂, tetrabutylammonium hydrogen sulphate (cat), then benzyl alcohol (340), Cl₃CCN (1.0 eq), 0°C to RT, 2 hrs; 
- **b.** Ester 337, CH₂Cl₂, RT, then TfOH (10mol%), RT, 15-18 hrs; 
- **c.** MeNH(OMe).HCl (2.5 eq), Et₂O:THF (1:1), 'PrMgCl (5.0 eq), -20°C 1 hr to 0°C 1 hr; 
- **d.** EtMgBr (3.0 eq), THF, 0°C to RT, 2 hrs.

**Scheme 4.1: Synthesis of (S)-Ketone 332**

With (S)-ketone 332 in hand, focus turned to installing the desired stereochemistry of the key aldehyde 330 fragment. This aldehyde 330 synthesis emulated that of Paterson’s synthesis of muamvatin²⁶ beginning with a modified titanium based aldol reaction,²⁷ followed by an Evans-Saksena reduction²⁸,²⁹ of the resulting β-hydroxy ketone 333 to produce the corresponding anti-diol 334 (Scheme 4.2).

Preparation of the (Z)-enolate of ketone 332 was performed by the initial reaction of titanium tetrachloride with titanium tetraisopropoxide at 0°C to form the mild Ti(OPr)Cl₃ chelate complex, which was then added to the newly prepared ketone 332 in CH₂Cl₂ at -78°C followed by Pr₂NEt addition. Freshly distilled propionaldehyde (266) was added to give the desired syn-syn-Felkin aldol product as a single observable stereoisomer in near quantitative yield. The reaction proceeded through a chair-like transition state (Scheme 4.2) where the β-benzyloxy group also coordinates to the Lewis acid (TS17) enhancing the observed stereoselectivity of the aldol adduct 333.²⁷ Reduction of the β-hydroxy ketone 333 using tetramethylammonium triacetoxyborohydride²⁸ also proceeds through a six-membered ring transition state TS18 which forces the intramolecular boron hydride
A Retro-Claisen Approach towards Dolabriferol

delivery to occur from the opposite face of the chelated β-alcohol to give the desired 2,3-anti-3,4-anti-4,5-syn-diol 334.

Reagents and Conditions: a. TiCl₄ (1.0 eq), Ti(1'OPr)₄ (0.3 eq), CH₂Cl₂, 0°C, 30 minutes then, 1'Pr₂NEt (1.2 eq) at -78°C, 30 minutes; propionaldehyde (266) (1.5 eq), CH₂Cl₂, -78°C, 2 hrs;
b. (Me)₄NBH(OAc)₃ (8.0 eq), CH₃COOH, CH₃CN, -20°C, 48 hrs.

Scheme 4.2: Synthesis of benzyl protected dial 334

The di-tert-butylsilylene diol protecting group was selected to protect the 3,5-anti-diol 334 due to its robustness and ease of removal under mild acidic conditions. The protection of the diol as the bis-tertbutylsilyl ether 335 was achieved through reaction of di-tert-butylsilyl bistriflate and 2,6-lutidine in dichloromethane at room temperature for six hours. The benzyl ether was reductively removed using palladium on carbon in ethanol, employing an excess of hydrogen gas at ambient temperature to generate the primary alcohol 336. The alcohol 336 was then oxidised as required to the desired aldehyde 330 fragment using Swern conditions (Scheme 4.3). The required aldehyde 330 was synthesised in 46% yield over five linear steps from ketone 332 and completed the construction of the C₅-C₆ stereochemical array of dolabriferol (10).
Reagents and Conditions: a. Di-tert-butylsilyl bistriflate (2.2eq), 2,6-lutidine (2.5eq), CH₂Cl₂, RT, 6 hrs; b. H₂, Pd/C, EtOH, RT, 6 hrs; c. DMSO (3.0eq), (COCl)₂ (1.5eq), CH₂Cl₂, NEt₃ (6.0eq), -78°C, 2 hrs.

Scheme 4.3: Construction of the key aldehyde 330 fragment

The ¹H NMR spectrum for aldehyde 330 (Figure 4.15) displays the expected aldehyde proton resonating at δ 9.82 (J = 3.1 Hz), which shows coupling to the methyl methine multiplet at δ 2.49. The multiplicity of the resonance at δ 2.49 is due to the additional coupling from the methyl doublet at δ 1.25 (J = 7.0 Hz) and the silyl oxymethine proton at 4.03 (J = 9.7, 2.5 Hz), which appears as a doublet of doublets. The other silyl oxymethine resonance at δ 3.87 appears as a doublet of triplets (J = 9.6, 4.9 Hz) and couples to the methyl methine signal at δ 2.33 (dqd, J = 9.6, 7.2, 5.1 Hz), and the diasterotopic methylene resonances at δ 1.46. The proton resonance at δ 2.33 shows the expected coupling to the methyl doublet at δ 0.82 (J = 7.2 Hz), while the diastereotopic methylenes display coupling to the methyl triplet at δ 1.04 (J = 7.3 Hz). In addition the large singlet signals present at δ 1.00 and δ 0.97 are consistent with the two t-butyl groups. The ¹³C NMR spectrum for the aldehyde 330 (Figure 4.16) shows the correct number of signals in the predicted regions. In particular, the aldehyde carbonyl signal at δ 205, and the two oxygen bearing carbons resonating at δ 78 and δ 76.
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Figure 4.18: The $^1$H NMR spectrum of aldehyde 330 in CDCl$_3$

Figure 4.19: The $^{13}$C NMR spectrum of aldehyde 330 in CDCl$_3$
4.3.3 Synthesis of a Diketone Model System

The bis-tert-butylsilyl ether was chosen as the desired protecting group as it was proposed this synthetic strategy did not require a selective deprotection at these positions. Cleavage of the silyl diether protecting group should then facilitate cyclisation to give a hemiacetal, which would serve as an intramolecular protecting group of the C5 alcohol. This approach was confirmed by implementation of a model system, (Scheme 4.4) which combined the synthesised aldehyde fragment 330 in a lithium hexamethyldisilazide aldol\textsuperscript{37,38} with 2-methyl-3-pentanone (342). This gave the desired anti-Felkin syn-product 343 in 76% yield, which was then exposed to HF/pyridine in buffered pyridine at 0°C for 3 hours.\textsuperscript{33,39} Silyl deprotection facilitated the cyclisation of the intermediate triol to form the predicted hemiacetal 344. NMR analysis (Figures 4.17 and 4.18) confirmed that the cyclisation to form the acetal had occurred with the absence of the tert-butyl methyl signals in the $^1$H NMR, and the presence of the δ 102 $^{13}$C NMR signal attributed to the newly formed acetal carbon. This hemiacetal 344 served to protect the C9-OH for the following double oxidation using Swern conditions\textsuperscript{26} to give the diketone 345 in 75% yield. The successful formation of this model diketone 345 showed the potential for this synthetic approach to be pursued towards the natural product (10), and hence construction of the major ketone fragment 331 was commenced.

\[ \text{Reagents and Conditions: a. LiHMDS (1.2eq), 2-methyl-3-pentanone (342), THF, -78°C, 1 hr then -50°C, 1 hr, then aldehyde 330 (1.0eq), THF, -78°C, 2hrs; b. HF/pyr/pyr (1.1eq), THF, 0°C, 3 hrs; c. DMSO (6.0eq), (COCl)$_2$ (3.0eq), CH$_2$Cl$_2$, NEt$_3$ (12.0eq), -78°C, 2 hrs.} \]

\textit{Scheme 4.4: Synthesis of model diketone hemiacetal 345}
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Figure 4.20: The $^1$H NMR spectrum of hemiacetal 344 in CDCl$_3$

Figure 4.21: The $^{13}$C NMR spectrum of hemiacetal 344 in CDCl$_3$
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4.3.4 Acquisition of the Key Ketone 331 Fragment

Bis-alkoxy ketone 331 was to be constructed through an enantioselective cross aldol between propionaldehyde (266) and isobutyraldehyde (265) to give β-hydroxy aldehyde 346 installing the C_{12} and C_{13} anti-configuration. Three functional group manipulations of aldehyde 346 would afford aldehyde 347, which was to undergo an anti-aldol reaction with lactate derived ketone 82 to create the other C_{10}-C_{11} anti-stereochemistry. Protection of the resultant alcohol and cleavage of the benzoyl auxiliary would furnish the required ketone 331 fragment (Figure 4.22).

It was recognised that β-benzylxy aldehyde 346 containing stereocentres at C_{12} and C_{13} in the anti-configuration could be installed using well known modern asymmetric cross aldol organocatalysis.\textsuperscript{40,41} Freshly distilled propionaldehyde (266) (CaH$_2$) was added over the course of 24 hours using a syringe pump to a mixture of isobutyraldehyde (265) and L-proline in DMF at 0°C to produce intermediate β-hydroxy aldehyde 346, identified by NMR spectroscopy. After NMR confirmation of the unrefined cross aldol product 346 was obtained, it was subsequently added to a solution of NaBH$_4$ in THF at 0°C to give stable diol 348\textsuperscript{42-44} in 52% yield over two steps. This diol 348 could then be protected as either the benzylidene acetal 349\textsuperscript{45} or the p-methoxy-benzylidene acetal 350\textsuperscript{42,44} using benzaldehyde dimethyl acetal or anisaldehyde dimethyl acetal with CSA in dichloromethane at room temperature for 48 hours. Selective reduction of acetals 349 and 350 with DiBALH in methylene chloride at -78°C gave the primary alcohols 351 and 352 quantitatively.\textsuperscript{42,44,46}
Oxidation to aldehydes 347 and 353 (Scheme 4.5) was performed under general Swern oxidation conditions as required for the following anti-dicyclohexylboron mediated aldol addition.

**Scheme 4.5: Synthesis of β-protected aldehydes 347 and 353**

Installation of the second anti-configuration required for the major ketone fragment 331 was envisioned to arise through a Paterson’s lactate ketone boron mediated anti-aldol reaction. The synthesis of Paterson’s lactate ketone 82 (Scheme 4.6) began with isobutyl-(R)-lactate (138), which was firstly converted to the corresponding Weinreb amide 354 before addition of the ethylmagnesium bromide to avoid potential over addition products. Protection of the secondary alcohol as the benzoyl ester provides both steric and electronic effects during the six-membered aldol transition state increasing the observed stereoselectivity for these types of reactions.
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Reagents and Conditions: a. MeNH(OMe).HCl (2.5eq), 1PrMgCl (5.0eq), 1:1 THF/Et$_2$O, -20°C, 1 hr, then 0°C, 1 hr; b. EtMgBr (3.0eq) THF, 0°C to RT, 2 hrs; c. Bz$_2$O (1.5eq), 4-DMAP (0.1eq), 1Pr$_2$NEt (2.0eq), THF, RT, 15 hrs.

Scheme 4.6: Synthesis of Paterson’s lactate derived (R)-ketone 82

It has been well documented$^{52}$ that reaction of this lactate ketone 82 with dialkylboron chloride reagents that the geometry of the resulting enolate is primarily determined by variations in the amine base and the alkyl ligand groups on the boron (detailed in Chapter 1). The combination of dicyclohexylboron chloride with triethylamine preferentially produces the (E)-enolate geometry, leading to the formation of anti-aldol products.$^{53,54}$ The dicyclohexylboron chloride (355) was synthesised as required by addition of monochloroborane methyl sulfide complex to two equivalents of cyclohexene (356) (Scheme 4.7).$^{55}$ The dicyclohexylboron chloride (355) reagent was found to be extremely hygroscopic and required all reagents and equipment to be vigilantly dried and purged with nitrogen during synthesis, and prior to use.

Reagents and Conditions: a. Cyclohexene (356) (2.0eq), Et$_2$O, BH$_2$Cl.SMe$_2$ (1.0eq), 0°C to RT, 2 hours.

Scheme 4.7: Synthesis of dicyclohexylboron chloride (355) from cyclohexene (356)

It was decided to initially employ PMB-aldehyde 353 in the dicyclohexylboron chloride mediated anti-aldol. PMB-aldehyde 353 was chosen as DDQ mediated oxidative cleavage, followed by intramolecular hydrolysis from the resultant anti-aldol adduct 357 would form the p-methoxybenzylidene acetal product 358.$^{25,56}$ The formation of this acetal along with the silyl ether acetal from aldehyde 330 was trialled initially to best imitate the presumed biosynthetic formation of dolabriferol (10) from a linear precursor. Reaction of (R)-lactate ketone 82 with dicyclohexylboron
chloride (355) and triethylamine produced the desired boron enolate, which when reacted with PMB-aldehyde 353 gave the mismatched anti-aldol adduct 357 through TS19 in 55% yield. The aldol adduct 357 was then converted to the p-methoxybenzylidene acetal 358 and following samarium diiodide cleavage of the benzoate57 gave ketone 359 in 83% yield, as shown in Scheme 4.8. The lactate derived ketone 82 is ultimately not a recoverable and recyclable chiral auxiliary but rather the presence of the α-stereocentre enables asymmetric control in the aldol reaction and its subsequent cleavage makes this ketone a powerful chiral pentan-3-one synthon. Following its use in the aldol reaction it is imperative that the resultant alcohol is protected prior to cleavage, as significant decomposition is observed if the reaction is carried out in the presence of the free alcohol.

![Scheme 4.8: Synthesis of PMB-acetal ketone 359](image)

**Reagents and Conditions:** a. cHex2BCl (357) (1.5eq), iPr2NEt (1.8eq), Et2O, -78°C-0°C, 2 hrs; b. Aldehyde 353 (1.0eq), Et2O, -78°C, 3 hrs then -20°C, 15 hrs; c. DDQ (1.2eq), CH2Cl2, pH 7 Buffer, RT, 3 hrs; d. SmI2 (4.0eq), THF, 0°C.

Although formation of this ketone 359 was achieved, problems associated with determining the optimum reaction concentration, reagent equivalents and reaction time were experienced in attempting this anti-boron mediated aldol. This process consumed all the synthesized PMB-aldehyde 353 and was only successful in producing a small amount of ketone product 359. Coupled with this
was the realisation that following the aldol addition with aldehyde 330 and silyl acetal removal, cleavage of this PMP-acetal would liberate a linear precursor 360 susceptible to the likely formation of spiroacetal 325 (Figure 4.19). This spiroacetal 325 was observed in studies conducted by Lister et al.\textsuperscript{10} on removal of the final C\textsubscript{13} silyl protecting group of acyclic ester precursor, which is believed to undergo tautomerisation and participate in an intramolecular Claisen condensation to produce the same linear precursor 360. Cyclisation of the C\textsubscript{5} and C\textsubscript{11} hydroxyl groups upon the C\textsubscript{9} carbonyl with the loss of H\textsubscript{2}O would most likely produce spiroacetal 325.

Due to these encountered problems and the perceived obstacles in the synthesis towards dolabriferol (10), the use of the PMB group was abandoned and replaced with the planned simultaneous synthesis of benzyl aldehyde 347. Differential protection of the resultant aldol adducts’ hydroxyl would then allow for a series of controlled cyclisation pathways towards the natural product (10).

As shown in Scheme 4.9, reaction of the lactate derived ketone 82 with dicyclohexylboron chloride (357) and triethylamine afforded the (\textregistered)-enolate geometry. The enolate was then reacted with the newly constructed β-benzyloxy aldehyde 347 through TS20 to give the \textit{anti}-aldol adduct 361 in 62% yield. The yield obtained from this reaction was lower than other boron mediated \textit{anti}-aldol reactions conducted throughout this chapter as this double stereodifferentiating reaction was mismatched and some aldehyde 347 material may have been lost through β-elimination due to the reaction conditions.
Assignment of the anti-aldol adduct’s 361 newly created stereocentres was based primarily on the enolate of the ketone’s overriding π facial selectivity for the 9,10-anti-10,11-anti-product\textsuperscript{49,50} 361. With the aldol product 361 in hand, attention turned to protection of the newly formed alcohol as the PMB-ether 362. Several attempts to protect\textsuperscript{25,58,59} this free alcohol as the PMB-ether 362 proved unsuccessful resulting in β-elimination of the aldol product 361. These difficulties encountered towards installation of the PMB-ether protecting group meant that the synthesis of ketone 331 had to be revised. It was decided to revise ketone 331 to that of ethyl ketone 363, where the anti-aldol product 361 would be protected as the TES-ether 364. Addition of 2,6-lutidine and TESOTf to a solution of alcohol 361 gave the TES-ether 364 in 94% yield. The TES protecting group\textsuperscript{10,60} was chosen due to the ease of installation and that previous studies had described difficulties in cleaving a TBS group from the dolabriferol (10) polyketide backbone.\textsuperscript{10} Although the aldehyde 330 fragment contained the bis-silyl ether, it was anticipated that this protecting group could still be cleaved in the presence of the newly installed TES-ether. Reductive removal of the benzoate from 364 using SmI\textsubscript{2}\textsuperscript{49,51,57} afforded the desired ethyl ketone 363 in an excellent 92% yield.

Reagents and Conditions: a. \textsuperscript{1}Hex\textsubscript{2}BCl (355) (1.5eq), \textsuperscript{1}Pr\textsubscript{2}NEt (1.8eq), Et\textsubscript{2}O, -78°C-0°C, 2 hrs; b. Aldehyde 347 (1.0eq), Et\textsubscript{2}O, -78°C, 3 hrs then -20°C, 15 hrs; c. 2,6-lutidine (2.0eq), CH\textsubscript{2}Cl\textsubscript{2}, -78°C, TESOTf (1.5eq), 1.5 hrs; d. SmI\textsubscript{2} (4.0eq), THF, 0°C.

Scheme 4.9: Synthesis of differentially protected ketone 363 fragment
The $^1$H NMR spectrum for ketone 363 (Figure 4.24) shows the TES and benzyl oxymethine protons resonate as doublets of doublets at $\delta$ 4.09 ($J = 8.3$, 1.9 Hz) and $\delta$ 3.33 (9.7, 2.2 Hz), respectively. The TES oxymethine proton displays coupling to the methyl methine resonance at $\delta$ 2.97 ($J = 7.1$ Hz), which also shows coupling to the methyl doublet at $\delta$ 1.06 ($J = 7.1$ Hz), and the two hydrogen multiplet at $\delta$ 1.95-1.85. This multiplet has additional coupling to the benzyl oxymethine signal at $\delta$ 3.33 and the methyl doublets at $\delta$ 0.95, $\delta$ 0.94 and $\delta$ 0.90 and thus comprises the $C_{12}$ and $C_{14}$ methyl methine protons. The newly created methyl methylene protons are diastereotopic and appear as doublets of quartets at $\delta$ 2.37 ($J = 18.5$, 7.3 Hz) and $\delta$ 2.27 ($J = 18.5$, 7.3 Hz) and show coupling to the methyl triplet at $\delta$ 0.93 ($J = 7.3$ Hz) in addition to reciprocal coupling. The signals present at $\delta$ 7.37-7.25, $\delta$ 4.74 ($J = 11.6$ Hz) and $\delta$ 4.63 ($J = 11.6$ Hz) are consistent with benzyl ether protecting groups, while the signals at $\delta$ 0.93 ($J = 8.0$ Hz) and $\delta$ 0.56 ($J = 8.0$ Hz) can be attributed to the ethyl substituents from the TES ether protecting group.

The $^{13}$C NMR spectrum for ketone 363 (Figure 4.25) displays the correct number of signals in the predicted regions. The ketone carbonyl appears at $\delta$ 215, the four signals for the benzyl aromatic group appear at $\delta$ 139, $\delta$ 128, $\delta$ 127, and $\delta$ 126 and the two oxymethine carbons resonate at $\delta$ 85 and $\delta$ 77. The carbons associated with the TES protecting group resonate at $\delta$ 7.0 and $\delta$ 5.0.
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**Figure 4.24:** The $^1$H NMR spectrum of ketone 363 in CDCl$_3$

**Figure 4.25:** The $^{13}$C NMR spectrum of ketone 363 in CDCl$_3$
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This short linear sequence afforded the amended major ketone fragment 363 in 21% yield over eight linear steps where the required C\textsubscript{10}-C\textsubscript{13} anti-anti stereochemistry was created exploiting cross aldol asymmetric organocatalysis and lactate derived ketone aldol methodology.

Successful construction of both the aldehyde 330 and ketone 363 fragments meant that the installation of the essential stereocentres for dolabriferol (10) was complete. With these two compounds in hand, attention turned to the union of these two fragments and exploitation of our retro-Claisen approach towards the total synthesis of dolabriferol (10).

4.3.5 Coupling of the Key Aldehyde 330 and Ketone 363 Fragments

Previous synthetic studies\textsuperscript{61} have shown the presence of the sensitive TES group on the ketone fragment when reacted under traditional Lewis acid/amine base aldol conditions led to partial desilylation and formation of β-hydroxy ketone, resulting in reduced enolisation and poor reactivity. As our aldehyde fragment 330 also contained the acid sensitive anti-bis-tert-butylsilyl ether the use of a strong sterically demanding amide base like lithium hexamethyldisilylazide (LiHMDS)\textsuperscript{37,38,62} emerged as an appropriate reagent to combine these two fragments (Scheme 4.10).

A solution of ketone 363 in THF at -78°C was added LiHMDS, the solution was stirred for 30 minutes and then warmed to -40°C and stirring continued for a further 30 minutes to ensure complete enolisation of the ketone as the (Z)-enolate before being re-cooled to -78°C for the addition of the aldehyde 330 in THF via cannula. After two hours the reaction mixture was warmed to -50°C for 30 minutes to complete the aldol addition confirmed by TLC analysis of the crude mixture.
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\[
\begin{align*}
363 & \xrightarrow{a.} \text{LiHMDS (1.2 eq), THF, -78°C, 1 hr then -50°C, 1 hr} \\
330 & \xrightarrow{b.} \text{Aldehyde (1.0 eq), THF, -78°C, 2 hrs.}
\end{align*}
\]

Scheme 4.10: Union of the synthesised aldehyde 330 and ketone 363 fragments using an LiHMDS aldol

Purification by column chromatography yielded one major isomeric product 365 in 77% yield, (as shown in Figures 4.26 and 4.27) indicating a high level of selectivity which was attributed to the \textit{anti}-Felkin preference usually exhibited by α-methyl aldehydes in aldol reactions with (Z)-enolates. The \textit{anti}-8,10 stereochemistry displayed across the carbonyl attributed to the preferred sense of induction of lithium based enolates was also satisfied. The formation of the lithium (Z)-enolate of the ketone 363 was highly dependent on the concentration of the enolate in the THF solvent. Taking into account the 1.0 M lithium hexamethyldisilazide reagent concentration (in THF) the optimum reaction concentration was 0.5 M. Lower concentrations greatly affected the formation of the lithium enolate resulting in poor reactivity between both the aldehyde 330 and ketone 363 fragments. The use of higher concentrations resulted in excellent formation of the lithium enolate but reduced the overall diastereoselectivity of the desired aldol product 365.
Figure 4.26: The $^1$H NMR of aldol adduct 365 in CDCl$_3$

Figure 4.27: The $^{13}$C NMR of aldol adduct 365 in CDCl$_3$
The $^1$H NMR for aldol adduct 365 (Figure 4.26) highlights the complexity of a heavily protected polypropionate linear compound. The signals present in the $^1$H NMR for this aldol adduct essentially comprises of the data obtained from the key aldehyde 330 and ketone 363 fragments, which assists in the confirmation of the successful formation of the aldol product 365. The most notable addition is the new hydroxymethine resonance at $\delta$ 4.01 (dd, $J = 9.3, 1.3$ Hz) which shows coupling to the methyl methine resonance at $\delta$ 2.48 (dq, $J = 7.2, 1.3$ Hz). This methyl methine also shows coupling to the 24H multiplet at $\delta$ 0.95-0.85, which contains half of the available methyl signals. Also readily apparent are the two 9H tertiary butyl methyl protecting group singlets between $\delta$ 1.02-0.99, the methylene quartet from the TES protecting group at $\delta$ 0.57 ($J = 7.9$ Hz), and the signals in the aromatic and oxygen substituted regions corresponding to the benzyl protecting group. The $^{13}$C NMR spectrum (Figure 4.27) of aldol adduct 365 displays the correct number of signals in their expected regions. The ketone carbonyl resonance at $\delta$ 218 and the required six oxygen bearing carbon resonances between $\delta$ 84-71 further confirm the successful union of both fragments.

The configurations of these newly generated stereocentres however are not highly significant as one is lost through oxidation and the other becomes epimerised through the planned retro-Claisen rearrangement step. However, the formation of one stereochemically pure isomer allowed the progression of further synthetic steps to be carried out, making structural identification of each new target product formed straightforward.

With aldol product 365 in hand, attention turned to the task of selectively removing the bis-tertbutylsilyl diether C$_3$ and C$_5$ protecting group in the presence of the secondary triethylsilyl ether (Scheme 4.11). To this date there are no examples in the literature for this process. However in 2011, Brimble et al. showed that it was possible to selectively cleave a primary tertbutylsilyl ether over a secondary TES group. Following these conditions the aldol product 365 was dissolved in THF at 0°C and HF/pyridine/pyridine was added. The reaction was kept at 0°C and monitored by TLC analysis for 6 hours. NMR analysis (shown in Figures 4.28 and 4.29) of the purified product revealed that the resulting product had not cyclised to the desired hemiacetal 366 as indicated by the methyl methine protons at $\delta$ 3.16 and $\delta$ 2.52 adjacent to the carbonyl. The presence of the carbonyl at $\delta$ 219 and the absence of the two equivalent tertiary butyl methyls confirm the deprotection of aldol adduct, 365 but highlighted the unsuccessful in situ formation of the predicted hemiacetal 365, and in fact this product was determined to be the triol 367. These results were in contrast to those...
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obtained for the model system, (Scheme 4.4) which cyclised to the desired hemiacetal 344 under neutral conditions. As the desired hemiacetal 366 had failed to form under neutral conditions used for the removal of the protecting group, it was decided to add a weak acid in the form of PPTS in deuterated chloroform to allow the potential conversion to be monitored by $^1$H NMR analysis.

Addition of 0.01eq of PPTS to the triol 367 in CDCl$_3$ unfortunately did not induce the desired cyclisation pathway, but instead promoted dehydration$^{66}$ of the $\beta$-hydroxy ketone into conjugation of the carbonyl to give intermediate compound 368 as indicated by only one $\alpha$-methine proton at $\delta$ 2.73, the vinyl methyl at $\delta$ 1.57 and the corresponding vinylic proton at $\delta$ 5.75. This intermediate compound 368 then followed our previously desired cyclisation pathway to produce hemiacetal 369 as the major product determined by NMR analysis. Numerous other reagents were employed including: NH$_4$Cl, LiCl and DBU in CDCl$_3$ to attempt to promote the desired cyclisation of triol 367 to produce the required hemiacetal 366 however, no reagent conditions managed to facilitate the desired cyclisation pathway. It is believed that the extra steric bulk surrounding the carbonyl supplied by the TES functionality prohibits the preferred cyclisation as seen in the designed model system. It is unclear if dehydration of the $\beta$-hydroxy substituent occurs first followed by the cyclisation (as shown in Scheme 4.11) or if this process occurs in reverse. As no desired hemiacetal product 366 was isolated following the addition of the PPTS, it is thought that dehydration of the $\beta$-hydroxy substituent take place first which allows the cyclisation to occur. This dehydration into conjugation is thought to flatten the area surrounding the carbonyl allowing nucleophilic attack from the C$_5$ alcohol moiety to occur to give hemiacetal 369. Prolonged exposure to the PPTS solution then causes cleavage of the TES group functionality to produce hemiacetal 370. After the exhaustive attempts to try to induce the required cyclisation pathway to achieve hemiacetal, 366 it was decided a revised approach was required to proceed towards our retro-Claisen approach to dolabriferol (10).
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Scheme 4.11: Silyl acetal deprotection and attempted cyclisations of triol 367

Reagents and Conditions: a. HF/pyr/pyr (1.2eq), THF, 0°C, 6 hrs; b. PPTS (0.01eq), CDCl₃ 1 to 2 hrs.
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Figure 4.28: The $^1$H NMR spectrum of triol 367 in CDCl$_3$

Figure 4.29: The $^{13}$C NMR spectrum of triol 367 in CDCl$_3$
After the union of the key aldehyde 330 and ketone 363 fragments via the lithium based aldol reaction, it was decided the resultant alcohol functionality would be oxidised to its required oxidation state within dolabriferol (10). Diketone 371 would then be selectively deprotected and it was anticipated that an oxidation of the less hindered C3 would produce the required linear trione 372 product (Scheme 4.12). Oxidation of the aldol adduct 365 was performed successfully with Dess-Martin periodinane and sodium bicarbonate in moist dichloromethane at ambient temperature for one hour to give the diketone compound 371. The successful oxidation was established by the presence of two carbonyls signals at δ 211 and δ 210 in the $^{13}$C NMR spectrum plus the predicted single quartet signal at δ 3.90 attributed the proton between the two carbonyls confirmed through proton-proton correlation experiments. The next step involved the deprotection of bis-tertbutylsilyl diether 65 as seen before in Scheme 4.11. This produced the expected diol 373 as seen by NMR analysis of the crude mixture; following silica-based column chromatography an unexpected result was obtained. It appeared as though the unprotected diol 373 was still present, but the proton signals attached at the C2 position were uncharacteristic of those adjacent to a carbon containing an alcohol, but more like those attached to carbonyl functionality. Even though there was ambiguity surrounding the diol compound 373, it was decided to oxidise that compound to achieve the preferred trione product 372. Oxidation of the diol 373 with DMP and NaHCO$_3$ in dichloromethane at room temperature produced hemiacetal, 374 which unfortunately was attributed to the competing cyclisation pathway plus oxidation of the remaining secondary alcohol. Based on this result it is predicted the initial unexpected product was that of the competing cyclisation mode hemiacetal.
Reagents and Conditions: a. DMP (1.5eq), NaHCO$_3$, CH$_2$Cl$_2$, RT, 1.5 hrs; b. HF/pyr/pyr (1.2eq), THF, 0°C, 6 hrs; c. DMP (1.5eq), NaHCO$_3$, CH$_2$Cl$_2$, RT, 1.5 hrs.

Scheme 4.12: Attempted synthesis of trione 372 through the deprotection and oxidation of diketone 371

Following this, an attempt was made to deprotect the TES-protecting group of diketone 371 in the presence of the bis-silylether functionality with p-TsOH to give alcohol 375. Unfortunately, NMR analysis of the purified product mixture did not completely confirm the success of this deprotection, and the subsequent addition of DBU failed to produce any desired retro-Claisen ester product 376 (Scheme 4.13).

These results highlighted the importance of maintaining the oxidation state at the C$_3$ position, and led to the decision that a new approach was required to synthesise an alternative aldehyde fragment that possessed dissimilar protecting groups to allow for selective deprotection and control of the possible cyclisation modes.
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Reagents and Conditions: a. p-TsOH (cat), 1:1 MeOH/CH₂Cl₂, 0°C, 1 hr. b. DBU (cat), C₆D₆, RT, 6 hrs.

Scheme 4.13: Attempted synthesis of ester 376 through the deprotection and retro-Claisen rearrangement of diketone 371

4.3.6 New Aldehyde 377 Synthesis with Differential Protecting Groups

This new proposed synthesis of the aldehyde 377 (Figure 4.30) initially involved the synthesis and use of TBS-protected ethyl ketone 378 as opposed to the analogous benzyl-ketone 332. The TBS group was chosen in preference to the traditional benzyl ether for this situation as it was envisioned that the eventual C₃ hydroxyl would be protected as the PMB ether, making the selective reduction of the primary benzyl ether complicated in its presence. Due to the success had in previous studies with the protection of the C₃ alcohol as a PMB ether and the C₅ hydroxy as a TBS-ether, this was to be replicated. Use of this alternate ketone 378 would then allow the simple kinetic removal of the primary TBS-group in preference to the additional sterically hindered TBS-protecting group, which could then be oxidised to the newly proposed aldehyde 377.

Figure 4.30: Alternate aldehyde 377 synthesis from ethyl ketone 378 and propionaldehyde (266)
Synthesis of the ethyl ketone 378 (Scheme 4.14) began with the well established TBS-Cl/imidazole procedure\textsuperscript{25,68,69} of (S)-roche ester 337 to give TBS-protected methyl ester 379 in 93% yield. Conversion of the methyl ester 379 to the corresponding Weinreb amide 380\textsuperscript{24} was achieved in 98% yield, and then addition of ethylmagnesium bromide at 0°C afforded the TBS-protected ethyl ketone 378\textsuperscript{25} in 74% yield, obtained over 3 linear steps.

![Scheme 4.14: Synthesis of TBS-protected ethyl ketone 378 from roche ester 337]

Reagents and Conditions: a. Imidazole (2.0eq), CH\textsubscript{2}Cl\textsubscript{2}, TBS-Cl (1.8eq), RT, 15 hrs; b. MeNH(OMe).HCl (2.5eq), iPrMgCl (5.0eq), 1:1 THF/Et\textsubscript{2}O, -20°C, 1 hr, then 0°C, 1 hr; c. EtMgBr (3.0eq) THF, 0°C to RT, 2 hrs.

With the TBS-protected ethyl ketone 378 in hand, attention turned to inducing the syn-syn stereochemistry of aldol product 381. This was achieved through use of the modified titanium aldol procedure\textsuperscript{27} seen in Scheme 4.15, where titanium tetrachloride was reacted with titanium tetraisopropoxide at 0°C to form the mild Ti(OPr)\textsubscript{4}Cl\textsubscript{3} chelate complex, which was then added to the newly prepared TBS-protected ketone 378 in CH\textsubscript{2}Cl\textsubscript{2} at -78°C, followed by iPr\textsubscript{2}NEt addition. Freshly distilled propionaldehyde (266) was then added and through TS21 gave the desired syn-syn-Felkin aldol product 381 in 77% yield and a minor amount (8%) of the anti-syn-aldol adduct that was easily separated by column chromatography. Reduction of the desired β-hydroxy ketone 381 product was performed with tetramethylammonium triacetoxyborohydride\textsuperscript{28} to deliver the vital hydride ion from the opposite face to produce the corresponding 2,3-anti-3,4-anti-4,5-syn-diol 382 in 83% yield.
A Retro-Claisen Approach towards Dolabriferol

Reagents and Conditions: a. TiCl₄ (1.0eq), Ti(OOPr)₄ (0.3eq), CH₂Cl₂, 0°C, 30 minutes then, iPr₂NEt (1.2eq) at -78°C, 30 minutes; b. Propionaldehyde (266) (1.5eq), CH₂Cl₂, -78°C, 2 hrs; c. (Me)₂NBH(OAc)₃ (8.0eq), CH₃COOH, CH₃CN, -20°C, 48 hrs.

Scheme 4.15: Synthesis of TBS-protected diol 382

Protection of the C₃ alcohol as the PMB-ether firstly required the synthesis of PMB-imidate 147, which was achieved in an identical manner as outlined above for the synthesis of benzyl imidate (Scheme 4.1) employing 4-methoxy benzyl alcohol (148) as the essential reagent. Protection of the C₃ alcohol as the p-methoxy benzyl ether was achieved through reaction triflic acid (0.001M in Et₂O) with PMB-imidate 147 in dichloromethane at ambient temperature for 48 hours, however the desired PMB protected product 383 was only achieved in a mediocre yield of 21% due to the sensitivity of the primary TBS-group to acidic conditions and the potential for the C₅ alcohol to also be protected as the PMB-ether. Even though conversion of the free C₅ secondary alcohol 383 to the corresponding TBS-ether 384 proceeded in excellent yield 92% (Scheme 4.16) the initial protection step prompted a revised approach to obtaining this fragment.
A Retro-Claisen Approach towards Dolabriferol

Reagents and Conditions: a. PMB-imidate 147 (1.5eq), CH₂Cl₂, TfOH (cat), RT, 48 hrs; b. 2,6-lutidine (2.0eq), CH₂Cl₂, TBSOTf (1.5eq), -78°C, 2 hrs.

Scheme 4.16: Synthesis of protected adduct 384

As the Evans-Saksena reduction requires an unprotected β-hydroxy ketone to complex to the boron to direct the addition of the hydride source to the opposite face of the ketone, generating the anti-diol. It is not possible to selectively reduce this carbonyl functionality after the protection of β-hydroxy as the PMB ether. As such, a revised approach was required to synthesise aldehyde 377 which was proposed to form through a lactate derived ketone 82 boron mediated aldol with a TBS-protected aldehyde 385, followed by an undiscerning boroxydride reduction of the C₃ carbonyl, as this would be oxidised back to its correct oxidation state during future synthetic steps. It was anticipated that the reduction and subsequent protection of the C₃-carbonyl would be crucial to avoid potential Cyclisation pathways at various stages throughout the revised synthesis towards dolabriferol (10).

It was planned to create the desired stereochemistry through a lactate derived anti-aldol reaction, cleavage of the benzoyl substituent and reduction of the C₃ carbonyl, followed by protection of the resultant alcohol as its p-methoxybenzyl ether derivative. Liberation of the primary TBS-ether would expose primary alcohol, which would oxidised under Swern conditions as required producing the aldehyde 377 fragment.

The synthesis of required aldehyde 385 (Scheme 4.17) began initially the TBS protection of the primary alcohol of (S)-roche ester 337 using the TBS-Cl and imidazole procedure, above in Scheme 4.14. The methyl ester was completely reduced to corresponding primary alcohol 386 employing DiBALH in dichloromethane at -78°C for 2 hours. Due to the use of the sensitive primary TBS group to acidic and basic solutions the application of traditional acid/base workups to neutralise the formation of aluminium salt emulsions had to be exchanged for Rochelle’s salt (sodium...
A Retro-Claisen Approach towards Dolabriferol

potassium tartrate solution). The alcohol 386 was then oxidised under Swern conditions\(^{48,70}\) to the (S)-TBS-protected aldehyde 385 in 79\% yield over 3 linear steps.

![Chemical structure](image)

**Reagents and Conditions:** a. Imidazole (2.0eq), CH\(_2\)Cl\(_2\), TBS-Cl (1.8eq), RT, 15 hrs; b. DiBALH (1.5eq), CH\(_2\)Cl\(_2\), -78°C, 2 hrs; c. DMSO (3.0eq), (COCl)\(_2\) (1.5eq), CH\(_2\)Cl\(_2\), NEt\(_3\) (6.0eq), -78°C, 2 hrs.

**Scheme 4.17:** Synthesis of TBS-protected aldehyde 385

Addition of the newly prepared (S)-TBS-aldehyde 385 to a solution of the (E)-enolate 387 formed by the addition of dicyclohexylboron chloride (355) and triethylamine to ethyl ketone 82 in Et\(_2\)O at -78°C,\(^{53,54}\) followed by stirring at -20°C overnight gave the 2,4-anti-4,5-anti-5,6-anti-Felkin aldol product 388\(^{25}\) in 75\% yield. This aldol reaction that displays the anti-Felkin product is mismatched with respect to the aldehyde 385 given its persistent Felkin preference as displayed by aldehydes involved in aldol reactions with (E)-enolates. The transition state\(^{49,50}\) TS22 (shown in Scheme 4.18) depicts the steric interaction shown between the methyl substituent of the enolate and the large side chain of the aldehyde 385, which causes this reaction to be mismatched. The selectively displayed for the anti-Felkin adduct is a demonstration of the π-facial control\(^{63,64}\) applied by the enolate of the lactate derived ketone 82. This indicates that the selectivity of the enolate 387 overrides the Felkin-Ahn model of induction from the aldehyde 385. Protection of the C\(_5\) alcohol as the TBS-ether was achieved using standard conditions (TBSOTf and 2,6-lutidine)\(^{72}\) to give the disilyl ether 389. The benzoate was cleaved\(^{39,51,57}\) using an excess of SmI\(_2\) in THF at 0°C to give ethyl ketone 390 in an excellent 66\% yield over three linear steps (Scheme 4.18).
As mentioned above, it was planned that the C₃ carbonyl be reduced and protected as p-methoxy benzyl ether to avoid potential cyclisation modes encountered at various stages of the synthesis, mainly upon removal of the primary TBS group as a lead up to the acquisition of the key aldehyde fragment. As a result, ketone 390 was reduced with NaBH₄ in ethanol at 0°C, then allowed to warm to room temperature for 6 hours. This produced a mixture of alcohol stereoisomers 391 and 392 (Scheme 4.19) (5:1 ratio) with the major isomer assigned as alcohol 391 based on the established Felkin-Ahn delivery of the hydride to the carbonyl. Although there was a slight potential for these isomers to be separated via column chromatography, no attempt was made to pursue this or increase the selectivity of the reduction as a future correction of the C₃ oxidation state would counteract any further enhancement of the major product. Due to the sensitivity of the primary TBS functionality, the amount of triflic acid to be added to the mixture was of concern as even common 0.01M conditions appeared to cause partial cleavage. Taking this into account, the combined stereoisomers (391 and 392) were protected as the PMB-ether 393 using PMB-acetimidate 147 (3.0eq) and triflic acid (0.001M) in Et₃O at room temperature for 48 hours. This process was completed after two recycles of starting material to give PMB ether 393 in 58% yield.
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\[ \text{Felkin} \quad \text{OTBS} \quad 392 \]
\[ \text{anti-Felkin} \quad \text{OH} \quad \text{OTBS} \quad 391 \]

Selectivity 391:392 - 5:1

**Reagents and Conditions:**

<table>
<thead>
<tr>
<th>Reagent/Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. NaBH₄ (2.5 eq)</td>
<td>EtOH, 0°C to RT, 6 hrs;</td>
</tr>
<tr>
<td>b. PMB-imidate 147</td>
<td>(3.0 eq), Et₂O, TfOH (cat), RT, 48 hrs.</td>
</tr>
</tbody>
</table>

**Scheme 4.19: Reduction and PMB-protection of ethyl ketone 390**

The decision to install the secondary TBS-ether at C₅ was made with the anticipation that the C₇ primary TBS-ether would be selectively cleaved in its presence. In practice this proved correct with application of a procedure by Paterson et al. Treatment of the disilyl ether 393 with a 1%HCl/ethanol solution at 0°C for 30 minutes afforded the primary alcohol 394 in 85% yield. The use of this literature ratio proved critical as under other standard silyl ether cleavage conditions both groups may have been deprotected. The alcohol 394 was then oxidised using standard Swern conditions to provide the targeted key aldehyde 377 fragment in 93% yield (Scheme 4.20).

\[ \text{PMBO} \quad \text{OTBS} \quad 393 \]
\[ \text{PMBO} \quad \text{OH} \quad \text{OTBS} \quad 394 \]
\[ \text{PMBO} \quad \text{O} \quad \text{H} \quad \text{TBS} \quad 377 \]

**Reagents and Conditions:**

<table>
<thead>
<tr>
<th>Reagent/Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. 1%HCl/EtOH</td>
<td>0°C, 30 minutes;</td>
</tr>
<tr>
<td>b. DMSO (3.0 eq), (COCl)₂ (1.5 eq), CH₂Cl₂, NEt₃ (6.0 eq), -78°C, 2 hrs.</td>
<td></td>
</tr>
</tbody>
</table>

**Scheme 4.20: Synthesis of the differentially protected aldehyde 377 fragment**
The $^1$H NMR spectrum for aldehyde 377 (Figure 4.31) shows the expected aldehyde proton resonance as a doublet at δ 9.77 ($J = 2.8$ Hz), which displays coupling to the methyl methine proton multiplet at δ 2.49. The multiplet is due to the additional coupling to the methyl doublet at δ 1.07 ($J = 7.1$ Hz) and TBS oxymethine resonance, which appears as a doublet of doublets at δ 4.10 ($J = 5.6$, 2.6 Hz). The PMB oxymethine resonance at δ 3.37 appears as a triplet of doublets ($J = 6.4$, 3.5 Hz) and couples to the methyl methine multiplet signal at δ 2.04 and the diastereotopic methylene resonances at δ 1.64 and δ 1.45. The signal at δ 2.04 shows the expected coupling to the methyl doublet at δ 0.81 ($J = 7.2$ Hz), while the diastereotopic methylene protons show coupling to the methyl triplet at δ 0.92 ($J = 7.4$ Hz). The signals at δ 7.24 (d, $J = 8.7$ Hz), δ 6.87 (d, $J = 8.7$ Hz), δ 4.44 (d, $J = 11.2$ Hz), δ 4.32 (d, $J = 11.2$ Hz) and δ 3.80 (s) are consistent with that of a $p$-disubstituted PMB protecting group. The $^{13}$C NMR spectrum for aldehyde 377 (Figure 4.32) displays the correct number of resonances in their expected regions. The aldehyde carbonyl resonates at δ 205, the four signals attributed to the $p$-disubstituted aromatic group appear at δ 159, δ 130, δ 129, and δ 128 and the four oxygen bearing carbons resonate at δ 80, δ 75, δ 70, δ 55.

![Figure 4.31: The $^1$H NMR spectrum of aldehyde 377 in CDCl$_3$](image-url)
4.3.7 Revised Approach towards the Synthesis of the Ketone 363 Fragment

Although a successful methodology had been achieved through the synthesis of the key ketone 363 fragment employing the asymmetric organocatalysis methodology\textsuperscript{40} it along with the benzyl acetal formation was incredibly time consuming in making aldehyde 347 (Scheme 4.5). As a result, it was decided to form the required anti-\textsuperscript{12} and \textsuperscript{13} stereochemistry using another lactate derived ketone 82 dicyclohexylboron aldol with isobutyraldehyde (265) following a known protocol.\textsuperscript{49,51} The (\textit{E})-enolate was prepared under standard conditions (\textsuperscript{\textit{E}}Hex$_3$BCl/NEt$_3$),\textsuperscript{49} and was reacted with freshly distilled isobutyraldehyde (265) to give 11,12-\textit{anti}-12,13-\textit{anti}-aldol adduct 395 as a single observable isomer in almost quantitative yield. The \textit{anti-anti}-stereocontrol observed\textsuperscript{49,51} for this aldol addition primarily comes from the strong diastereofacial preference of the (\textit{E})-enolate, which results from the stabilising hydrogen bonding depicted in transition state TS23.

With aldol adduct 395 in hand, attention turned to installation of the preferred benzyl ether at the \textsuperscript{13} position. As there had only been a handful of literature examples for this type of installation it was decided to initially attempt the traditional benzyl acetimidate 338 and triflic acid in a 2:1
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cyclohexane/dichloromethane solution at 0°C, which was warmed to room temperature for four hours. This gave the desired benzyl ether 396 in an excellent 76% yield. The benzoate ketone 396 was reduced\textsuperscript{10,75} using LiBH\textsubscript{4} in THF at -78°C, warmed to room temperature for 15 hours to produce diol 397. Oxidative cleavage\textsuperscript{10,75} of the diol 397 was then performed with sodium periodate in methanol to give the essential aldehyde 347. As the oxidative cleavage reaction of diol 397 to form aldehyde 347 was complete within 10 minutes at room temperature, it could then be used immediately in the following anti-dicyclohexylboron aldol with lactate derived ketone 82 following the previously mentioned enolisation conditions. Following the revised synthesis of aldehyde 347 (Scheme 4.21) the remaining steps towards the main ketone fragment 363 followed those synthetic steps already described above in Scheme 4.9.

Scheme 4.21: Revised synthesis of benzyl-protected aldehyde 347

4.3.8 Coupling of the New Aldehyde Fragment 377 with Ketone Fragment 363:

With the successful synthesis of the new aldehyde fragment 377, the coupling of this fragment with the main ketone fragment 363 was achieved using the same lithium hexamethyldisilyladiazide in THF...
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conditions\textsuperscript{37,38,62} as mentioned above in Scheme 4.10 to generate the differentially protected linear polyketide aldol product 398 in 62\% yield (Scheme 4.22). Once again the high level of selectivity observed from the reaction was attributed the anti-Felkin preference of α-methyl aldehydes in aldol reactions\textsuperscript{63,64} with (Z)-enolates, and the anti-selectivity displayed across the developing carbonyl, which is the preferred mode of induction shown for lithium enolates was satisfied.

\[ \text{Reagents and Conditions: a. LiHMDS (1.2eq), THF, -78°C, 1 hr then -50°C, 1 hr, Aldehyde 378 (1.0eq), THF, -78°C, 2hrs.} \]

\textit{Scheme 4.22: Merger of the synthesised aldehyde 377 and ketone 363 fragments using an LiHMDS aldol}

The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra obtained for aldol adduct 398 (Figures 4.33 and 4.34) is highly complex and consists mainly the data obtained for both aldehyde 377 and ketone 363. Analysis of the \textsuperscript{1}H NMR spectrum indicates the presence of the new hydroxymethine resonance as a doublet at $\delta$ 3.93 (10.3 Hz) which couples to the methyl methine resonance at $\delta$ 2.55 (qd, $J = 6.9$, 1.5 Hz). The new methyl methine in turn also couples to the doublet observed at $\delta$ 1.04 ($J = 6.9$ Hz). Also readily apparent are the two methyl singlets between $\delta$ 0.07 and $\delta$ 0.05 accounting for the methyl groups attached to the TBS protecting group. The TES methylene quartet at $\delta$ 0.53 ($J = 7.8$ Hz), the aromatic signals associated with benzyl and $p$-methoxy benzyl at $\delta$ 7.37 and $\delta$ 6.87 and their corresponding diastereotopic oxybenzylic protons between $\delta$ 4.82 and $\delta$ 4.35.

The \textsuperscript{13}C NMR displays the correct number of unique carbon resonances in their expected regions. The ketone carbonyl resonance at $\delta$ 217, the seven oxycarbon resonances at $\delta$ 84.98, $\delta$ 80.40, $\delta$
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77.20, δ 76.26, δ 74.16, δ 72.46, δ 69.89, and the eight sp² aromtic carbons at δ 158.89, δ 139.50, δ 131.40 δ 128.88, δ 128.11, δ 126.92, δ 126.70, δ 113.63 are of particular interest and confirm the successful union of the major fragments.

Figure 4.33: The $^1$H NMR spectrum of aldol adduct 398 in CDCl$_3$
4.3.9 Synthesis of Trione 400

The successful joining of the two major fragments using aldol methodology to create the aldol adduct 398 then allows for the final planned synthetic steps that involve selective deprotections, correction of oxidation states and the planned retro-Claisen rearrangement to proceed uninhibited towards the synthesis of dolabriferol (10).

With the aldol product 398 in hand, attention first turned to correction of the C₃ and C₇ oxidation states to that displayed in the natural product dolabriferol (10) (Scheme 4.23). To do this, the differentially protected aldol adduct 398 was dissolved in a mixture of methylene chloride and water (9:1), then DDQ was added at 0°C and the reaction stirred for one hour to complete the deprotection of PMB ether, at the C₃ position, to produce the diol 399 in 96% yield. The diol 399 was then exposed to double the equivalents used for traditional Swern oxidations to effect the oxidation of both the C₃ and C₇ hydroxyl groups to form the trione 400 in 68% yield.
Surprisingly, the stability of the triketone 400 as a single epimer is shown through analysis of the $^1$H and $^{13}$C NMR spectra (Figures 4.35 and 4.36). Commonly, when β-dicarbonyl species are acquired in CDCl$_3$ there is enough residual HCl to promote enolisation leading to mixtures of epimers and enols. As this synthesis incorporated the use of several silyl ether protecting groups sensitive to acid hydrolysis, special care was taken with the addition of potassium carbonate and filtering of the CDCl$_3$ solvent through neutral alumina prior to use. This vigilant handling of the CDCl$_3$ NMR solvent may have been the cause for the apparent stability of triketone 400.

Reagents and Conditions: a. DDQ (1.3eq), CH$_2$Cl$_2$/H$_2$O (9:1), 0°C, 1 hr; b. DMSO (6.0eq), (COCl)$_2$ (3.0eq), CH$_2$Cl$_2$, NEt$_3$ (12.0eq), -78°C, 2 hrs.

Scheme 4.23: Synthesis of trione 400 following PMB-deprotection and double Swern oxidation

The $^1$H NMR contains a methyl methine quartet resonance at δ 3.74 (J = 7.1 Hz) and is indicative of a proton located between a β-dicarbonyl moiety. This resonance is located in amongst the three oxymethine resonances which appear at δ 4.38 (dd, J = 8.3, 5.0 Hz), δ 4.13 (d, J = 9.4 Hz) and δ 3.29 (J = 12.3, 2.0 Hz). There is also three α-carbonyl methyl methine protons that can be seen in close together at δ 2.95 (qd, J = 9.3, 7.0 Hz), δ 2.76 (qn, J = 7.3 Hz) and δ 2.66 (qd, J = 7.0, 6.9 Hz) with each proton displaying coupling to their respective methyl doublets. The methylene protons attached adjacent to the C$_3$ ketone are diastereotopic mirror-image signals that resonate as doublets of quartets at δ 2.56 (J = 18.1, 7.2 Hz) and δ 2.45 (J = 18.1, 7.2 Hz) which couple to the methyl triplet at δ 1.03 (J = 7.2 Hz). The other signals present in the $^1$H NMR spectrum are consistent with the assigned trione 400 structure. The $^{13}$C NMR spectrum shows the presence of three carbonyl signals.
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at δ 211, δ 210 and δ 209. The spectrum also shows the remaining four oxycarbon resonances at δ 84, δ 76, δ 74 and δ 73 and the four benzyl sp² carbons at δ 139, δ 128, δ 127, and δ 126 confirming the trione’s assigned structure.

Figure 4.35: The ¹H NMR spectrum of trione 400 in CDCl₃
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Figure 4.36: The $^{13}$C NMR spectrum of trione 400 in CDCl$_3$

4.3.10 Removal of the Silyl Protecting Groups

It has been shown in previous studies$^{61}$ for a similar trione that the steric bulk of the TBS-ether prevented the desired hemiacetal formation following a selective deprotection of the TES-ether under acidic conditions. Deprotection of this TES-ether under basic reaction conditions also led to the formation of a conjugated enone product through β-elimination. As a result, it was decided that both the TBS and TES silyl ethers had to be removed simultaneously (Scheme 4.24).

The Roush group$^{76,77}$ discovered that TAS-F (tris(dimethylamino)sulfur (trimethylsilyl)difluoride was a mild reagent for the deprotection of silyl ethers in base sensitive substrates. Their need for such a sensitive reagent stemmed from similar unwanted β-elimination products during their TBAF silyl deprotection attempts to form natural product bafilomycin A$_1$. The development and use of TAS-F in the final deprotection step enabled the group the complete the total synthesis of this complex macrolide natural product.
Following the procedure outlined by Roush et al., trione 400 was treated with five equivalents of TAS-F and ten equivalents of water in DMF at room temperature for 2 hours. This procedure resulted in the desired cleavage of the C₅ and C₁₁ silyl ethers and on workup produced a complex mixture of products. It is known that some hemiacetals are prone to decomposition in acidic media, and as a result this complex mixture was analysed in deuterated benzene. Analysis of the ¹H NMR spectra indicated the presence of a complex mixture. It showed that the silyl groups had been cleaved and that hemiacetals 401 and 402 could be present in this complex mixture. As it was believed the desired hemiacetal 402 required for our retro-Claisen approach was present, the mixture was treated with a catalytic amount of DBU to invoke this rearrangement. Amazingly, this resulted in the rapid conversion of the complex mixture into one single observable compound by ¹H NMR. This product was isolated by column chromatography in 94% yield and confirmed as 2,4,6-trioxadamantane 403 by spectroscopic analysis. This unique compound results from the removal of the C₅ and C₁₁ silyl protecting groups, which leads to an equilibrium formation of hemiacetals 401 and 402. Upon the addition of DBU, the hemiacetals’ 401 alcohol attacks the C₃ carbonyl, which in turn reacts with the C₇ carbonyl in a cascade cyclisation leading to the formation of the trioxadamantane 403. Surprisingly, the desired hemiacetal 402, which results from the cyclisation of the free C₁₁ alcohol onto the C₇ carbonyl, or the potential spiroacetal 404, which is a further cyclisation of the hemiacetal alcohol on the C₃ carbonyl were not observed.
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Reagents and Conditions: a. TAS-F (5.0eq), H$_2$O (10.0eq), DMF, RT, 2 hrs; b. DBU (cat), C$_6$D$_{6}$, RT, 5 minutes.

Scheme 4.24: Dual silyl deprotection and formation of 2,4,6-trioxaadamantane 403

Looking at the $^1$H NMR spectrum of the 2,4,6-trioxaadamantane 403 in C$_6$D$_{6}$ (Figure 4.37) shows the loss of both the TES and TBS protecting groups. The benzyloxymethine resonates as a doublet of doublets at δ 3.78 (J = 9.3, 1.9 Hz) and shows coupling to the methyl methine resonances at δ 2.26 and δ 1.92. The hydroxymethine resonance at δ 4.31 (J = 8.3 Hz) appears as doublet and shows coupling to the two hydrogen methyl methine multiplet at δ 2.26. The methyl triplet at δ 0.91 (J = 7.4 Hz) couples to the methyl methylene multiplets at δ 1.58-1.51 and δ 1.38-1.27, which also display reciprocal coupling. The shift of these methylene signals indicates the absence of a carbonyl group at the C$_3$ position verifying the conversion of this position to an acetal and the assigned trioxaadamantane structure. Analysis of the $^{13}$C NMR spectrum (Figure 4.38) showed three signals at δ 106, δ 102 and δ 97, which are present in the characteristic region for acetal carbon centres confirming the presence of trioxaadamantane moiety. Additionally, the oxidation states of the other four oxymethine carbons remained the same and resonated at δ 84, δ 78, δ 77, and δ 73. Also of note was the absence of the previous three carbonyl signals, as the desired hemiacetal 402 would have still possessed two ketone resonances.
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**Figure 4.37:** The $^1$H NMR spectrum of 2,4,6-trioxaadamantane 403 in $C_6D_6$

**Figure 4.38:** The $^{13}$C NMR spectrum of 2,4,6-trioxaadamantane 403 in $C_6D_6$
4.3.11 Retro-Claisen Rearrangement towards the Acquisition of Ester 405

Although the formation of an analogue of 2,4,6-trioxadamantane 403 was seen in the previous work of Lister and Perkins, at that time it did not seem like a suitable precursor to initiate the planned retro-Claisen rearrangement, as this compound resulted from the incorrect hemiacetal (cf. 401) cyclisation. It was discovered through the work of Lister and Perkins that prolonged exposure of 2,4,6-trioxadamantane (cf. 403) to DBU did achieve the desired retro-Claisen rearrangement.

In this work when the purified trioxadamantane 403 was treated with DBU over an extended period of time the desired retro-Claisen rearrangement to form ester 405 was observed in the crude reaction mixture (spectra confirmation of the structure follows in Figures 4.39 and 4.40). But before all the trioxadamantane 403 starting material was consumed the ester 405 product was observed to undergo partial β-elimination to give enone 407. As a result, the reaction mixture was separated after an optimum reaction time of 10 hours at room temperature, with the recovered trioxadamantane 403 resubjected to the base catalysed retro-Claisen fragmentation. Although the formation of the elimination by-product 407 was unfortunate it did help to confirm the identity of the ester product 405 being formed within this complex hemiacetal mixture.

It is apparent that under the basic reaction conditions the trioxadamantane 403 substrate slowly unravels to reform the original hemiacetal mixture (401 and 402). These reaction conditions facilitate rapid cyclisation of hemiacetal 401 back to the trioxadamantane 403 preventing an analogous retro-Claisen rearrangement of this acetal 401 to produce ester 406. The thermodynamic stability of the trioxadamantane 403 and its rapid formation from hemiacetal 401 enables this unique compound to operate as a protecting group against the analogous retro-Claisen rearrangement of hemiacetal 401. The slow formation of required hemiacetal 402 then proceeds to undertake the desired retro-Claisen rearrangement to form the preferred ester 405.
Reagents and Conditions: a. TAS-F (5.0eq), H₂O (10.0eq), DMF, RT, 2 hrs; b. DBU (cat), C₆D₆, RT, 8 hrs, then purified and recycled.

Scheme 4.25: Retro-Claisen rearrangement of hemiacetal 402 to give the acyclic ester 405 precursor

The ¹H NMR spectrum of ester 405 (Figure 4.39) shows an oxymethylene proton resonance at δ 5.45 (dd, J = 7.7, 4.1 Hz), which shows coupling to both the methyl methine proton multiplet signals at δ 3.08 and δ 2.10. This downfield oxymethylene resonance at δ 5.45 is indicative of an ester moiety. The methyl methine at δ 2.10 also shows additional coupling to the benzyloxymethylene proton resonance at δ 3.19 (dd, J = 7.1, 3.9 Hz). The benzyloxymethylene also displays the predicted coupling to the dimethyl methine resonance at δ 1.82 (mq, J = 6.9, 4 Hz) and in turn shows coupling to the methyl doublets at δ 1.00 (J = 6.9 Hz) and δ 0.97 (J = 6.9 Hz) completing the isopropyl carbon chain. The remaining oxymethylene proton resonates at δ 3.77 as a broad singlet and shows coupling to the
two methyl methine protons at δ 2.67-2.62 (m). The downfield chemical shift of this multiplet is indicative of the methyl methine protons location near carbonyl moieties. The resonances attributed to the two ethyl ketone diastereotopic methylene proton resonances occur between δ 2.22-1.99 (4H, m) and couple to the two methyl triplets at δ 0.95 (J = 7.2 Hz) and δ 0.92 (J = 7.2 Hz). The signals located at δ 7.40-7.10 and δ 4.66-4.53 account for the resonances attributed to the remaining benzyl protecting group. The $^{13}$C NMR spectrum of ester 405 (Figure 4.40) was in accordance with that expected for this compound. In particular, the two ketone carbonyl signals at δ 214 and δ 212 along with the newly constructed ester carbonyl at δ 174. The four oxymethine carbon signals at δ 86, δ 78, δ 76 and δ 74 and the benzyl protecting group resonances at δ 139, δ 129, δ 128 and δ 126.

![Figure 4.39: The $^1$H NMR spectrum of acyclic ester 405 precursor in C$_6$D$_6$](image-url)
4.3.12 Completion of the Total Synthesis of Dolabriferol

After several recycles through of trioxaadamantane 403 with DBU catalyst enough acyclic ester 405 precursor was sourced to proceed with the final crucial removal of the C₁₃ benzyl ether protecting group by hydrogenolysis.⁶⁰,⁶¹ (Scheme 4.26) The ester 405 was added to Pd/C and dissolved in anhydrous ethanol, then excess hydrogen gas was supplied and the mixture was stirred at ambient temperature for 12 hours, then filtered over a small amount of celite to remove the palladium catalyst. Concentration of the sample and spectroscopic analysis revealed that indeed the benzyl ether had definitely been removed under the conditions described above. Interestingly, the NMR spectra obtained did not match that of the natural product. On closer inspection though, there did appear to be a minor product within the initial NMR spectra that resembled that of the natural product, dolabriferol (10). After leaving the product mixture in the deuterated chloroform at room temperature overnight the sample was rerun, and on this occasion the spectra was in closer agreement with that of the natural product dolabriferol (10).
Leaving the sample at room temperature in the deuterated chloroform solvent was planned as it was believed prior to this the sample had been kept under extremely neutral conditions and that the product of the benzyl ether cleavage of ester 405 was likely just the non-cyclised form of dolabriferol (10). This assumption proved correct as after 12 hours at room temperature in deuterated chloroform NMR analysis confirmed that cyclisation had in fact occurred, and on purification by column chromatography dolabriferol (10) was achieved as a white powder in 92% yield.

The $^1$H NMR spectrum of dolabriferol (10), shown in Figure 4.41 shows an oxymethine proton resonance downfield at $\delta$ 5.25 (t, $J = 2.7$ Hz) indicative of an ester moiety, which shows coupling to both the methyl methine proton multiplet signals at $\delta$ 1.91 (dq, 7.2, 2.7 Hz) and $\delta$ 1.79 (dqd, 10.5, 6.9, 2.7 Hz). The methyl methine at $\delta$ 1.79 (dqd, 10.5, 6.9, 2.7 Hz) shows further coupling to the oxymethine proton resonance in the lactol ring at $\delta$ 3.60 (dd, 10.5, 2.2 Hz). This oxymethine resonance also displays additional coupling to the isopropyl group at $\delta$ 1.83 (dqq, 6.9, 2.2 Hz). The remaining oxymethine signal at $\delta$ 3.76 and the two hydroxyl protons at $\delta$ 3.61 and $\delta$ 3.46 appear as broad signals. Through $^1$H-$^1$H coupling experiments the broad oxymethine resonance at $\delta$ 3.76 is shown to display coupling to the methyl methine protons present at $\delta$ 2.79 (dq, 7.2, 7.2 Hz) and $\delta$ 2.73 (dq, 7.1, 4.8 Hz). The diastereotopic methylene adjacent to the carbonyl at $\delta$ 2.57 and $\delta$ 2.46 and the hemiketal methylene at $\delta$ 1.60 both appear as doublets of quartets, whereas the eight remaining methyl substituents appears as six doublets and two triplets between $\delta$ 1.33 and $\delta$ 0.78.
A Retro-Claisen Approach towards Dolabriferol

Figure 4.41: The $^1$H NMR spectrum of dolabriferol (10) in CDCl$_3$

Figure 4.42: The $^1$H NMR spectrum of authentic dolabriferol (10) in CDCl$_3$
Comparison of the $^1$H NMR spectra (shown in Figure 4.42) for authentic dolabriferol (10) shows that the synthetic material made herein is identical to that obtained by previous groups. This in turn matches the data published (Table 4.1) of the authentic isolated dolabriferol (10) sample by Ciavatta and co-workers. Comparison of the spectra also highlights that there are a number of extra signals present which can be attributed to minor impurities, as it was found that the natural product (10) appeared to decompose in the CDCl$_3$ NMR solvent. As a result, a carbon spectrum was unable to be obtained of the natural product (10) however; both $^1$H-$^1$H COSY and $^1$H-$^{13}$C HMQC experiments were obtained for dolabriferol (10) and are available in Appendix 1. High resolution mass spectrometry though verified the synthesised product possessed the molecular formula C$_{21}$H$_{38}$O$_6$, identical to that of the natural product dolabriferol (10), confirming its successful total synthesis in 17 linear synthetic steps from ($S$)-roche ester (337).

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Table 4.1: $^1$H and $^{13}$C spectral data acquired for dolabriferol (10) by Ciavatta and co-workers.

4.4 Conclusion

This research detailed above represents an unrefined total synthesis of the marine polypropionate natural product dolabriferol (10). The strategy as detailed above afforded synthetic dolabriferol (10) as a single observable isomer within a crude mixture in 0.63% overall yield from 17 linear steps beginning with (S)-roche ester (337). The synthesis employed lactate derived ketone 82 in three separate substrate controlled anti-boron mediated aldol reactions to install all but the C₆ stereocentre in dolabriferol (10), which was obtained directly from the commercially available (S)-roche ester (337), demonstrating its vast capability in the synthesis of complex natural products. The designed synthesis followed a pseudo-biomimetic approach, such that the ester moiety of dolabriferol (10) was created from an acyclic precursor through deprotection of trione 400 and retro-Claisen rearrangement of the resulting hemiacetal 402. This hemiacetal 402 was concealed within trioxaadamantane 403, and following retro-Claisen rearrangement gave ester precursor 405. The success obtained in this total synthesis of dolabriferol (10) illustrates that this unusual polypropionate ester linkage could be the direct result of a retro-Claisen fragmentation of an intermediate hemiacetal obtained from an entirely deprotected linear precursor in nature. As such, other known polypropionates like the baconipyrones A-D (276-279), siserrone A (280) and micromelones A-B (281-282) that possess this atypical ester linkage could be formed naturally and synthetically using this retro-Claisen approach.
Scheme 4.27: Summary of unrefined total synthesis to give dolabriferol (10)
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4.5 References

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A Retro-Claisen Approach towards Dolabriferol
5.1 General Procedures

Analytical thin layer chromatography (tlc) was conducted on aluminium-backed 0.2mm thick silica gel 60 \( F_{254} \) plates (Merck) and the plates were visualised under a 254nm UV lamp and/or by treatment with either anisaldehyde dip (p-anisaldehyde, 9.2mL; \( H_2SO_4 \), 12.5mL; \( CH_3CO_2H \), 3.75mL; EtOH, 338mL) or potassium permanganate dip (\( KMN_2O_4 \), 3.0g; \( K_2CO_3 \), 20g; 5% NaOH, 5mL; \( H_2O \), 300mL), followed by heating with heat gun. The retention factor (\( R_F \)) quoted is rounded the nearest 0.01. Column chromatography was conducted using silica gel 60 (mesh size 0.040-0.063mm) as the stationary phase and the analytical reagent solvents indicated. Purification of compounds with acid sensitivity, column chromatography was performed on buffered silica as indicated. Silica gel was buffered by spinning 100g of silica gel with 10mL of pH 7 phosphate buffer on a rotary evaporator overnight at atmospheric pressure.

Proton (\( ^1H \)) and carbon (\( ^{13}C \)) NMR spectra were recorded on a Bruker Ultrashield spectrometer operating at 400 or 600 MHz for proton and 100 or 150 MHz for carbon nuclei, respectively. Chemical shifts were recorded as \( \delta \) values in parts per million (ppm). Spectra were acquired in either deuterochloroform (\( CDCl_3 \)) or deuterobenzene (\( C_6D_6 \)) at ambient temperature. For \( ^1H \) NMR spectra recorded in \( CDCl_3 \), the peak due to residual \( CHCl_3 \) (\( \delta \) 7.26) was used as internal reference, and the spectra recorded in \( C_6D_6 \), the peak due to residual \( C_6H_6 \) (\( \delta \) 7.15) was used as internal reference. \( ^1H \) NMR data were recorded as follows: chemical shift (\( \delta \)), relative integral, multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, br = broad), coupling constants = J (Hz), assignment. For proton-decoupled \( ^{13}C \) NMR spectra recorded in \( CDCl_3 \), the central peak (\( \delta \) 77.0) of \( CDCl_3 \) triplet was used as the internal reference. The \( ^{13}C \) NMR spectra recorded in \( C_6D_6 \), the central peak (\( \delta \) 128.0) of the \( C_6D_6 \) triplet was used as the internal reference. The assignments recorded in the various NMR spectra were confirmed by conducting homonuclear (\( ^1H-^1H \)) correlation spectroscopy (COSY), attached proton test (APT), heteronuclear (\( ^1H-^{13}C \)) correlation spectroscopy (HMQC) experiments.
X-ray crystallography was performed at the Bragg Crystallography Facility at the University of Adelaide on a Mo-target Oxford Diffraction X-Calibur X-ray diffractometer. High resolution mass spectrometry using electrospray ionisation, was performed on a Waters/Micromass Quattro 2695 HPLC/MS/MS by direct injection into the MS/MS.

Most starting materials and reagents were available from the Sigma Aldrich Chemical Company and were used as supplied, or dried and distilled using standard procedures. Triethylamine (NEt₃), pyridine and commercially available aldehydes were distilled from calcium hydride under nitrogen prior to use. Purchased organolithium reagents were freshly standardised by titration prior to use. All reactions were performed under an atmosphere of nitrogen or argon unless otherwise specified, in flame-dried apparatus. Anhydrous reagents were handled under nitrogen using standard techniques.

Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried using sodium metal, and then distilled as required from sodium-benzophenone ketyl under nitrogen. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride under nitrogen as required. All other solvents used in reactions, extractions and column chromatography purification were distilled prior to use.

Room temperature (RT) varied between 20-30°C.
5.2 Experimental Procedures for Chapter Two

3-Hydroxy-butyric acid ethyl ester (124)

Sodium borohydride (436 mg; 11.5 mmol) was added to ethyl acetoacetate (126) (1.0 g; 7.7 mmol) in ethanol (40 mL) with stirring at -10°C, and the mixture was stirred for 30 minutes. The reaction was quenched at -10°C by the addition of saturated NH$_4$Cl solution (100 mL), extracted with Et$_2$O (3*100 mL), washed with brine (100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (20% Et$_2$O/CH$_2$Cl$_2$) gave the β-hydroxy ester 124 (0.88 g; 86%) as yellow oil. $R_f = 0.33$, $^1$H NMR (600MHz; CDCl$_3$) δ 4.20-4.13 (1H, m, CH$_2$(OH)) 4.15 (2H, q, 7.2 Hz, OCH$_2$CH$_3$) 3.09 (1H, brs, CH(OH)) 2.46 (1H, dd, 16.4, 3.4 Hz, CH(OH)CH$_2$CH$_3$(=O)) 2.40 (1H, dd, 16.4, 8.8 Hz, CH(OH)CH$_2$CH$_3$(=O)) 1.25 (3H, t, 7.2 Hz, OCH$_2$CH$_3$) 1.20 (3H, d, 6.4 Hz, CH$_3$CH(OH)) $^{13}$C NMR (150MHz; CDCl$_3$) δ 172.91, 64.17, 60.61, 42.69, 22.34, 14.10.

3-Oxo-butyric acid (125)

To a solution of ethyl acetoacetate (126) (2.0 g; 15.5 mmol) in THF (12 mL) and H$_2$O (130 mL) at room temperature was added a sodium hydroxide solution (50 mL; 0.5 M) and the mixture was stirred for 4 hours. The reaction mixture was washed with ethyl acetate (3*100 mL) and quenched via acidification to a pH of 2 using HCl (2 M). The organic layer was extracted with ethyl acetate (3*100 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give β-keto acid 125 (1.11 g; 70%) as a clear oil. $^1$H NMR (600MHz; CDCl$_3$) δ 11.26 (1H, brs, COOH) 3.49 (2H, s, C(=O)CH$_2$COOH) 2.26 (3H, s, CH$_3$C(=O)) $^{13}$C NMR (150MHz; CDCl$_3$) δ 201.17, 172.52, 64.17, 60.61, 42.69, 22.34, 14.10.
3-Oxo-butyric acid 2-ethoxycarbonyl-1-methyl-ethyl ester (123)

![Chemical structure of 123](image)

To a stirring solution of β-hydroxy-ester 124 (1.0 g; 7.6 mmol) in CH₂Cl₂ (150 mL) at 0°C was added DMAP (1.40 g; 11.6 mmol), then the β-keto acid 125 (1.60 g; 15.7 mmol) DCC (3.76 g; 18.2 mmol) was added and the reaction was stirred for 15 minutes at 0°C before warming to ambient temperature and stirring continued for 15 hours. The resulting suspended solution was filtered, crystals rinsed with CH₂Cl₂ (3*10 mL) and the filtrated concentrated in vacuo. The mixture was purified by column chromatography (5% Et₂O/CH₂Cl₂) to yield diester 123 (1.23 g; 75%) as yellow oil. Rf = 0.30, ¹H NMR (600MHz; CDCl₃) δ 5.27 (1H, m, CH₃C(HO)CH₂) 4.07 (2H, q, 7.2 Hz, OCH₂CH₃) 3.35 (2H, s, C(=O)C₃H₂C(=O)) 2.58 (1H, dd, 15.7, 7.7 Hz, C(=O)C₃H₂CH) 2.45 (1H, dd, 15.7, 5.5 Hz, C(=O)CH₃C) 2.19 (3H, s, CH₃C(=O)) 1.25 (3H, d, 6.4 Hz, CH₃CHO) 1.18 (3H, t, 7.2 Hz, OCH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 200.30, 169.86, 166.15, 68.33, 60.54, 50.07, 40.45, 29.88, 19.58, 13.97.

5-Hydroxy-3-oxo-hexanoic acid tert-butyl ester (143)

![Chemical structure of 143](image)

To a slurry of NaH (0.34 g; 0.025 mol) in THF (150 mL) t-butyl acetoacetate (141) (1.0 g; 6.32 mmol) was added at 0°C, and stirred for 10 minutes. The reaction was cooled to -10°C and n-BuLi (4.2 mL; 6.32 mmol) was added and the resulting mixture was stirred for an additional 10 minutes before being cooled to -78°C. Acetaldehyde (142) (0.75 mL; 0.06 mol) was added and the reaction was stirred for one hour at -78°C and then allowed to warm to RT. The reaction was quenched with NH₄Cl (70 mL), extracted with Et₂O (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo to give the acetate-alcohol product 143 (2.03 g) as a yellow oil which contained a minor amount of residual solvent that was used without further purification. Rf = 0.1 (10% Et₂O/CH₂Cl₂), ¹H NMR (200MHz, CDCl₃) δ 4.22 (1H, m, CH₃C(HO)CH₂) 3.38 (1H, d, 15 Hz, C(=O)CH₂C(=O)) 3.34 (1H, d, 15 Hz, C(=O)CH₂C(=O)) 2.66 (1H, dd, 12, 4 Hz, CH(OH)CC₂H₂C(=O)) 2.61 (1H, dd, 12, 4 Hz, CH(OH)CC₂H₂C(=O)) 1.44 (9H, s, C(CH₃)₃) 1.18 (3H, d, 6.4 Hz, CH₃CH(OH)) ¹³C NMR (50MHz, CDCl₃) δ 204.13, 166.15, 82.21, 63.68, 51.40, 51.02, 27.85, 22.31.
Experimental Procedures for Chapter Two

5-(tert-Butyl-dimethyl-silanyloxy)-3-oxo-hexanoic acid tert-butyl ester (144)

To a stirred solution of β-ketoester 143 (0.30 g; 14.8 mmol) in CH₂Cl₂ (40 mL) was added TBSOTf (0.50 mL; 22 mmol) and 2,6-lutidine (0.34 mL; 29.6 mmol) at -78°C. The reaction was stirred for 2 hours and then quenched with NaHCO₃ (50 mL) extracted with CH₂Cl₂ (3*20 mL) washed with brine (10 mL) dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (50%CH₂Cl₂/hexanes) gave the TBS-protected β-Keto-ester 144 (0.40 g; 84%) as a clear yellow oil. Rₚ = 0.33, ¹H NMR (200MHz, CDCl₃) δ 4.29 (1H, m, CH₃C(HOTBS)CH₂) 3.36 (2H, s, C(=O)C₆H₅C(=O)) 2.70 (1H, dd, 7, 15 Hz, CH(HOTBS)C(=O)₆H₅C(=O)) 2.53 (1H, dd, 7, 15 Hz, CH(HOTBS)C(=O)₆H₅C(=O)) 1.45 (9H, s, C₃(C₆H₃)₃) 1.17 (3H, d, 6 Hz, C₆H₅CH(HOTBS)CH₂) 0.85 (9H, s, OSi(CH₃)₂C(C₆H₃)₃) 0.05 (3H, s, OSi(C₆H₃)₂C(CH₃)₃) 0.03 (3H, s, OSi(CH₃)₂C(CH₃)₃) ¹³C NMR (50MHz, CDCl₃) δ 202.31, 166.33, 81.80, 65.50, 52.28, 52.03, 27.99, 25.78, 23.94, 17.94

Ethyl-3-oxo-2-acetylhexanoate (146)

Dry magnesium chloride (0.93 g; 10 mmol) in CH₂Cl₂ (10 mL) was added to a solution of ethyl acetoacetate (126) (1.3 mL; 10 mmol). The resulting mixture was immersed in an ice bath 0°C for 10 minutes then pyridine (1.6 mL; 20 mmol) was added. The reaction was allowed to stir for a further 15 minutes and then butyryl chloride (145) (1.1 mL; 10 mmol) was added. The resulting mixture was stirred for an additional 10 minutes at 0°C and four hours at room temperature. The mixture was cooled to 0°C and HCl (3 mL; 10.18 mol) was added, extracted with Et₂O (3*20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by vacuum distillation yielded the acylated product 146 (1.09 g; 64%) as a clear oil, Bp. (59°C 0.3 mmHg), ¹H NMR (200MHz, CDCl₃) δ 17.8 (1H, s, C=C(OH)) 4.26 (2H, m, 7 Hz, CH₃CH₂O) 2.62 (2H, t, 7.3 Hz, (C=O)CH₂CH₂CH₃) 2.34 (3H, s, CH₃(C=O)) 1.65 (2H, m, 7.3 Hz, CH₃CH₂CH₂) 1.34 (3H, t, 7 Hz,
Experimental Procedures for Chapter Two

OCH$_2$CH$_3$ 0.96 (3H, t, 7.3 Hz, CH$_2$CH$_3$CH$_3$); $^{13}$C NMR (50MHz, CDCl$_3$) δ 198.55, 195.66, 167.16, 108.56, 60.60, 39.51, 25.58, 19.11, 14.01, 13.71

5-(tert-Butyl-dimethyl-silyloxy)-2-butyryl-3-oxo-hexanoic acid tert-butyl ester (140)

Dry magnesium chloride (45 mg; 0.78 mmol) in CH$_2$Cl$_2$ (4 mL) was added to a solution of TBS-protected β-Ketoester 144 (150 mg; 0.47 mmol). The resulting mixture was immersed in an ice bath 0°C for 10 minutes then pyridine (76 μL; 0.94 mmol) was added. The reaction was allowed to stir for a further 15 minutes and then butyryl chloride (145) (49 μL; 0.47 mmol) was added. The resulting mixture was stirred for an additional 10 minutes at 0°C and four hours at room temperature. The mixture was cooled to 0°C and extracted with Et$_2$O (3*20 mL). The organic extracts were washed with aqueous CuSO$_4$ (2*20 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) yielded the TBS protected acylated product 140 (121 mg; 66%) as a clear oil. R$_f$ = 0.53, $^1$H NMR (200MHz, CDCl$_3$) δ 17.40 (1H, s, C=C(OH)) 4.33 (1H, m, CH$_3$CH(OTBS)CH$_3$) 2.80 (1H, dd, 7, 15 Hz, CH(OTBS)CC(CH$_3$)$_2$C(=O)) 2.63 (1H, dd, 7, 15 Hz, CH(OTBS)CC(CH$_3$)$_2$C(=O)) 2.54 (2H, m, C(=O)CH$_2$CH$_2$CH$_3$) 1.66 (2H, m, C(=O)CH$_2$CH$_2$CH$_3$) 1.55 (9H, s, C(CH$_3$)$_3$), 1.19 (3H, d, 6 Hz, CH$_2$CH(OTBS)CH$_3$) 0.96 (3H, t, 7.2 Hz, C(=O)CH$_2$CH$_2$CH$_3$) 0.84 (9H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$) 0.03 (3H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$) -0.01 (3H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$) $^{13}$C NMR (50MHz, CDCl$_3$) δ 197.43, 194.00, 166.73, 111.72, 81.52, 66.36, 46.78, 39.44, 28.12, 25.72, 24.30, 19.23, 17.93, 13.88.

3-Butyryl-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one (139)

To a stirring solution of the TBS-protected compound 140 (50 mg; 0.13 mmol) in THF (1 mL) was added HF/Pyridine/Pyridine (860 μL; 0.13 mmol) and H$_2$O (86 μL) at RT. The reaction was stirred at RT for one
day then diluted with Et<sub>2</sub>O (10 mL) and quenched with NaHCO<sub>3</sub> (20 mL). The organic extract was washed with CuSO<sub>4</sub> (20 mL), brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The deprotected TBS compound (20 mg; 0.07 mmol) was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and TFA (1 μL; 0.007 mmol) was added at RT. The reaction was stirred at room temperature for one day then concentrated in vacuo. Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) yielded the model compound **139** (8 mg; 57%) as a clear oil, R<sub>f</sub> = 0.60, <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ 13.17 (1H, bs, C=C(OH)) 4.62 (1H, m, OCH(CH<sub>3</sub>)CH<sub>2</sub>) 3.03 (2H, m, OCH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>C(=O) 2.63 (2H, t, 5.6 Hz, C(=O)CH<sub>2</sub>CH<sub>2</sub>) 1.70 (2H, m, C(=O)CH<sub>2</sub>CH<sub>3</sub>) 1.54 (3H, d, 6 Hz, OCH(CH<sub>3</sub>)CH<sub>2</sub>) 0.99 (3H, t, 7.2 Hz, C(=O)CH(CH<sub>3</sub>)<sub>2</sub>) 13<sup>C</sup> NMR (50MHz, CDCl<sub>3</sub>) δ 195.36, 192.93, 164.60, 106.04, 75.60, 41.16, 37.04, 20.46, 19.82, 13.96

**Para-methoxybenzyl trichloroacetimidate (147)**

![Chemical Structure](image)

To a solution of p-methoxy benzyl alcohol (148) (18 mL; 0.14 mol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at 0°C was added 50% aqueous KOH (100 mL) followed by tetrabutylammonium hydrogen sulphate (0.3 g) and the resulting mixture was stirred vigorously. After five minutes trichloroacetonitrile (17 mL; 0.16 mol) was added dropwise and the resulting mixture was warmed to room temperature and stirred for two hours. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3* 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Purification by kugelrhor Bp. 150°C at 1.0 mmHg gave PMB-imidate 147 (36.3 g; 94%) as clear oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.39 (1H. s, NH) 7.39 (2H, d, 8.6 Hz, ArH) 6.92 (2H, d, 8.6 Hz, ArH) 5.29 (2H, s, OCH<sub>2</sub>PMP) 3.82 (3H, s, OCH<sub>3</sub>) 13<sup>C</sup> NMR (100MHz; CDCl<sub>3</sub>) δ 207.33, 162.64, 159.78, 129.75, 127.56, 113.94, 70.77, 55.25.
(S)-Ethyl 2-(4-methoxybenzyloxy) propanoate (133)

\[
\text{HO} \quad \text{O} \quad \text{Et} \quad \overset{\text{PMB-Imidate}}{\text{C}} \quad \text{SA} \quad \text{132} \quad \overset{\text{O}}{\text{Et}} \quad \text{O} \quad \\
\]

To a solution of ethyl-(S)-lactate (132) (10.0 mL; 0.07 mol) in CH₂Cl₂ (400 mL) PMB-imidate 147 (25 mL; 0.09 mol) was added at 25°C. CSA (2.02 g; 8.40 mmol) was added in portions, and the reaction mixture stirred at room temperature for 4 days, during this time additional PMB-imidate and CSA were added as appropriate by TLC analysis. The reaction was quenched with NaHCO₃ (200 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3*100 mL). Organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. The slurry produced was triturated (25% CH₂Cl₂/hexanes) and concentrated in vacuo. Purification by column chromatography (2% Et₂O/CH₂Cl₂) gave the protected hydroxy-ester 133 (11.84 g, 71%) as yellow oil. Rₐ = 0.23 (CH₂Cl₂), ¹H NMR (600MHz, CDCl₃) δ 7.26 (2H, d, 8.2 Hz, ArH), 6.85 (2H, d, 8.2 Hz, ArH), 4.60 (1H, d, 11.1 Hz, OCH₂CH₂PMP), 4.36 (1H, d, 11.1 Hz, OCH₂CH₂PMP), 4.19 (2H, q, 7 Hz, OCH₂CH₃), 3.99 (1H, q, 6.8 Hz, CH(CH₂)OPMB), 3.77 (3H, s, OCH₂CH₃), 1.39 (3H, d, 6.8 Hz, CH(C₂H₅)OPMB), 1.28 (3H, t, 7 Hz, OCH₂CH₃), ¹³C NMR (150MHz, CDCl₃) δ 173.20, 159.23, 129.55, 129.50, 113.66, 73.57, 71.47, 60.64, 55.11, 18.57, 14.10.

(S)-1-Bromo-3-(4-Methoxybenzyloxy)-butan-2-one (134)

\[
\text{O} \quad \text{O} \quad \text{Et} \quad \overset{\text{CH}_2\text{Br}_2}{\text{CH}_3\text{Li}} \quad \text{133} \quad \overset{\text{O}}{\text{Br}} \quad \\
\]

To a solution of stirring hydroxy-ester 133 (5.0 g; 21 mmol) and CH₂Br₂ (2.95 mL; 42 mmol) in THF (38 mL) CH₃Li (26.5 mL of a 1.6 M solution in Et₂O; 42 mmol) was added dropwise at -78°C. The solution was stirred for 2 hours, then acetic acid (5 mL; 84 mmol) was added and the temperature was allowed to rise to 0°C for 15 minutes. The reaction was poured into an ice-water solution (150 mL), extracted with diethyl ether (3*100 mL), washed with brine (100 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the brominated-ketone 134 (4.76 g, 79%) as a yellow oil. Rₐ = 0.40, ¹H NMR (600MHz, CDCl₃) δ 7.27 (2H, d, 7.2 Hz, ArH), 6.89 (2H, d, 7.2 Hz, ArH), 6.55 (2H, d, 7.2 Hz, ArH).
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(1H, d, 11 Hz, OCH$_3$CH$_2$PMP) 4.50 (1H, d, 11 Hz, OCH$_3$CH$_2$PMP) 4.18 (1H, q, 6.8 Hz, CHOPMB) 4.15 (2H, s, CH$_2$Br) 3.80 (3H, s, OCH$_3$) 1.38 (3H, d, 6.8 Hz, CH(CH$_3$)OPMB)

$^{13}$C NMR (150MHz, CDCl$_3$) δ 203.41, 159.59, 129.66, 129.11, 114, 78.63, 71.87, 55.31, 31.95, 17.25

(S)-1-Acetoxy-3-(p-methoxybenzylxoy)-butan-2-one (135)

To a solution of brominated ketone 134 (3.8 g; 13.5 mmol) in DMF (60 mL) anhydrous NaOAc (6.6 g; 80.5 mmol) was added and the resulting mixture stirred at RT for 4hrs. The mixture was poured into cold water (150 mL), extracted with diethyl ether (3*100 mL), washed with brine (50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave the ester product 135 (2.87 g; 80%) as a clear yellow oil, R$_f$ 0.15, $^1$H NMR (600MHz, CDCl$_3$) δ 7.23 (2H, d, 8.3 Hz, ArH) 6.85 (2H, d, 8.3 Hz, ArH) 4.90 (1H, d, 17.6 Hz, OCH$_3$CH$_2$C(=O)) 4.84 (1H, d, 17.6 Hz, OCH$_3$CH$_2$C(=O)) 4.50 (1H, d, 11 Hz, OCH$_3$CH$_2$PMP) 4.45 (1H, d, 11 Hz, OCH$_3$CH$_2$PMP) 3.99 (1H, q, 6.8 Hz, CH(CH$_3$)OPMB) 3.75 (3H, s, OCH$_3$) 2.10 (3H, s, CH$_3$C(=O)) 1.32 (3H, d, 6.8 Hz, CH(CH$_3$)OPMB) $^{13}$C NMR (150MHz, CDCl$_3$) δ 204.93, 169.97, 159.28, 129.25, 129.05, 113.71, 78.78, 71.31, 65.80, 65.72, 54.96, 20.18, 16.73.

Methyl triphenylphosphonium Iodide (149)

To a solution of triphenylphosphine (20.0 g; 76.3 mmol) in Et$_2$O (100 mL) was added methyl iodide (4.73 mL; 76.0 mmol) and the resulting solution was stirred at room temperature for 4 days. The precipitate was filtered under vacuum and washed with Et$_2$O (3*30 mL). The salt was dried under vacuum to give the ylide salt 149 (25.6 g; 83%) as a white powder which was used without further purification. m.p. 182°C, $^1$H NMR (400MHz; CDCl$_3$) 7.78-7.67 (15H, m, ArH) 3.25 (3H, d, 13.2 Hz, PCH$_3$).
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**(S)-3-(4-Methoxy-benzyloxy)-2-methylene-butan-1-ol (137)**

![Chemical structure of 135 and 137](image)

To a stirred suspension of CH3Ph3P (149) (1.2 g; 4 mmol) in THF (25 mL) at -78°C was added n-BuLi (2.5 mL of a 1.6 M solution in Et2O; 4 mmol). The temperature was allowed to rise to ambient temperature, and when the solution became clear the mixture was cooled back to -78°C. The ester 135 (1.0 g; 3.8 mmol) was added via cannula (5 mL; THF) and the reaction was warmed slowly to RT, stirred for 30 minutes, diluted with diethyl ether (50 mL), filtered through celite and concentrated in vacuo. The crude intermediate product 136 was dissolved in anhydrous methanol (25 mL), K2CO3 (55 mg; 0.4 mmol). The mixture was stirred at room temperature for 3 hours then filtered through celite and concentrated in vacuo. Purification by column chromatography (20% Et2O/CH2Cl2) yielded the hydroxy-alkene 137 (0.65 g; 77%) as clear oil. Rf = 0.20, 1H NMR (600MHz, CDCl3) δ 7.27 (2H, d, 8.5 Hz, ArH), 6.89 (2H, d, 8.5 Hz, ArH) 5.22 (1H, s, HOCH2C=CH2), 5.12 (1H, s, HOCH2C=CH2), 4.48 (1H, d, 11.4 Hz, OC=CH2PMP) 4.34 (1H, d, 11.4 Hz, OCH3CH2PMP) 4.29 (1H, d, 13.5 Hz, CH2CH2OH) 4.17 (1H, d, 13.5 Hz, CH2CH2OH) 4.10 (1H, q, 6.6 Hz, CH(CH3)OPMB) 3.81 (3H, s, OC3H3) 1.36 (3H, d, 6.6 Hz, CH(CH3)OPMB) 13C NMR (150MHz, CDCl3) δ 159.18, 148.52, 130.34, 128.62, 113.83, 112.67, 77.10, 69.91, 63.14, 55.25, 20.19.

**(S)-3-(4-Methoxy-benzyloxy)-2-methylene-butyraldehyde (131)**

![Chemical structure of 137 and 131](image)

To a stirring solution of the hydroxy-alkene 137 (0.5 g; 2.24 mmol) in CH2Cl2 (30 mL) was added DMP (1.25 g; 2.91 mmol). The reaction was stirred for one hour then quenched with Na2S2O3 (3.6 g in 60 mL of NaHCO3) diluted with diethyl ether (40 mL) washed with NaHCO3 (30 mL), brine (20 mL), dried (Na2SO4) and concentrated in vacuo. Purification by column chromatography (CH2Cl2) yielded the α-β-unsaturated aldehyde 131 (0.46 g; 94%) as a clear oil. Rf = 0.33, 1H NMR (600MHz; CDCl3) δ 9.66 (1H, s, CH=O), 7.28 (2H, d, 8.4 Hz, ArH) 6.91 (2H, d, 8.4 Hz, ArH) 6.61 (1H, s, CH3CH2) 6.17 (1H, s, CH=CH2)
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4.48-4.35 (1H, m, CH(CH₃)OPMB) 4.44 (1H, d, 11.1 Hz, OCH₆CH₆PMP) 4.37 (1H, d, 11.1 Hz, OCH₆CH₆PMP) 3.83 (3H, s, OCH₃) 1.35 (3H, d, 6.3 Hz, CH(CH₃)OPMB) 7.15 (1H, s, CHOPMB). 13C (150MHz; CDCl₃) δ 193.75, 159.07, 151.70, 133.56, 130.16, 129.10, 113.67, 70.57, 70.46, 55.11, 21.28

2-Iodoxybenzoic acid (151)

\[
\begin{align*}
\text{152} & \quad \text{KBrO}_3 \quad \text{H}_2\text{SO}_4 \\
\text{151} & \quad
\end{align*}
\]

To a mixture of 2-iodobenzoic acid (152) (45.8 g; 0.18 mol) in a 0.7 M solution of H₂SO₄ (370 mL) at 55°C was added KBrO₃ (40.2 g; 0.24 mol) in small portions over 30 minutes. The resulting mixture was stirred at 70°C for 4 hours. The mixture is cooled on ice and filtered under vacuum, washed with H₂O (500 mL) and EtOH (2*50 mL). The product was dried on a high vacuum pump to give the 2-Iodoxybenzoic acid (151) (50 g; 96%) as a white solid, m.p. 232-234°C.

1,1,1-Triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1H)-one (150)

\[
\begin{align*}
\text{151} & \quad \text{p-TsOH} \quad \text{Ac}_2\text{O} \\
\text{150} & \quad
\end{align*}
\]

To a solution of 2-iodoxybenzoic acid (151) (50 g; 0.17 mol) in dry acetic anhydride (250 mL) under argon atmosphere was added p-TsOH.H₂O (250 mg; 0.74 mmol). The mixture was heated at 80°C for 2-3 hrs then cooled on ice overnight. The solid precipitate was filtered under vacuum and washed with Et₂O (5*50 mL) then dried on the high vacuum pump to give Dess-Martin periodinane (150) (55 g, 76%) as a fine white solid, m.p. 132°C The product was transferred to an amber glass bottle under a stream of nitrogen and stored in the freezer.
(S)-3-Hydroxy-5-(4-methoxy-benzylxy)-4-methylene-hexanoic acid tert-butyl ester (129)

![Chemical structure of the reaction](image)

To a solution of LiHMDS (4 mL; of a 1 M solution in THF; 4 mmol) in THF (10 mL) at -78°C t-butyl acetate (130) (0.46 g; 4 mmol) was added and the reaction was stirred for 30 minutes, then aldehyde 131 (0.5 g; 2.27 mmol) was added via cannula (10 mL; THF) and the reaction was stirred at this temperature for 30 minutes before being warmed to 0°C over 2 hours. The reaction was further stirred for 30 minutes at this temperature then quenched with NH₄Cl (100 mL), extracted Et₂O (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (5% Et₂O/CH₂Cl₂) gave the acetate-aldol product 129 (0.72 g; 95%) as a clear oil. Rf = 0.32, ¹H NMR (600MHz, CDCl₃) δ 7.26 (2H, d, 8.1 Hz, ArH) 6.87 (2H, d, 8.1 Hz, ArH) 5.30 (1H, s, CH₃CHC(=CCH₂PMP)) 5.21 (1H, s, CH₃CHC(=CHCH₂PMP)) 4.60 (1H, m, CHO) 4.44 (1H, d, 12 Hz, OCH₃CH₂CHB) 4.30 (1H, d, 12 Hz, OCH₃CH₂PMP) 4.08 (1H, q, 6.6 Hz, CH₃OPMB) 3.80 (3H, s, OCH₃) 2.59 (2H, m, C(=O)CH₂C(=O)) 1.46 (9H, s, C(CH₃)₃) 1.36 (3H, d, 6.6 Hz, CH₃CHPMB) ¹³C NMR (150MHz, CDCl₃) δ 172.08, 159.10, 150.41, 130.50, 129.21, 113.76, 112.13, 81.30, 75.97, 59.80, 67.87, 65.21, 41.82, 28.04, 20.74

Pyridinium chlorochromate (153)

![Chemical structure of the reaction](image)

Concentrated hydrochloric acid (8.3 mL; 0.1 mol) was added dropwise to pyridine (8.1 mL; 0.1 mol) at 0°C. The mixture was stirred for 10 minutes then added to solid CrO₃ (10 g; 0.1 mol) and stirring continued vigorously for 30 minutes to produce an orange precipitate. The solid was collected via filtration and washed with cold water (2*10 mL) to give pyridinium chlorochromate (153) (17.2 g; 80%) as an orange powder, m.p. 206°C.
(S)-5-(4-Methoxy-benzylx)oxo-4-methylene-3-oxo-hexanoic acid tert-butyl ester (128)

To a stirring solution of β-hydroxy ester 129 (500 mg; 1.5 mmol) in CH₂Cl₂ (10 mL) was added PCC (690 mg; 3.2 mmol) and celite (690 mg 1:1 w/w with PCC) in one portion at room temperature. The reaction mixture was stirred for 4 hours, then filtered through celite and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) produced the β-keto ester 128 (375 mg; 75%) as clear oil. \( R_f = 0.60 \),

**Ketone:** \(^{1}\)H NMR (600MHz, CDCl₃) δ 7.23 (2H, d, 8.6 Hz, ArH) 6.88 (2H, d, 8.6Hz, ArH) 6.24 (1H, s, CH₃CHC(=C(CH₃)CH₃)) 6.15 (1H, s, CH₃CHC(=CH(CH₃)CH₃)) 4.44 (1H, q, 6.6 Hz, CHOPMB) 4.36 (1H, d, 12 Hz, OC(H)CH₂CH₂PMP) 4.32 (1H, d, 12 Hz, OCH₂CH₂PMP) 3.80 (3H, s, CH₃) 3.68 (1H, d, 15 Hz, C(=O)CH₂CH₂C(=O)) 3.62 (1H, d, 15 Hz, C(=O)CH₂CH₂C(=O)) 1.45 (9H, s, C(CH₃)₃) 1.28 (3H, d, 6.6 Hz, CH₂CH₂PMP) 13C NMR (150MHz, CDCl₃) δ 193.95, 166.65, 159.20, 150.20, 130.44, 129.31, 125.32, 113.83, 81.98, 71.88, 70.57, 55.27, 47.14, 27.92, 22.01.

**Enol:** \(^{1}\)H NMR (600MHz; CDCl₃) δ 12.35 (1H, s, COH) 7.25 (2H, d, 8.6 Hz, ArH) 6.93 (2H, d, 8.6Hz, ArH) 6.01 (1H, s, CH₃CHC(=CH(CH₃)CH₃)) 5.62 (1H, s, CH₃CHC(=CH(CH₃)CH₃)) 5.27 (1H, s, C(O)=CHC(=O)) 4.52 (1H, q, 6.6 Hz, CHOPMB) 4.45 (1H, d, 12 Hz, OCH₂CH₂PMP) 4.25 (1H, d, 12 Hz, OCH₂CH₂PMP) 3.81 (3H, s, CH₃) 1.43 (9H, s, C(CH₃)₃) 1.36 (3H, d, 6.6 Hz, CH₂CH₂PMP)

**(S)-2-Methyl butyric acid (155)**

To a solution of (S)-2-methyl butanol (154) (5 g; 56.7 mmol) in acetone (115 mL) at 0°C was added a premixed solution of CrO₃ (10 g; 0.1 M), H₂SO₄ (8.6 mL) and H₂O (36 mL) dropwise until an orange colour persisted in the reaction mixture. The mixture was stirred for 30 minutes at 0°C, and then ethanol was added to quench the excess Jones reagent as indicated by a deep-green reaction mixture. The mixture was extracted with Et₂O (2*100 mL) and the combined organic extracts were washed with a solution of saturated sodium bicarbonate solution (100 mL), dried (Na₂SO₄) and concentrated in vacuo. Distillation
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of the concentrated mixture gave (S)-2-methyl-butanoic acid (155) (4.92 g; 85%) as a clear oil. b.p. 78°C; 15mmHg, 1H NMR (600MHz; CDCl₃) δ 2.38 (1H, qn, 7.0 Hz, CHCH₃) 1.69 (1H, dqn, 14.2, 7.7 Hz, CH₂CH₂CH₃) 1.48 (1H, dqn, 14.2, 7.7 Hz, CH₃CH₂CH₃) 1.15 (3H, d, 7.0 Hz, CH₃) 0.92 (3H, t, 7.7 Hz, CH₂CH₃) 13C NMR (150MHz; CDCl₃) δ 183.49, 40.85, 26.45, 16.25, 11.43.

(S)-2-Methyl-butyryl chloride (120)

Thionyl Chloride (7.50 mL; 103 mmol) was added dropwise to (S)-2-methyl-butanoic acid (155) (3.50 g; 35 mmol) at room temperature. The mixture was heated at 50°C for 2 hours, then distilled to remove excess SOCl₂ (78°C) and give the (S)-2-methyl butyryl chloride (120) product (3.6 g; 86%) as a clear oil. b.p. 112-115°C, 1H NMR (600MHz; CDCl₃) δ 2.80 (1H, qn, 6.9 Hz, CHCH₃) 1.82 (1H, dqn, 14.2, 7.7 Hz, CH₃CH₂CH₃) 1.60 (1H, dqn, 14.2, 7.7 Hz, CH₃CH₂CH₃) 1.27 (3H, d, 6.9 Hz, CHCH₃) 0.97 (3H, t, 7.7 Hz, CH₂CH₃) 13C NMR (150MHz; CDCl₃) δ 177.72, 52.94, 26.58, 16.53, 11.17.

5-(4-Methoxy-benzylxy)-3-(2-methyl-butyryloxy)-4-methylene-hex-2-enoic acid tert-butyl ester (127)

Dry magnesium chloride (15 mg; 0.16 mmol) in CH₂Cl₂ (3 mL) was added to a solution of unsaturated β-keto ester 128 (50 mg; 0.16 mmol). The resulting mixture was immersed in an ice bath 0°C for 10 minutes then pyridine (26 µL; 0.32 mmol) was added. The reaction was allowed to stir for a further 15 minutes and then (S)-2-methyl butyryl chloride (120) (25 µL; 0.20 mmol) was added. The resulting mixture was stirred for an additional 10 minutes at 0°C and four hours at room temperature. The mixture was cooled to 0°C and pH 7 buffer solution (10 mL) was added and extracted with Et₂O (3*10 mL). The organic extracts were washed with CuSO₄ solution (5 mL), then dried (Na₂SO₄) and
concentrated in vacuo. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had occurred and that β-keto ester $128$ was recovered following purification by column chromatography.

5-(4-Methoxy-benzyloxy)-2-(2-methyl-butyryl)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (127)

To a solution of racemic unsaturated β-keto ester $128$ (100 mg; 0.30 mmol) in THF (1 mL) at -78°C was added $^1$PrMgCl (0.15 mL of a 2 M solution in hexanes; 0.30 mmol). The mixture was stirred at -78°C for 15 minutes, then (S)-2-methyl butyryl chloride ($120$) (44 µL; 0.35 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred for an additional two hours at -78°C then warmed to room temperature for a further 15 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with $\text{Et}_2\text{O}$ ($3\times5$ mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had occurred and that β-keto ester $128$ was recovered following purification by column chromatography.

5-(4-Methoxy-benzyloxy)-2-(2-methyl-butyryl)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (127)

To a solution of racemic unsaturated β-keto ester $128$ (150 mg; 0.45 mmol) in THF (1.5 mL) at -78°C was added t-BuLi (0.26 mL of a 1.7 M solution in hexanes; 0.46 mmol). The mixture was stirred at -78°C for 15 minutes, then (S)-2-methyl butyryl chloride ($120$) (68 µL; 0.55 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred for an additional two hours at -78°C then warmed to room temperature for a further two hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with $\text{Et}_2\text{O}$ ($3\times5$ mL), dried (Na$_2$SO$_4$) and concentrated in vacuo.
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_vacuo_. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had occurred and that β-keto ester 128 was recovered following purification by column chromatography.

**Methylacryloyl chloride (158)**

\[
\begin{align*}
\text{159} & \quad \text{(COCl)}_2 \\
\text{CH}_2\text{Cl}_2/\text{DMF} & \quad \text{158}
\end{align*}
\]

To a solution of methylacrylic acid (159) (5.0 g; 5.8 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C was added DMF (5 drops) and oxalyl chloride (3 mL of a 2 M solution in CH$_2$Cl$_2$; 6 mmol) dropwise. The mixture was heated to reflux (40°C) for 3 hours then distilled to give the acid chloride 158 (4.32 g; 72%) as clear viscous oil. b.p. 98°C, $^1$H NMR (400MHz; C$_6$D$_6$) δ 6.14 (1H, s, C=C\text{CH}_\text{B}) 5.20 (1H, s, C=CH\text{A}\text{C}\text{H}_\text{B}) 1.71 (3H, s, CC\text{H}_3).

**2-Acetyl-4-methyl-3-oxo-pent-4-enoic acid ethyl ester (160)**

\[
\begin{align*}
\text{126} & \quad \text{i}^1\text{PrMgCl} \\
\text{160}
\end{align*}
\]

To a solution of ethyl acetoacetate (126) (75 µL; 0.76 mmol) in THF (5 mL) at -78°C was added i^1\text{PrMgCl} (0.45 mL of a 2 M solution in THF; 0.9 mmol) dropwise. The mixture was stirred for 30 minutes then methacryloyl chloride (158) (80 mg; 0.76 mmol) was also added in dropwise. The reaction mixture was stirred for 2 hours at -78°C then warmed to room temperature for a further 30 minutes and quenched with a saturated NH$_4$Cl solution (10 mL), extracted with Et$_2$O (3*10 mL), dried (Na$_2$SO$_4$) and concentrated _in vacuo_. Purification by column chromatography (CH$_2$Cl$_2$) gave the tricarbonyl adduct 160 (97 mg; 65%) as clear oil. R$_f$ = 0.74, **Ketone:** $^1$H NMR (600MHz; CDCl$_3$) δ 5.76 (1H, s, C=C\text{CH}_\text{A}\text{CH}_\text{B}) 5.11 (1H, s, C=CH\text{A}\text{C}\text{H}_\text{B}) 4.24 (2H, q, 7.3 Hz, O\text{CH}_2\text{CH}_3) 3.71 (1H, s, C(=O)\text{CH}(=O)) 2.28 (1H, s, C(=O)\text{CH}_3) 1.92 (3H, s, CH$_3$C=CH$_2$) 1.27 (3H, t, 7.3 Hz, O\text{CH}_2\text{CH}_3), **Enol:** $^1$H NMR (600MHz; CDCl$_3$) δ 16.85 (1H, s, COH) 5.77 (1H, s, C=CH$_2$) 5.22 (1H, s, C=CH$_2$) 4.15 (2H, q, 7.3 Hz, O\text{CH}_2\text{CH}_3) 2.31 (3H, s, C(=O)\text{CH}_3) 1.96 (3H, brs, CH$_3$C=CH$_2$) 1.25
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(3H, t, 7.3 Hz, OCH₂CH₃) Enol 1: ¹H NMR (600MHz; CDCl₃) δ 12.86 (1H, s, COH) 5.77 (1H, s, C=CH₂CH₃) 5.24 (1H, s, C=CH₂CH₃) 4.18 (2H, q, 7.3 Hz, OCH₂CH₃) 2.27 (3H, s, C=CH₂CH₃) 1.93 (3H, brs, CH₃C=CH₂) 1.21 (3H, t, 7.3 Hz, OCH₂CH₃)

2-Acetyl-4-methyl-3-oxo-pent-4-enoic acid tert-butyl ester (161)

![Reaction diagram]

To a solution of t-butyl acetoacetate (141) (104 µL; 0.63 mmol) in THF (5 mL) at -78°C was added iPrMgCl (0.38 mL of a 2 M solution in THF; 0.75 mmol) dropwise. The mixture was stirred for 30 minutes then methacryloyl chloride (158) (66 mg; 0.63 mmol) was also added in dropwise. The reaction mixture was stirred for 2 hours at -78°C then warmed to room temperature for a further 30 minutes and quenched with a saturated NH₄Cl solution (10 mL), extracted with Et₂O (3×10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the tricarbonyl adduct 161 (101 mg; 71%) as clear oil. Rf = 0.71, Ketone: ¹H NMR (600MHz; CDCl₃) δ 6.03-5.99 (1H, m, C=C₇H₃CH) 5.84-5.80 (1H, m, C=CH₂CH₃) 4.85 (1H, s, C(=O)C₇H₃) 2.18 (3H, s, C(=O)C₇H₃) 1.91 (3H, m, C₇H₃C=CH₂) 1.47 (9H, s, OC(C₇H₃)₃) ¹³C NMR (150MHz; CDCl₃) 199.18, 192.41, 164.55, 144.18, 126.84, 83.23, 69.02, 29.22, 27.97, 19.05. Enol 1: ¹H NMR (600MHz; CDCl₃) δ 16.69 (1H, s, COH) 5.70-5.67 (1H, m, C=CH₂CH₃) 5.25-5.22 (1H, m, C=CH₂CH₃) 2.28 (3H, s, C(=O)CH₃) 1.95 (3H, brs, CH₃C=CH₂) 1.44 (9H, s, OC(CH₃)₃) ¹³C NMR (150MHz; CDCl₃) 196.24, 176.60, 170.67, 146.64, 124.52, 105.98, 82.54, 27.98, 24.25, 17.22. Enol 2: ¹H NMR (600MHz; CDCl₃) δ 12.99 (1H, s, COH) 5.88-5.86 (1H, m, C=CH₂CH₃) 5.71-5.68 (1H, m, C=CH₂CH₃) 2.25 (3H, s, C(=O)CH₃) 1.89 (3H, brs, CH₃C=CH₂) 1.40 (9H, t, 7.3 Hz, OC(CH₃)₃) ¹³C NMR (150MHz; CDCl₃) 193.81, 192.80, 166.77, 142.53, 118.16, 109.97, 81.42, 27.72, 19.55, 17.44.
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(5)-2-Methyl butyraldehyde (162)

To a solution of DMSO (5 mL; 72 mmol) in CH₂Cl₂ (180 mL) at -78°C was added oxalyl chloride (18 mL of a 2 M solution in CH₂Cl₂; 36 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 151 (2.0 g; 24 mmol) in CH₂Cl₂ (20 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt₃ (20 mL; 144 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH₄Cl (200 mL) then extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and carefully concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the desired aldehyde 162 (1.86 g; 90%) as a colourless oil. Rᶠ = 0.55, ¹H NMR (600MHz; CDCl₃) δ 9.63 (1H, d, 1.9 Hz, CHO), 2.33-2.18 (1H, m, CH₃CH₂CH₃), 1.85-1.64 (1H, m, CH₂CH₃CH₃) 1.54-1.33 (1H, m, CH₂CH₃CH₃) 1.09 (3H, d, 7.0 Hz, CH₃CH₃) 0.95 (3H, t, 7.3 Hz, CH₂CH₃) ¹³C NMR (100MHz; CDCl₃) δ 205.52, 47.74, 23.58, 12.85, 11.33.

3-Hydroxy-4-methyl-hexanoic acid tert-butyl ester (163)

To a solution of LiHMDS (34 mL of a 1 M solution in THF; 34 mmol) in THF (20 mL) at -78°C was added t-butyl acetate (130) (4.0 mL; 30 mmol) and the reaction was stirred for 30 minutes, then aldehyde 162 (1.0 g; 11.6 mmol) was added via cannula (THF; 30 mL) and the reaction was stirred at this temperature for 1 hour before being warmed to 0°C over 2 hours. The reaction was quenched with NH₄Cl (80 mL), extracted Et₂O (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% Et₂O/hexanes) gave the acetate-aldol products 163 (1.78 g; 76%) as a mixture of inseparable isomers. Rᶠ = 0.24, ¹H NMR (400MHz; CDCl₃) δ 3.93-3.77 (1H, m, CHO), 2.81 (1H, brs, CHO), 2.45-2.30 (2H, m, C(OH)CH₂C(=O)) 1.58-1.71 (11H, m, CHCH₃, CH₂CH₃CH₂, OC(CH₃)₃) 1.22-1.09 (1H, m, CH₂CH₃CH₃) 0.94-0.86 (6H, m, CHCH₃, CH₂CH₃) ¹³C NMR (100MHz; CDCl₃) δ 172.89, 80.94, 71.52, 39.69, 38.87, 27.97, 25.38, 14.31, 11.61.
4-Methyl-3-oxo-hexanoic acid tert-butyl ester (156)

![Chemical structure](image1)

To a stirring solution of β-hydroxy ester 163 (1.0 g; 5.0 mmol) in CH₂Cl₂ (40 mL) was added PCC (2.15 g; 10 mmol) and celite (2.15 g 1:1 w/w with PCC) in one portion at room temperature. The reaction mixture was stirred for 4 hours, then filtered through celite and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) produced the β-keto ester 156 (0.82 g; 82%) as clear oil. Rᵢ = 0.43,

**Ketone:** ¹H NMR (600MHz; CDCl₃) δ 3.37 (2H, s, C(=O)C₂H₂C(=O)) 2.56 (1H, dq, 6.9, 6.6 Hz, C₂H₃CH₃) 1.73-1.66 (1H, m, CH₃CH₂CH₃) 1.45 (9H, s, OC(CH₃)₃) 1.08 (3H, d, 6.9 Hz, CHCH₃) 0.88 (3H, t, 7.3 Hz, CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 206.78, 166.46, 81.61, 49.00, 47.85, 27.87, 25.49, 15.37, 11.36.

**Enol:** ¹H NMR (600MHz; CDCl₃) δ 12.46 (1H, s, CH=COH) 4.86 (1H, CH=COH) 2.09 (1H, dq, 6.9, 6.6 Hz, CHCH₃) 1.67-1.61 (1H, m, CH₃CH₂CH₃) 1.48 (9H, s, OC(CH₃)₃) 1.44-1.38 (1H, m, CH₃CH₂CH₃) 1.10 (3H, d, 6.9 Hz, CHCH₃) 0.89 (3H, t, 7.3 Hz, CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 180.80, 172.84, 89.25, 80.47, 41.03, 28.24, 26.91, 25.80, 17.47, 11.61.

4-Methyl-2-(2-methyl-acryloyl)-3-oxo-hexanoic acid tert-butyl ester (164)

![Chemical structure](image2)

To a solution of (S)-β-ketoester 156 (200 mg; 1 mmol) in THF (8 mL) at -78°C was added iPrMgCl (0.6 mL of a 2 M solution in THF; 1.2 mmol) dropwise. The mixture was stirred for 30 minutes then methacroleoyl chloride (158) (105 mg; 1 mmol) was also added in dropwise. The reaction mixture was stirred for 2 hours at -78°C then warmed to room temperature for a further 30 minutes and quenched with a saturated NH₄Cl solution (15 mL), extracted with Et₂O (3*10 mL), dried (Na₂SO₄) and concentrated in vacuo.
vacuo. Purification by column chromatography (CH₂Cl₂) gave the tricarbonyl adduct 164 (196 mg; 73%) as clear oil. Rf = 0.68, Ketone: ¹H NMR (600MHz; CDCl₃) δ 5.51 (1H, s, C=CH₂CH₃) 5.29 (1H, m, C=CH₂CH₃) 4.87 (1H, s, C(=O)CH₃=O)) 2.59-2.53 (1H, m, CHCH₃) 1.93 (3H, brs, CH₂C=CH₂) 1.75-1.65 (1H, m, CH₃CH₂CH₂) 1.45 (9H, s, OC(CH₃)₃) 1.33-1.25 (1H, m, CH₃CH₂CH₂) 1.08 (3H, d, 6.9 Hz, CHCH₂) 0.87 (3H, t, 7.3 Hz, CH₂CH₂) Enol 1: ¹H NMR (600MHz; CDCl₃) δ 16.88 (1H, s, COH) 5.78 (1H, s, C=CH₂CH₃) 5.73 (1H, s, C=CH₂CH₃) 2.30-2.25 (1H, m, CHCH₂) 1.99 (3H, brs, CH₂C=CH₂) 1.75-1.65 (1H, m, CH₃CH₂CH₂) 1.42 (9H, s, OC(CH₃)₃) 1.30-1.23 (1H, m, CH₃CH₂CH₂) 1.11 (3H, d, 6.9 Hz, CHCH₂) 0.89 (3H, t, 7.3 Hz, CH₂CH₂) Enol 2: ¹H NMR (600MHz; CDCl₃) δ 12.97 (1H, s, COH) 5.31 (1H, s, C=CH₂CH₃) 5.25 (1H, s, C=CH₂CH₃) 2.11-2.07 (1H, m, CHCH₂) 2.00 (3H, brs, CH₂C=CH₂) 1.72-1.61 (1H, m, CH₃CH₂CH₂) 1.45 (9H, s, OC(CH₃)₃) 1.31-1.22 (1H, m, CH₃CH₂CH₂) 1.15 (3H, d, 6.9 Hz, CHCH₂) 0.85 (3H, t, 7.3 Hz, CH₂CH₂)

3-(4-Methoxy-benzyloxy)-2-methylene-butyric acid (166)

![Chemical structure](image)

To a stirred solution of aldehyde 131 (250 mg; 1.25 mmol) in t-BuOH (15 mL) and 2-methyl-2-butene (8 mL) at room temperature was added NaClO₂ (0.56 g; 6.25 mmol) and NaH₂PO₄·2H₂O (0.6 g; 5 mmol) in water (5 mL) dropwise. The reaction mixture was stirred for two hours before being diluted with CH₂Cl₂/H₂O (150 mL; 2:1) and acidified with TFA to pH 3. The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3*75 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂ + 0.5% AcOH) gave the acid 166 (265 mg; 90%) as a colourless oil. Rf = 0.6, ¹H NMR (600MHz; CDCl₃) δ 7.26 (2H, d, 8.8 Hz, ArH) 6.88 (2H, d, 8.8 Hz, ArH) 6.48 (1H, s, C=CH₂CH₃) 6.06 (1H, s, C=CH₂CH₃) 4.49 (1H, d, 11.4 Hz, OCH₃CH₂PMP) 4.42 (1H, q, 6.6 Hz, CHOPMB) 4.35 (1H, d, 11.4 Hz, OCH₃CH₂PMP) 3.80 (3H, s, OCH₃) 1.36 (3H, d, 6.6 Hz, CHCH₂) ¹³C NMR (150MHz; CDCl₃) δ 159.16, 141.71, 132.32, 130.12, 129.29, 127.03, 113.79, 72.74, 70.50, 55.22, 21.77.

¹H NMR (600MHz; C₆D₆) δ 7.17 (2H, d, 8.8 Hz, ArH) 6.77 (2H, d, 8.8 Hz, ArH) 6.40 (1H, s, C=CH₂CH₃) 5.91 (1H, s, C=CH₂CH₃) 4.44 (1H, q, 6.6 Hz, CHOPMB) 4.30 (1H, d, 11.4 Hz, OCH₃CH₂PMP) 4.16 (1H, d, 11.4 Hz, OCH₃CH₂PMP) 3.29 (3H, s, OCH₃) 1.32 (3H, d, 6.6 Hz, CHCH₂) ¹³C NMR (150MHz; C₆D₆) δ 160.27, 143.11, 131.46, 129.95, 128.88, 127.55, 114.63, 73.44, 71.17, 55.31, 22.61.
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3-(4-Methoxy-benzyl-oxy)-2-methylene-butyryl chloride (165)

To a solution of acid 166 (50 mg; 0.21 mmol) in CH₂Cl₂ (3 mL) at room temperature was added 1-chloro-N,N-2-trimethyl-1-propenylamine (30 µL; 0.21 mmol) dropwise. The mixture was stirred for 3 hours at room temperature then concentrated in vacuo to give acid chloride 165 (48 mg; 90%) as a clear oil.¹H NMR (600MHz; C₆D₆) δ 7.09 (2H, d, 8.7 Hz, ArH) 6.76 (2H, d, 8.7 Hz, ArH) 6.30 (1H, s, C=C₃H₂A) 5.97 (1H, s, C=CH₂A) 4.21 (1H, q, 6.4 Hz, CH₂OPMB) 4.10 (1H, d, 11.3 Hz, OCH₂₃CH₂PMP) 3.99 (1H, d, 11.3 Hz, OCH₃CH₂PMP) 3.30 (3H, s, OCH₃) 1.12 (3H, d, 6.4 Hz, CHC₃).¹³C NMR (150MHz; C₆D₆) δ 168.03, 160.38, 148.13, 133.77, 129.95, 128.90, 114.66, 73.79, 71.34, 55.36, 22.18.

5-[1-(4-Methoxy-benzyl-oxy)-ethyl]-4-oxo-2-propyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester (167)

To a solution of β-ketoester 156 (40 mg; 0.20 mmol) in THF (5 mL) at -78°C was added 'PrMgCl (110 µL of a 2 M solution in THF; 0.22 mmol) dropwise. The mixture was stirred for 30 minutes then acid chloride 165 (50 mg; 0.20 mmol) was added via cannula (THF). The reaction mixture was stirred for 2 hours at -78°C then warmed to room temperature for a further 30 minutes and quenched with a saturated NH₄Cl solution (15 mL), extracted with Et₂O (3*15 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the γ-lactone 167 (59 mg; 71%) as clear oil. Rf = 0.64,¹H NMR (600MHz; CDCl₃) δ 7.23 (2H, d, 8.8 Hz, ArH) 6.86 (2H, d, 8.8 Hz, ArH) 4.61 (1H, dd, 11.7, 8.1 Hz, OCH₃CH₃CHC(=O)) 4.52 (1H, d, 11.0 Hz, OCH₃CH₃CHC(=O)) 4.49 (1H, dd, 11.7, 4.8 Hz, OCH₃CH₃CHC(=O)) 4.39 (1H, d, 11.0 Hz, OCH₃CH₃CHC(=O)) 4.35 (1H, d, 11.0 Hz, OCH₃CH₃CHC(=O)) 4.32 (1H, q, 6.4 Hz, CHOPMB) 3.80 (3H, s, OCH₃) 2.45-2.37 (2H, m,
CH(CH₃)CH₂CH₃, C(=O)CH₂CH₂OPMB) 1.67-1.58 (2H, m, CH₂CH₂CH₃) 1.45 (9H, s, OC(CH₃)₃) 1.26 (3H, d, 6.4 Hz, CHCH₃OPMB) 1.13 (3H, dd, 6.9, 3.1 Hz, CH(CH₃)CH₂CH₃) 0.93 (3H, t, 7.4 Hz, CH₂CH₂CH₃) ¹³C NMR (100MHz; CDCl₃) δ 188.73, 178.76, 165.75, 159.20, 130.26, 129.43, 113.73, 112.88, 81.66, 71.10, 68.40, 67.51, 55.23, 35.45, 35.24, 27.87, 20.29, 18.07, 11.98, 13.76

2,5-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester (168)

Under the above acylation reaction conditions and on post reaction workup and purification the intramolecular enol conjugate addition of the resultant tricarbonyl product was isolated in (35 mg; 23%) as clear oil. ¹H NMR (400MHz; CDCl₃) δ 4.38 (1H, dd, 11.4, 5.4 Hz, OCH₃CH₂CH₂CH₃) 4.16 (2H, q, 7.1 Hz, OCH₂CH₃) 3.98 (1H, t, 11.4 Hz, OCH₃CH₂CH₂CH₃) 2.54-2.48 (1H, m, C(=O)CH₂CH₂CH₃) 2.07 (3H, s, C=CH₂) 1.46 (9H, s, OC(CH₃)₃) 1.04 (3H, d, 7.0 Hz, C(=O)CH₂CH₃) ¹³C NMR (100MHz; CDCl₃) δ 190.31, 175.93, 165.45, 111.82, 72.50, 60.72, 37.91, 19.77, 13.89, 10.29.

2,5-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid tert-butyl ester (169)

Under the above acylation reaction conditions and on post reaction workup and purification the intramolecular enol conjugate addition of the resultant tricarbonyl product was isolated in (36 mg; 25%) as clear oil. ¹H NMR (400MHz; CDCl₃) δ 4.39 (1H, dd, 11.4, 5.4 Hz, OCH₃CH₂CH₂CH₃) 3.99 (1H, t, 11.4 Hz, OCH₃CH₂CH₂CH₃) 2.58-2.50 (1H, m, C(=O)CH₂CH₃) 2.08 (3H, s, C=CH₂) 1.46 (9H, s, OC(CH₃)₃) 1.04 (3H, d, 7.0 Hz, C(=O)CH₂CH₃) ¹³C NMR (100MHz; CDCl₃) δ 190.51, 174.42, 164.90, 113.67, 81.44, 72.55, 37.98, 27.97, 19.58, 10.35.
2-sec-Butyl-5-methyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid tert-butyl ester (170)

![Chemical Structure]

Under the above acylation reaction conditions and on post reaction workup and purification the intramolecular enol conjugate addition of the resultant tricarbonyl product was isolated in (54 mg; 20%) as clear oil. $^1$H NMR (600MHz; CDCl$_3$) δ 4.41 (1H, qd, 11.2, 5.4 Hz, OC$_3$H$_7$CH$_2$CH$_3$) 3.99 (1H, td, 11.2, 7.0 Hz, OCH$_3$CH$_2$CH$_3$) 2.63-2.56 (1H, m, C(=O)C$_3$H$_7$CH$_3$) 1.62-1.56 (1H, m, CH$_3$CH$_2$CH$_3$) 1.48 (9H, s, OC(CH$_3$)$_3$) 1.44-1.37 (1H, m, CH$_3$CH$_2$CH$_3$) 1.12 (3H, dd, 6.9, 3.1 Hz, CH(CH$_3$)$_3$CH$_3$) 1.07 (3H, t, 7.1 Hz, OCH$_2$CHCH$_3$) 0.85 (3H, t, 7.4 Hz, CH$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 191.32, 179.10, 165.09, 113.92, 81.45, 72.64, 39.15, 38.21, 27.97, 26.81, 17.58, 11.97, 10.68.

(S)-Phenylalanol (174)

![Chemical Structure]

To a solution of (S)-Phenylalanine (173) (10.0 g; 60.5 mmol) in THF (30.5 mL) was added BF$_3$OEt$_2$ (7.70 mL; 60.8 mmol) dropwise over a 30 minute period with stirring, and the resulting mixture was heated at reflux for 2 hours. To a vigorously refluxing solution was slowly added BH$_3$.SMe$_2$ (7.00 mL; 70 mmol) and the solution was maintained at reflux for an additional 6 hours. The reaction mixture was then allowed to cool to room temperature and the excess borane was quenched by the slow addition of a 1:1 THF/H$_2$O (10 mL) followed by 5M aqueous sodium hydroxide solution (45 mL). The resulting two phase mixture was heated at reflux for a further 12 hours, cooled to ambient temperature and filtered. The residual solid was washed with THF (2*10 mL) and the final filtrate concentrated in vacuo. The resulting slurry was extracted with CH$_2$Cl$_2$ (3*50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Recrystallisation from EtOAc gave the alcohol 174 (8.40 g; 92%) as white needles. mp. 91°C, $^1$H NMR (600MHz; CDCl$_3$) δ
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7.30 (2H, t, 7.4 Hz, ArH) 7.21 (1H, t, 7.4 Hz, ArH) 7.17 (2H, d, 7.4 Hz, ArH) 3.62 (1H, dd, 10.7, 3.7 Hz, CH$_2$CH$_2$OH) 3.38 (1H, dd, 10.7, 7.2 Hz, CH$_2$CH$_2$OH) 3.10 (1H, m, CH$_2$NH$_2$) 2.78 (1H, dd, 13.5, 5.1 Hz, CH$_2$CH$_2$Ph) 2.50 (1H, dd, 13.5, 8.7 Hz, CH$_2$CH$_2$Ph) 2.35 (3H, brs, CH$_2$N$\mathrm{H}_2$, CH$_2$O$\mathrm{H}$)

$^{13}$C NMR (150MHz; CDCl$_3$) δ 138.59, 129.12, 128.49, 126.32, 65.97, 54.11, 40.58.

(5)-4-benzyl-1,3-thiazolidinone-2-thione (175)

To a stirring solution of $\beta$-amino alcohol 174 (3.30 g; 21.8 mmol) in aqueous 1 M potassium hydroxide solution (110 mL) was added carbon disulphide (6.5 mL; 109 mmol) and the solution was heated to reflux for 16 hours. The reaction mixture was cooled to room temperature and extracted with CH$_2$Cl$_2$ (3*100 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Recrystallisation from ethanol afforded the auxiliary 175 (3.83 g; 84%) as white needles. mp. 79°C, $^1$H NMR (600MHz; CDCl$_3$) δ 8.27 (1H, brs, NH) 7.33 (2H, m, ArH) 7.26 (1H, m, ArH) 7.19 (2H, m, ArH) 4.46 (1H, qn, 7.4 Hz, NHCH$_2$Ph) 3.51 (1H, dd, 11.2, 7.8 Hz, CH$_3$CH$_2$S) 3.27 (1H, dd, 11.2, 6.6 Hz, CH$_3$CH$_2$S) 3.04 (1H, dd, 13.6, 7.2 Hz, CH$_3$CH$_2$Ph) 2.95 (1H, dd, 13.6, 7.1 Hz, CH$_3$CH$_2$Ph) $^{13}$C NMR (150MHz; CDCl$_3$) δ 200.46, 135.58, 128.90, 128.84, 127.15, 64.97, 39.61, 37.78.

3-acetyl-(5)-4-benzyl-1,3-thiazolidinone-2-thione (82)

To a solution of thiazolidinethione 175 (3.50 g; 16.7mmol) in THF (76 mL) at -78°C was added n-BuLi (10.5 mL of a 1.6 M solution in Et$_2$O; 16.8 mmol) dropwise and the mixture was stirred at that temperature for 20 minutes. Acetyl chloride (22) (1.45 mL; 20 mmol) was then added and the reaction was stirred at -78°C for 1 hour, then warmed to room temperature and stirred for a further 30 minutes.
The reaction was quenched with aqueous 10% K₂CO₃ and extracted first with Et₂O (3*50 mL), then CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the acetyl auxiliary 82 (3.94 g; 94%) as yellow powder. mp. 105°C, ¹H NMR (600MHz; CDCl₃) δ 7.36-7.26 (5H, m, ArH) 5.37 (1H, ddd, 10.6, 7.0, 3.7 Hz, NCH₂Ph) 3.38 (1H, dd, 11.5, 7.0 Hz, CH₂CH₃S) 3.21 (1H, dd, 13.2, 3.7 Hz, CHCH₂CH₃Ph) 3.03 (1H, dd, 13.2, 10.6 Hz, CHCH₂CH₃Ph) 2.88 (1H, d, 11.5 Hz, CH₂CH₃S) 2.79 (3H, s, C(=O)CH₃) ¹³C NMR (150MHz; CDCl₃) δ 201.48, 170.62, 136.41, 129.36, 128.81, 127.13, 68.12, 36.56, 31.72, 27.00.

1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3R-hydroxy-5-(4-methoxy-benzyl)oxy)-4-methylene-hexan-1-one (176) and 1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3S-hydroxy-5-(4-methoxy-benzyl)oxy)-4-methylene-hexan-1-one (177)

To a solution of N-acetyl-(4S)-benzylthiazolidinethione (82) (955 mg; 3.8 mmol) in CH₂Cl₂ (30 mL) at -40°C was added dropwise TiCl₄ solution (3.85 mL; 1 M solution in CH₂Cl₂; 3.85 mmol). The solution was stirred for 30 minutes. iPr₂NEt (0.84 mL; 4.79 mmol) was then added and stirring continued for an additional hour. The mixture was then cooled to -78°C and aldehyde 131 (500 mg; 2.5 mmol) was added via cannula (5 mL; CH₂Cl₂) and stirring continued at -78°C for a further two hours. The reaction mixture was diluted with CH₂Cl₂ (50 mL) then quenched by the addition of saturated NH₄Cl solution (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Separation of the two diastereomers was achieved by column chromatography (20% EtOAc/hexanes) to give the major isomer 176 (1.40 g; 78%) and the minor isomer 177 (0.12 g; 7%) as yellow oils. Major diastereomer: Rf = 0.1, ¹H NMR (600MHz; CDCl₃) δ 7.36-7.27 (7H, m, ArH) 6.87 (2H, d, 8.6 Hz, ArH) 5.37 (1H, m NCH₂Ph) 5.35 (1H, s, C=CH₃CH₃) 5.24 (1H, s, C=CH₂CH₃) 4.83 (1H, d, 9.4 Hz, CHO) 4.47 (1H, d, 11.5 Hz, OCH₂CH₃PMP) 4.33 (1H, d, 11.5 Hz, OCH₂CH₃PMP) 4.11 (1H, q, 6.6 Hz, CHOPMB) 3.79 (3H, s, OCH₃) 3.72 (1H, dd, 18.0, 1.8 Hz, C(=O)CH₂CH₃CHOH) 3.47 (1H, dd, 18.0, 9.6 Hz, C(=O)CH₂CH₃CHOH) 3.36 (1H, dd, 11.4, 7.2 Hz, SCH₂CH₃CHBN) 3.22 (1H, dd, 13.2, 3.6 Hz, CHCH₂CH₃Ph) 3.03 (1H, dd, 13.2, 10.5 Hz, CHCH₂CH₃Ph) 2.88 (1H, d, 11.4 Hz, SCH₂CH₃CHBN) 1.39 (3H, d, 6.6 Hz, CH(CH₃)OPMB) ¹³C NMR (150MHz;
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CDCl₃ δ 201.30, 172.90, 159.18, 150.19, 136.53, 130.40, 129.40, 129.24, 128.90, 127.23, 113.91, 113.01, 76.36, 69.94, 68.48, 67.39, 55.38, 45.76, 36.84, 32.12, 20.72. Minor diastereomer R<sub>f</sub> = 0.15, <sup>1</sup>H NMR (600MHz; CDCl₃) δ 7.38-7.26 (7H, m, ArH) 6.89 (2H, d, 8.6 Hz, ArH) 5.36 (1H, m NCHCH₂Ph) 5.33 (1H, s, C=CH(CH₃)₃) 5.27 (1H, s, C=CH₃CH₃) 4.70 (1H, d, 9.4 Hz, CHOH) 4.50 (1H, d, 11.5 Hz, OCH₃CH₃PMP) 4.34 (1H, d, 11.5 Hz, OCH₃CH₃PMP) 4.08 (1H, q, 6.6 Hz, CHOPMB) 3.80 (3H, s, OC₃H₃) 3.67 (1H, dd, 18.0, 1.8 Hz, C(=O)CH₃CH₃CHOH) 3.56 (1H, dd, 18.0, 9.6 Hz, C(=O)CH₃CH₃CHOH) 3.39 (1H, dd, 11.4, 7.2 Hz, S(CH₃)₂CH₃CHBn) 3.24 (1H, d, 11.4 Hz, S(CH₃)₂CH₃CHBn) 1.38 (3H, d, 6.6 Hz, CH(C₃H₇)OPMB) 0.87 (9H, s, Si(CH₃)₃) 0.05 (3H, s, Si(CH₃)₃) 13C NMR (150MHz; CDCl₃) δ 201.41, 172.88, 159.12, 150.34, 129.41, 129.21, 128.92, 127.26, 113.79, 112.68, 75.88, 69.94, 68.39, 68.13, 55.25, 45.17, 36.70, 31.93, 20.87.

To a solution of aldon adduct 176 (500 mg; 1.06 mmol) in CH₂Cl₂ (40 mL) at -78°C was added 2,6-lutidine (0.24 mL; 2.12 mmol) followed by TBSOTf (0.36 mL; 1.6 mmol) dropwise. The reaction mixture was stirred for 3 hours at -78°C, then diluted with CH₂Cl₂ (50 mL) and warmed to ambient temperature for a further hour. The mixture was quenched with NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of column chromatography (CH₂Cl₂) gave the TBS-protected aldon product 178 (571 mg; 92%) as yellow oil. R<sub>f</sub> = 0.62, <sup>1</sup>H NMR (600MHz; CDCl₃) δ 7.37-7.26 (7H, m, ArH) 6.87 (2H, d, 8.6 Hz, ArH) 5.38 (1H, m, C=CH₃CH₃) 5.23-5.19 (2H, m, C=CH₃CH₃, NCHCH₂Ph) 4.46 (1H, d, 9.5, 2.2 Hz, CHOTBS) 4.46 (1H, d, 11.2 Hz, OCH₃CH₃PMP) 4.30 (1H, d, 11.2 Hz, OCH₃CH₃PMP) 4.07 (1H, q, 6.4 Hz, CHOPMB) 3.79 (3H, s, OCH₃) 3.70 (1H, dd, 16.8, 9.2 Hz, C(=O)CH₃CH₃CHOH) 3.34-3.24 (3H, m, C(=O)CH₃CH₃CHOH, S(CH₃)₂CH₃CHBn, CHCH₂CH₃Ph) 3.01 (1H, dd, 13.2, 11.0 Hz, CHCH₂CH₃Ph) 2.88 (1H, d, 11.4 Hz, S(CH₃)₂CH₃CHBn) 1.38 (3H, d, 6.4 Hz, CH(CH₃)OPMB) 0.87 (9H, s, Si(CH₃)₃) 0.05 (3H, s, Si(CH₃)₃) 13C NMR (150MHz; CDCl₃) δ 201.68, 171.86, 159.02, 151.05, 136.65, 130.55,
To a solution of amide 178 (230 mg; 0.40 mmol) in THF (5 mL) at -78°C was added t-BuLi (0.23 mL of a 1.7 M solution in hexanes; 0.40 mmol). The mixture was stirred at -78°C for 15 minutes, then (S)-2-methyl butyryl chloride (120) (62 µL; 0.50 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred for an additional two hours at -78°C then warmed to room temperature for a further two hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with Et₂O (3 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Analysis of the crude ¹H NMR spectrum indicated that no acylation had occurred and that amide 178 was recovered following purification by column chromatography.

To a solution of aldol adduct 176 (200 mg; 0.44 mmol) in CH₂Cl₂ (23 mL) and H₂O (3 mL) at 0°C was added DDQ (120 mg; 0.53 mmol) in one portion. The mixture was warmed to room temperature and stirred for 2 hours, then quenched by the addition of a saturated NaHCO₃ solution (100 mL). The
aqueous layer was extracted with CH$_2$Cl$_2$ (3*30 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (20% Et$_2$O/CH$_2$Cl$_2$) gave the PMP-acetal 180 (176 mg; 85%) as a yellow oil. 

$R_f = 0.71$, $^1$H NMR (600MHz; CDCl$_3$) δ 7.43 (2H, m, ArH) 7.35 (2H, m, ArH) 7.29 (3H, m, ArH) 6.86 (2H, m, ArH) 5.83 (1H, s, C=CH$_2$Ph) 5.12 (1H, s, C=C=CH$_2$) 5.05 (1H, d, C(=O)CH$_2$C=CH$_2$) 5.00 (1H, dd, 8.1, 4.0 Hz, C(=O)CH$_2$CHO) 4.50 (1H, q, 6.2 Hz, CH(Ph)$_2$CHO) 3.78 (2H, m, C(=O)C$_2$H$_5$CHO) 3.77 (3H, s, OC$_2$H$_5$) 3.33 (1H, dd, 11.5, 7.1 Hz, SC$^\text{Bu}$CH$_2$Ph) 3.24 (1H, dd, 13.1, 3.6 Hz, CHCH$_2$Ph) 3.05 (1H, dd, 11.5, 10.6 Hz, CHCH$_2$CH$_2$Ph) 2.86 (1H, d, 11.5 Hz, SCH$_2$CH$_2$CHBn) 1.50 (3H, d, 6.2 Hz, CH(Ph)$_2$) 13C NMR (150MHz; CDCl$_3$) δ 201.36, 171.06, 159.86, 144.85, 136.38, 130.52, 129.40, 128.83, 127.50, 127.15, 113.48, 107.61, 101.10, 74.99, 74.67, 55.21, 40.83, 36.55, 32.11, 17.45.

1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-2-[2-(4-methoxy-phenyl)-6-methyl-5-methylene-[1,3]dioxan-4-yl]-4-methyl-hexane-1,3-dione (181)

To a solution of PMP-acetal 180 (185 mg; 0.40 mmol) in THF (5 mL) at -78°C was added t-BuLi (0.23 mL of a 1.7 M solution in hexanes; 0.40 mmol). The mixture was stirred at -78°C for 15 minutes, then (S)-2-methyl butyryl chloride (120) (62 µL; 0.50 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred for an additional two hours at -78°C then warmed to room temperature for a further two hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with Et$_2$O (3*5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had occurred and that PMP-acetal 180 was recovered following purification by column chromatography.
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(5,5,5)-1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-hydroxy-4-methyl-hexan-1-one (182) and (5,5,R)-1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-hydroxy-4-methyl-hexan-1-one (183)

![Chemical Structure]

To a solution of N-acetyl-(4S)-benzylthiazolidinethione (82) (650 mg; 2.60 mmol) in CH₂Cl₂ (15 mL) at -40°C was added dropwise TiCl₄ solution (2.68 mL; 1 M solution in CH₂Cl₂; 2.68 mmol). The solution was stirred for 30 minutes. iPr₂NEt (0.60 mL; 2.80 mmol) was then added and stirring continued for an additional hour. The mixture was then cooled to -78°C and (5)-2-methyl-aldehyde (162) (0.28 mL; 2.65 mmol) was added via cannula (5 mL; CH₂Cl₂) and stirring continued at -78°C for a further two hours. The reaction mixture was diluted with CH₂Cl₂ (50 mL) then quenched by the addition of saturated NH₄Cl solution (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Separation of the two diastereomers was achieved by column chromatography (20% EtOAC/hexanes) to give the major isomer 182 (702 mg; 80%) and the minor isomer 183 (70 mg; 8%) as yellow oils. Major diastereomer: Rf = 0.15, ¹H NMR (600MHz; CDCl₃) δ 7.37-7.27 (5H, m, ArH) 5.39 (1H, td, 10.5, 7.2, 4.0 Hz, NCH₂CH₂Ph) 4.04 (1H, dd, 10.1, 5.8 Hz, CHOH) 3.57 (1H, dd, 17.7, 1.9 Hz, C(=O)CH₂CH₄CHOH) 3.39 (1H, dd, 11.5, 7.2 Hz, SCH₂CH₆CHBn) 3.22 (1H, dd, 13.2, 4.0 Hz, CHCH₂CH₆Ph) 3.17 (1H, dd, 17.7, 10.1 Hz, C(=O)CH₂CH₆CHOH) 3.04 (1H, dd, 13.2, 10.5 Hz, CHCH₂CH₆Ph) 2.88 (1H, d, 11.5 Hz, SCH₂CH₂CHBn) 2.16 (1H, brs, CHOH) 1.60-1.52 (2H, m, CH₂CH₃) 1.23-1.18 (1H, m, CH(CH₃)₂CH₂CH₃) 0.93 (3H, d, 7.3 Hz, CH(CH₃)₂CH₂CH₃) 0.91 (3H, d, 6.9 Hz, CH₂CH₃) ²³C NMR (150MHz; CDCl₃) δ 201.29, 173.64, 136.26, 129.27, 128.75, 127.09, 71.04, 68.24, 42.50, 39.64, 36.62, 31.89, 24.92, 14.44, 11.42; Minor diastereomer: Rf = 0.19, ¹H NMR (400MHz; CDCl₃) δ 7.37-7.27 (5H, m, ArH) 5.42 (1H, td, 10.5, 7.2, 4.0 Hz, NCH₂CH₂Ph) 4.03-4.01 (1H, m, CHOH) 3.54 (1H, dd, 17.7, 1.9 Hz, C(=O)CH₂CH₄CHOH) 3.40 (1H, dd, 11.5, 7.2 Hz, SCH₂CH₆CHBn) 3.29 (1H, dd, 13.2, 4.0 Hz, CHCH₂CH₆Ph) 3.23 (1H, dd, 17.7, 10.1 Hz, C(=O)CH₂CH₆CHOH) 3.05 (1H, dd, 13.2, 10.5 Hz, CHCH₂CH₆Ph) 3.00 (1H, brs, CHOH) 2.91 (1H, d, 11.5 Hz, SCH₂CH₆CHBn) 1.62-1.46 (2H, m, CH₂CH₆CH₃, CH(CH₃)₂CH₂CH₃) 1.26-1.15 (1H, m, CH₂CH₆CH₃) 0.95 (3H, d, 7.3 Hz, CH(CH₃)₂CH₂CH₃) 0.92 (3H, d, 6.9 Hz, CH₂CH₃) ²³C NMR (100MHz; CDCl₃) δ 201.43, 174.08, 136.24, 129.28, 128.77, 127.10, 71.23, 68.21, 42.89, 39.84, 36.61, 31.86, 25.37, 13.91, 11.70.
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1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-(tert-butyl-dimethyl-silanyloxy)-4-methyl-hexan-1-one (184)

To a solution of aldol adduct 182 (280 mg; 0.83 mmol) in CH₂Cl₂ (20 mL) at -78°C was added 2,6-lutidine (105 µL; 0.91 mmol) followed by TBSOTf (190 µL; 0.85 mmol) dropwise. The reaction mixture was stirred for 3 hours at -78°C, then diluted with CH₂Cl₂ (20 mL) and warmed to ambient temperature. The mixture was quenched with NaHCO₃ (30 mL) and extracted with CH₂Cl₂ (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of column chromatography (CH₂Cl₂) gave the TBS-protected aldol product 184 (348 mg; 93%) as yellow oil. Rₐ = 0.52, ¹H NMR (400MHz; CDCl₃) δ 7.38-7.27 (5H, m, ArH) 5.35 (1H, td, NCHCH₂Ph) 4.29 (1H, td, 9.6, 4.3 Hz, CHOTBS) 3.47-3.44 (2H, m, ) 3.35 (1H, dd, 17.3, 1.6 Hz, SCH₂CH₂CHBn) 3.22 (1H, dd, 19.7, 5.3 Hz, ) 3.05 (1H, dd, 19.7, 16.0 Hz, ) 2.87 (1H, d, 17.3 Hz, SCH₂CH₂CHBn) 1.64-1.54 (1H, m, CH₃CH₂CH₃) 1.53-1.44 (1H, m, CH(CH₃)₂CH₂CH₃) 1.71-1.06 (1H, m, CH₃CH₂CH₃) 0.90-0.85 (15H, m, SiCH₃) 3.15, 1.73, 136.56, 129.40, 128.87, 127.17, 71.89, 68.62, 43.03, 40.57, 36.70, 31.59, 25.83, 25.03, 18.07, 13.90, 12.20, -2.99, -4.61.

13C NMR (100MHz; CDCl₃) δ 200.96, 172.17, 136.56, 129.40, 128.87, 127.17, 71.89, 68.62, 43.03, 40.57, 36.70, 31.59, 25.83, 25.03, 18.07, 13.90, 12.20, -2.99, -4.61.

1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-(tert-butyl-dimethyl-silanyloxy)-4-methyl-hexan-1-one (185)

To a solution of amide 184 (125 mg; 0.28 mmol) in THF (3 mL) at -78°C was added t-BuLi (0.17 mL of a 1.7 M solution in hexanes; 0.30 mmol). The mixture was stirred at -78°C for 15 minutes, then acetyl chloride (22) (28 µL; 0.40 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred for an additional two hours at -78°C then warmed to room temperature for a further two hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with Et₂O (3*5 mL), dried (Na₂SO₄) and concentrated in vacuo. Analysis of the crude ¹H NMR spectrum
indicated that no acylation had occurred and that amide 184 was recovered following purification by column chromatography.

**N-Methoxy-N-methyl-acetamide (186)**

\[
\begin{align*}
\text{O} & \quad \text{MeONH(Me).HCl} \\
\text{OEt} & \quad \text{i-PrMgCl} \\
119 & \quad \text{THF} \\
\rightarrow & \quad \text{O} \\
\text{N.OMe} & \quad 186
\end{align*}
\]

To a solution of ethyl acetate (119) (0.5 g; 5.68 mmol) in THF (5 mL) and Et₂O (5 mL) was added N,O-dimethyldihydroxylamine hydrochloride (1.36 g; 14 mmol). The mixture was cooled to -20°C and iPrMgCl (14 mL; of a 2 M solution in THF; 28 mmol) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at -20°C for a further 30 minutes then at 0°C for a further 30 minutes before saturated NH₄Cl (50 mL) was added cautiously. The mixture was extracted with Et₂O (3*20 mL) and CH₂Cl₂ (3*10 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc/hexanes) to give the amide 186 (503 mg; 86%) as a colourless oil. Rf = 0.35, ¹H NMR (600MHz; CDCl₃) δ 3.67 (3H, s, NOC₃H₃) 3.16 (3H, s, NC₃H₃) 2.11 (3H, s, C(=O)C₃H₃)

**3-Hydroxy-4-methyl-hexanoic acid methoxy-methyl-amide (187)**

\[
\begin{align*}
\text{O} & \quad LiHMDS \\
\text{N.OMe} & \quad 186 \\
\rightarrow & \quad \text{O} \\
\text{OH} & \quad 187
\end{align*}
\]

To a solution of LiHMDS (4.4 mL; of a 1 M solution in THF; 4.4 mmol) at -78°C amide 186 (450 mg; 4.37 mmol) was added and the reaction was stirred for 30 minutes, then aldehyde 162 (430 mg; 5 mmol) was added via cannula (30 mL; THF) and the reaction was stirred at this temperature for 30 minutes before being warmed to 0°C over 2 hours. The reaction was further stirred for 30 minutes at this temperature then quenched with NH₄Cl (30 mL), extracted Et₂O (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (50% EtOAc/hexanes) gave the acetate-aldol product 187 (632 mg; 76%) as a clear oil. Rf = 0.57, ¹H NMR (600MHz; CDCl₃) δ 3.72 (1H, ddd, 8.1, 5.4, 2.7 Hz, CH₂OH) 3.16 (3H, d, 1H, ddd, 8.1, 5.4, 2.7 Hz, CH₂OH) 2.11 (3H, s, C(=O)CH₃) 13C NMR (150MHz; CDCl₃) δ 175.43, 61.16, 32.28, 25.15.
(3H, s, NOCH₃) 3.15 (3H, s, NCH₃) 2.32 (1H, dd, 14.5, 5.4 Hz, CH₃CH₂C(=O)) 2.17 (1H, dd, 14.5, 2.7 Hz, CH₃CH₂C(=O)) 1.45-1.39 (1H, m, CH₂CH₃) 2.32 (1H, dd, 14.5, 2.7 Hz, CH₂CH₃) 1.11-1.02 (1H, m, CH₃CH₂CH₃) 1.11 (3H, s, NC₃H₃) 1.09 (3H, d, 6.9 Hz, CHCH₂CH₃) 0.93 (3H, t, 7.3 Hz, CH₂CH₃) 0.90 (3H, d, 6.9 Hz, CHCH₂CH₃) 13C NMR (150MHz; CDCl₃) δ 178.33, 73.07, 61.44, 38.15, 31.88, 26.73, 17.92, 13.90, 12.24

3-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-hexanoic acid methoxy-methyl-amide (188)

To a solution of unsaturated β-hydroxy amide 187 (5 g; 38.5 mmol) in DMF (35 mL) was added imidazole (5.24 g; 77 mmol) followed by TBS-Cl (5.77 g; 38.5 mmol) at room temperature. The mixture was stirred overnight then quenched by the addition of saturated NaHCO₃ solution (150 mL). The aqueous layer was extracted with Et₂O (3*50 mL) and CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo.
Purification by column chromatography (20% EtOAc/hexanes) gave the TBS-protected adduct 188 (8.8 g; 94%) as a clear oil. Rf = 0.47, ¹H NMR (600MHz; CDCl₃) δ 4.23 (1H, dt, 12.8, 4.4, 3.3 Hz, OTBS) 3.69 (3H, s, NOCH₃) 3.16 (3H, brs, NCH₃) 2.30 (1H, dd, 14.6, 4.4 Hz, CH₂CH₂C(=O)) 2.18 (1H, dd, 14.6, 3.3 Hz, CH₂CH₂C(=O)) 1.46-1.41 (1H, m, CHCH₃) 1.40-1.33 (1H, m, CH₃CH₂CH₃) 1.13-1.03 (1H, m, CH₃CH₂CH₃) 0.90 (3H, t, 7.3 Hz, CH₂CH₃) 0.89 (3H, d, 6.9 Hz, CHCH₂CH₃) 0.85 (9H, s, Si(CH₃)₃) 0.05 (3H, s, SiCH₃) 0.00 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 178.85, 72.47, 61.16, 40.78, 35.74, 35.74, 31.87, 25.76, 25.39, 17.98, 13.98, 12.21, -4.63, -5.02.

2-Acetyl-3-(tert-butyl-dimethyl-silanyloxy)-4-methyl-hexanoic acid methoxy-methyl-amide (189)

To a solution of TBS-protected amide 188 (100 mg; 0.33 mmol) in THF (1.5 mL) at -78°C was added t-BuLi (0.23 mL of a 1.5 M solution in hexanes; 0.35 mmol). The mixture was stirred at -78°C for 15 minutes, then acid chloride (22) (35 µL; 0.5 mmol) in THF (0.5 mL) was added via cannula. The mixture was stirred...
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for an additional 2 hours at -78°C then warmed to 0°C over 30 minutes and quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with Et₂O (3*5 mL), dried (Na₂SO₄) and concentrated in vacuo. Analysis of the crude ¹H NMR spectrum indicated that no acylation had occurred and that amide 188 was recovered following purification by column chromatography.

3-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-hexanoic acid tert-butyl ester (190)

To a solution of aldol adduct 163 (2.0 g; 10 mmol) in DMF (20 mL) was added imidazole (1.36 g; 20 mmol) and TBS-Cl (1.58 g; 10.5 mmol) at room temperature in one portion. The reaction mixture was stirred for 15 hours overnight then quenched by the addition of NaHCO₃ (200 mL), extracted with CH₂Cl₂ (3*100 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (80% CH₂Cl₂/hexanes) gave the TBS protected adduct 190 (2.79 g; 88%) as a clear oil. Rₛ = 0.85, ¹H NMR (600MHz; CDCl₃) δ 4.08-4.04 (1H, m, CΗOTBS) 2.31 (1H, dd, 7.6, 5.8 Hz, CHOTBSCH₂CH₃C(=O)) 2.25 (1H, dd, 6.6, 5.8 Hz, CHOTBSCH₂CH₃C(=O)) 1.56-1.48 (1H, m, CH₃CH₂CH₃) 1.43 (9H, s, OC(CH₃)₃) 1.39-1.31 (1H, m, CH(CH₃)CH₂CH₃) 1.10-1.00 (1H, m, CH₂CH₂CH₃) 0.89 (3H, t, 7.3 Hz, CH₂CH₃) 0.85 (9H, s, Si(CH₃)₃) 0.82 (3H, d, 6.9 Hz, CH(CH₃)CH₂CH₃) 0.05 (3H, s, SiCH₃) 0.04 (3H, s, SiCH₃) 13C NMR (150MHz; CDCl₃) δ 171.73, 80.11, 72.21, 40.80, 39.38, 28.12, 25.84, 25.29, 18.05, 13.88, 12.21, -4.54, -4.67

3-(tert-Butyl-dimethyl-silanyloxy)-2-butyryl-4-methyl-hexanoic acid tert-butyl ester (191)

To a solution of TBS-protected ester 190 (100 mg; 0.31 mmol) in THF (3 mL) at -78°C was added t-BuLi (0.21 mL of a 1.5 M solution in hexanes; 0.30 mmol). The mixture was stirred at -78°C for 15 minutes, then acetyl chloride (22) (28 µL; 0.4 mmol) was added dropwise. The mixture was stirred for an additional 2 hours at -78°C then warmed to 0°C over 30 minutes and quenched by the addition of
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Saturated ammonium chloride solution (5 mL), extracted with Et₂O (3*5 mL), dried (Na₂SO₄) and concentrated in vacuo. Analysis of the crude ¹H NMR spectrum indicated that no acylation had occurred and that ester 190 was recovered in reduced yield following purification by column chromatography.

6-Methyl-dihydro-pyran-2,4-dione (192)

To a solution of β-hydroxy-diketone 143 (300 mg; 1.48 mmol) in CH₂Cl₂ (20 mL) at 0°C was added TFA (125 µL; 1.60 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirring continued for 15 hours. The mixture was concentrated in vacuo and purified by column chromatography (50% Et₂O/CH₂Cl₂) to give the β-keto-lactone product 192 (153 mg; 81%) as clear oil. Rf = 0.45, ¹H NMR (600MHz; CDCl₃) δ 4.79 (1H, dqd, 11.3, 6.3, 2.9 Hz, OC₃H₇CH₃) 3.56 (1H, d, 18.7 Hz, C(=O)C₆H₄CH₃C(=O)) 3.42 (1H, d, 18.7 Hz, C(=O)CH₆CH₃C(=O)) 2.71 (1H, dd, 18.3, 2.9 Hz, C(=O)CH₆CH₃CH(CH₃) 2.46 (1H, dd, 18.3, 11.3 Hz, C(=O)CH₆CH₃CH₃) 1.51 (3H, d, 6.3 Hz, OCH₃) ¹³C NMR (150MHz; CDCl₃) δ 200.02, 167.27, 71.91, 46.80, 44.94, 20.43.

Butyric acid 2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (197)

To a solution of diketopyranone 192 (100 mg; 0.78 mmol) in toluene (5 mL) was added DBU (120 µL; 0.80 mmol) at room temperature and stirring continued for 20 minutes. The mixture was cooled to 0°C and butyryl chloride (145) (87 µL; 0.85 mmol) was added dropwise and the solution was stirred for a further 2 hours. pH Buffer (5 mL) was added to quench the reaction and the mixture extracted with toluene (2*2 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography.
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(CH₂Cl₂) gave the O-acylated diester product 197 (110 mg; 72%) as clear colourless oil. R₂ = 0.25, ¹H NMR (600MHz; CDCl₃) δ 5.90 (1H, d, 1.9 Hz, C=CH(C=O)) 4.61 (1H, m, OCHCH₃) 2.63 (1H, td, 17.5, 11.5, 1.9 Hz, CH₃CH₂CHCH₃) 2.45 (1H, m, CH₃CH₂CHCH₃) 2.44 (2H, t, 7.3 Hz, C(=O)CH₂CH₂CH₃) 1.70 (2H, dq, 7.4, 7.3 Hz, C(=O)CH₂CH₂CH₃) 1.44 (3H, d, 6.3 Hz, OCHCH₃) 0.97 (3H, t, 7.4 Hz, C(=O)CH₂CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 169.87, 165.59, 163.93 106.50, 72.87, 36.08, 33.99, 20.39, 17.98, 13.41.

3-Butyryl-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one (198)

The diester 197 (70 mg; 0.35 mmol) was dissolved in toluene (3 mL) and DMAP (3 mg; 0.02 mmol) was added in one portion at room temperature. The mixture was heated to 85°C and stirring continued for 15 hours at that temperature before concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the racemic acyl pyranone product 198 (45 mg; 66%) as clear oil. R₂ = 0.21, ¹H NMR (600MHz; CDCl₃) 17.92 (1H, s, C=C(OH)) 4.51 (1H, m, OCHCH₃) 3.04 (1H, m, C(=O)CH₃CH₂CH₂CH₃) 2.96 (1H, m, C(=O)CH₃CH₂CH₂CH₃) 2.61 (2H, m, CH₃CHCH₃) 1.67 (2H, m, C(=O)CH₂CH₂CH₃) 1.44 (3H, d, 6.3 Hz, OCHCH₃) 0.97 (3H, t, 7.4 Hz, C(=O)CH₂CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 204.43, 194.90, 164.25, 102.96, 70.23, 40.33, 39.32, 20.56, 18.29, 13.77.
2-Methyl-butyric acid 2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (200)

To a solution of diketopyranone 192 (100 mg; 0.78 mmol) in toluene (5 mL) was added DBU (120 µL; 0.80 mmol) at room temperature and stirring continued for 20 minutes. The mixture was cooled to 0°C and 2-methyl butyryl chloride (199) (105 µL; 0.85 mmol) was added dropwise and the solution was stirred for a further 2 hours. pH Buffer (5 mL) was added to quench the reaction and the mixture extracted with toluene (2*2 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the O-acylated diester product 200 (140 mg; 84%) as clear colourless oil. R_F = 0.26, ^1H NMR (600MHz; CDCl₃) δ 5.88 (1H, d, 2.1 Hz, C=C(H)C(=O)) 4.62 (1H, m, OC(H)CH₃) 2.64 (1H, dtd, 17.5, 11.5, 2.1 Hz, C(H)A CH₃CHCH₃) 2.51 (1H, dq, 7.0, 6.9 Hz, C(=O)CHCH₃) 2.63 (1H, td, 17.5, 11.5, 1.9 Hz, CH₃CH₆CHCH₃) 2.43 (1H, td, 17.5, 3.7, 2.6 Hz, CH₃CH₂CHCH₃) 1.73 (1H, m, CH₃CH₆CHCH₃) 1.55 (1H, m, CH₃CH₆CHCH₃) 1.45 (3H, d, 6.2 Hz, OCHCH₃) 1.20 (3H, d, 7.0 Hz, C(=O)CHCH₃) 0.94 (3H, t, 7.4 Hz, CH₂CH₃) 13C NMR (150MHz; CDCl₃) δ 172.93, 165.51, 164.11, 106.46, 72.84, 41.03, 33.93, 26.33, 20.32, 16.08, 11.32.

4-Hydroxy-6-methyl-3-(2-methyl-buturyl)-5,6-dihydro-pyran-2-one (201)

The diester 200 (100 mg; 0.47 mmol) was dissolved in toluene (5 mL) and DMAP (4 mg; 0.03 mmol) was added in one portion at room temperature. The mixture was heated to 85°C and stirring continued for 15 hours at that temperature before concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the racemic acyl pyranone product 201 (70 mg; 70%) as clear oil. R_F = 0.21, Isomer 1: ^1H NMR (600MHz; CDCl₃) δ 18.14 (1H, s, C=C(OH)) 4.52 (1H, m, OCHCH₃) 3.81 (1H, dq, 6.7 Hz, C(=O)CHCH₃) 2.64 (1H, dd, 10.0, 1.00 Hz, CH₃CH₆CHCH₃) 2.62 (1H, dd, 10.0 Hz, 3.6 Hz, CH₃CH₆CHCH₃) 1.75 (2H, m,
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CH₂CH₃ 1.45 (3H, d, 6.3 Hz, OCHCH₃) 1.17 (3H, d, 6.7 Hz, C(=O)CHCH₃) 0.93 (3H, t, 7.5 Hz, CH₂CH₃ 13C NMR (150MHz; CDCl₃) δ 208.12, 195.80, 164.18, 102.74, 70.21, 41.39, 39.72, 26.79, 20.56, 16.69, 11.79.

Isomer 2: ¹H NMR (600MHz; CDCl₃) δ 18.12 (1H, s, C=C(OH)) 4.51 (1H, m, OCHCH₃) 3.77 (1H, dq, 6.7 Hz, C(=O)CHCH₃) 2.64 (1H, dd, 10.0 Hz, 3.6 Hz, CH₂C₂CH₃) 1.70 (2H, m, CH₂CH₃) 1.44 (3H, d, 6.3 Hz, OCHCH₃) 1.12 (3H, d, 6.7 Hz, C(=O)CHCH₃) 0.86 (3H, t, 7.5 Hz, CH₂CH₃ 13C NMR (150MHz; CDCl₃) δ 208.23, 195.72, 164.05, 102.50, 70.14, 40.95, 39.67, 26.68, 20.55, 16.53, 11.59.

5-Hydroxy-4-methylene-3-oxo-hexanoic acid tert-butyl ester (203)

To a solution of β-keto ester 128 (240 mg; 0.74 mmol) in CH₂Cl₂ (20 mL) and H₂O (2 mL) at 0°C was added DDQ (200 mg; 0.88 mmol) in one portion. The mixture was warmed to room temperature and stirred for 2 hours, then quenched by the addition of a saturated NaHCO₃ solution (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the β-hydroxy-diketone 203 (145 mg; 91%) as a clear oil. Rf = 0.15, ¹H NMR (600MHz; CDCl₃) δ 6.10 (1H, s, C=CH₂CH₃) 6.04 (1H, s, C=CH₃CH₆) 4.65 (1H, q, 6.4 Hz, CHO) 3.63 (1H, d, 15.4 Hz, C(=O)CH₃CH₃C(=O)) 3.59 (1H, d, 15.4 Hz, C(=O)CH₂CH₆C(=O)) 2.77 (1H, brs, CHO) 1.41 (9H, s, OC(CH₃)₃) 1.31 (3H, d, 6.4 Hz, HOCHCH₃) 13C NMR (150MHz; CDCl₃) δ 194.98, 166.49, 150.98, 125.26, 82.05, 66.25, 47.03, 27.80, 22.19.

6-Methyl-5-methylene-dihydro-pyran-2,4-dione (202)

To a solution of β-hydroxy-diketone 203 (0.5 g; 2.33 mmol) in CH₂Cl₂ (50 mL) at 0°C was added TFA (170 µL; 2.2 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirring
continued for 15 hours. The mixture was concentrated in vacuo and purified by column chromatography (30% Et₂O/CH₂Cl₂) to give the unsaturated-β-keto-lactone product 202 (280 mg; 86%) as clear oil. R_f = 0.22, ¹H NMR (600MHz; CDCl₃) Ketone δ 6.42 (1H, d, 1.2 Hz, C=CH₂CH₃) 5.66 (1H, d, 1.2 Hz, C=CH₂CH₃) 5.28 (1H, q, 6.6 Hz, CHCH₃) 3.75 (1H, d, 17.8 Hz, C(=O)CH₂CH₃C(=O)) 3.56 (1H, d, 17.8 Hz, C(=O)CH₂CH₃C(=O)) 1.65 (3H, d, 6.6 Hz, CHCH₃) 13C NMR (150MHz; CDCl₃) δ 189.05, 167.10, 140.09, 136.80, 74.17, 47.10, 17.55. Enol δ 15.43 (1H, s, COH) 5.94 (1H, s, C=CCH₂CH₃) 5.42 (1H, s, C=CH₂CH₃) 5.38 (1H, s, C(ОН)C=CHC(=O)) 5.12 (1H, q, 6.5 Hz, CHCH₃) 1.56 (3H, d, 6.5 Hz, CHCH₃) 13C NMR (150MHz; CDCl₃) δ 169.00, 164.96, 123.96, 116.39, 92.65, 75.53, 20.59.

2-Methyl-butryc acid 2-methyl-3-methylene-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (204)

To a solution of unsaturated diketopyranone 202 (100 mg; 0.71 mmol) in toluene (5 mL) was added DBU (190 µL; 0.75 mmol) at room temperature and stirring continued for 20 minutes. The mixture was cooled to 0°C and (S)-2-methyl butyryl chloride (120) (100 µL; 0.80 mmol) was added dropwise and the solution was stirred for a further two hours. A buffer solution (5 mL; pH 7) was added to quench the reaction and the mixture extracted with toluene (2*2 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the O-acylated product 204 (123 mg; 77%) as a clear colourless oil. R_f = 0.27, ¹H NMR (600MHz; CDCl₃) δ 5.90 (1H, d, 2.1 Hz, C=CCH(=O)) 4.63 (1H, m, OCHCH₃) 2.62 (1H, dtd, 17.5, 11.5, 2.1 Hz, CH₂CH₂CH₂CH₃) 2.50 (1H, dq, 7.0, 6.9 Hz, C(=O)CHCH₃) 2.45 (1H, td, 17.5, 3.7, 2.6 Hz, CH₂CH₂CH₂CH₃) 1.71 (1H, m, CH₂CH₂CH₂CH₃) 1.55 (1H, m, CH₂CH₂CH₂CH₃) 1.46 (3H, d, 6.2 Hz, OCHCH₃) 1.22 (3H, d, 7.0 Hz, C(=O)CH₂CH₃) 0.93 (3H, t, 7.4 Hz, CH₂CH₃) 13C NMR (150MHz; CDCl₃) δ 172.94, 165.55, 164.15, 106.45, 72.87, 41.01, 33.92, 26.35, 20.34, 16.10, 11.34.
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4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)

\[ \text{DMAP} \quad \text{Toluene} \]

The diester 204 (70 mg; 0.35 mmol) was dissolved in toluene (3 mL) and DMAP (3 mg; 0.02 mmol) was added in one portion at room temperature. The mixture was heated to 85°C and stirring continued for 15 hours at that temperature before concentrated in vacuo. Analysis of the crude NMR mixture indicated the loss of CR377’s vinylic protons along with the decomposition of the lactone 204. On some occurrences the (S)-2-methyl butyric acid (155) was isolated as a sole product following purification by column chromatography.

3-Hydroxy-2-methylene-butyric acid methyl ester (210)

\[ \text{DABCO} + \text{H} \]

To a solution of methyl acrylate (209) (30 mL; 0.33 mol) in 1,4-dioxane (350 mL) and water (350 mL) at room temperature was added DABCO (12.34 g; 0.11 mmol) and the mixture was stirred for 1 hour. Acetaldehyde (142) (6.4 mL; 0.11 mol) was then added in one portion and the reaction was allowed to stir for a further 48 hours. The reaction was extracted with Et₂O (5*100 mL). The organic extracts were washed with H₂O (2*100 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the unsaturated hydroxyl ester 210 (10 g; 70%) as clear oil. \( R_f = 0.20 \), \( ^1\text{H NMR} \) (600MHz; CDCl₃) \( \delta \) 6.19 (1H, s, C=CH₂CH₃) 5.81 (1H, s, C=CH₂CH₃) 4.60 (1H, q, 6.4 Hz, CHO₂H) 3.76 (3H, s, OCH₃) 2.87 (1H, brs, CHO₂H) 1.35 (3H, d, 6.4 Hz, CH₂CH₃) \( ^{13}\text{C NMR} \) (150MHz; CDCl₃) \( \delta \) 167.04, 143.35, 124.19, 66.98, 51.87, 21.99.
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3-(4-Methoxy-benzyloxy)-2-methylene-butyric acid methyl ester (211)

![Chemical Structure]

To a solution of methyl ester 210 (2.0 g; 15.4 mmol) in CH₂Cl₂ (100 mL) PMB-imidate 147 (3.3 mL; 16 mmol) was added at room temperature. CSA (348 mg; 1.5 mmol) was added in portions, and the reaction mixture stirred at room temperature for 4 days, during this time additional PMB-imidate 147 and CSA were added as deemed appropriate by TLC analysis. The reaction was quenched with NaHCO₃ (100 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 80 mL). Organic extracts were combined and concentrated in vacuo. The slurry produced was triturated (25% CH₂Cl₂/Hexanes), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the PMB-hydroxy-ester 211 (2.50 g; 65%) as a colourless oil. Rₚ = 0.35, ¹H NMR (600 MHz; CDCl₃) δ 7.25 (2H, d, 8.7 Hz, ArH), 6.87 (2H, d, 8.7 Hz, ArH), 6.31 (1H, d, 1.3 Hz, C=C₃H₂), 5.95 (1H, t, 1.3 Hz, C=CH₃), 4.46 (1H, d, 11.3 Hz, OC₃H₂PMP), 4.41 (1H, qd, 6.3, 0.8 Hz, C₃H₂OPMB), 4.33 (1H, d, 11.3 Hz, OCH₃C₃H₂PMP), 3.79 (3H, s, PhOC₃H₂), 3.77 (3H, s, C(=O)OC₃H₂), 1.32 (3H, d, 6.3 Hz, CHC₃H₂), 13C NMR (150 MHz; CDCl₃) δ 166.77, 159.10, 142.35, 130.43, 129.20, 124.47, 113.75, 72.86, 70.43, 55.24, 51.79, 21.90.

3-(tert-Butyl-dimethyl-silanyloxy)-2-methylene-butyric acid methyl ester (216)

![Chemical Structure]

To a solution of unsaturated β-hydroxy ester 210 (5 g; 38.5 mmol) in DMF (35 mL) was added imidazole (5.25 g; 77 mmol) followed by TBS-Cl (5.77 g; 38.5 mmol) at room temperature. The mixture was stirred overnight for 15 hours then quenched by the addition of saturated NaHCO₃ solution (150 mL). The aqueous layer was extracted with Et₂O (3 x 50 mL) and CH₂Cl₂ (3 x 50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the TBS-protected adduct 216 (8.8 g; 94%) as a clear oil. Rₚ = 0.45, ¹H NMR (600 MHz; CDCl₃) δ 6.18 (1H, s, C=C₃H₂), 5.95 (1H, s, C=CH₃), 4.68 (1H, dq, 6.2, 1.1 Hz, CHOTBS), 3.74 (3H, s, OCH₃), 1.25 (3H, d, 6.2 Hz, CHCH₃), 0.88 (9H, s,
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$\text{SiC(CH}_3)_3 \ 0.08 \ (3\text{H}, \text{s}, \text{SiC}_3) \ 0.05 \ (3\text{H}, \text{s}, \text{SiC}_3) \ \text{C}^{13} \text{NMR (150MHz; CDCl}_3 \, \delta \ 166.75, \ 145.13, \ 123.54, \ 66.76, \ 51.65, \ 25.77, \ 25.62, \ 18.16, \ -3.61, \ -5.02.$

3-(tert-Butyl-dimethyl-silyloxy)-2-methylene-butan-1-ol (217)

To a solution of unsaturated TBS-protected methyl ester 216 (3.0 g; 12.27 mmol) in CH$_2$Cl$_2$ (100 mL) at -78°C was added DIBALH (37 mL of a 1 M solution in toluene; 36.8 mmol) dropwise. The mixture was stirred for 3 hours at -78°C then warmed to 0°C for a further hour. The mixture was quenched by the addition of potassium sodium tartrate (100 mL), extracted with CH$_2$Cl$_2$ (3*100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (10% Et$_2$O/CH$_2$Cl$_2$) gave the primary alcohol 217 (2.0 g; 75%) as clear oil. R$_f$ = 0.35, $^1$H NMR (600MHZ; CDCl$_3$) $\delta$ 5.01 (1H, s, C=C$\text{H}_2$) 5.00 (1H, s, C=CH$\text{H}_2$) 4.45 (1H, q, 6.6 Hz, C$\text{H}$OTBS) 4.30 (1H, dd, 13.2, 4.7 Hz, C$\text{H}$A$\text{CH}_2$OH) 4.13 (1H, dd, 13.2, 6.9 Hz, C$\text{H}$B$\text{CH}_2$OH) 1.30 (3H, d, 6.6 Hz, CH$\text{C}_3$H$_3$) 0.89 (9H, s, SiC(CH$_3)_3$) 0.08 (3H, d, SiC$_3$) 0.07 (3H, s, SiC$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 151.16, 110.31, 71.64, 63.63, 25.72, 25.61, 23.64, 18.05, -4.89, -5.04.

3-(tert-Butyl-dimethyl-silyloxy)-2-methylene-butyraldehyde (218)

To a solution of DMSO (1.72 mL; 24.3 mmol) in CH$_2$Cl$_2$ (50 mL) at -78°C was added oxalyl chloride (6 mL of a 2 M solution in CH$_2$Cl$_2$; 12.1 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 217 (1.75 g; 8.1 mmol) in CH$_2$Cl$_2$ (10 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt$_3$ (6.75 mL; 48.6 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH$_4$Cl (80 mL) then extracted with CH$_2$Cl$_2$ (3*50 mL), dried (Na$_2$SO$_4$) and carefully concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave the desired aldehyde 218 (1.56 g; 90%) as a colourless oil. R$_f$ =
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0.43, $^1$H NMR (600MHz; CDCl$_3$) δ 9.57 (1H, s, CHO) 6.57 (1H, s, C=CH$_2$CH$_3$) 6.03 (1H, s, C=CH$_2$H$_3$) 4.68 (1H, q, 6.2 Hz, CHOTBS) 1.25 (3H, d, 6.2 Hz, CHCH$_3$) 0.89 (9H, s, SiC(CH$_3$)$_3$) 0.05 (3H, s, SiC($C_3$H$_3$)$_3$) 0.01 (3H, s, SiC($C_3$H$_3$)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 193.68, 154.75, 133.42, 65.05, 25.76, 24.25, 18.15, -4.98, -5.09.

5-(tert-Butyl-dimethyl-silanyloxy)-3-hydroxy-4-methylene-hexanoic acid tert-butyl ester (219)

To a solution of LiHMDS (7.6 mL; of a 1 M solution in THF; 7.6 mmol) at -78°C tert-butyl acetate (130) (1.0 mL; 7.5 mmol) was added and the reaction was stirred for 30 minutes, then aldehyde 218 (1.50 g; 7 mmol) was added via cannula (60 mL; THF) and the reaction was stirred at this temperature for 30 minutes before being warmed to 0°C over 2 hours. The reaction was further stirred for 30 minutes at this temperature then quenched with NH$_4$Cl (10 mL), extracted Et$_2$O (3*10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (10% EtOAc/hexanes) gave an inseparable mixture of diastereomeric acetate-aldol products 219 (1.92 g; 83%) as a clear oil. R$_f$ = 0.29,

**Major Diastereomer:** $^1$H NMR (600MHz; CDCl$_3$) δ 5.10 (1H, s, C=C\(\text{H}_2\)CH) 5.07 (1H, s, C=CH\(\text{H}_2\)CH) 4.57 (1H, m, CHOH) 4.43 (1H, q, 6.6 Hz, CHOTBS) 3.40 (1H, s, CHO\(\text{H}_2\)CH) 2.66 (1H, dd, 16.5, 3.6 Hz, CH(OH)\(\text{CH}_3\)\(\text{CH}_3\)C(=O)) 2.51 (1H, dd, 16.5, 8.8 Hz, CH(OH)\(\text{CH}_3\)\(\text{CH}_3\)C(=O)) 1.49 (9H, s, OC(\(\text{CH}_3\))$_3$) 1.30 (3H, d, 6.6 Hz, CH\(\text{CH}_3\)) 0.88 (9H, s, SiC\(\text{CH}_3\)$_3$) 0.06 (3H, s, Si\(\text{CH}_3\)$_3$) 0.04 (3H, s, Si\(\text{CH}_3\)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 172.08, 153.36, 109.68, 80.98, 70.44, 67.52, 42.10, 27.96, 25.72, 23.99, 18.00, -4.89, -4.98.

**Minor Diastereomer:** $^1$H NMR (600MHz; CDCl$_3$) δ 5.09 (1H, s, C=CH\(\text{H}_2\)CH) 5.08 (1H, s, C=CH\(\text{H}_2\)CH) 4.61-4.58 (1H, m, CHOH) 4.45 (1H, q, 6.6 Hz, CHOTBS) 3.40 (1H, s, CHO\(\text{H}_2\)CH) 2.66 (1H, dd, 16.5, 3.6 Hz, CH(OH)\(\text{CH}_3\)\(\text{CH}_3\)C(=O)) 2.51 (1H, dd, 16.5, 8.8 Hz, CH(OH)\(\text{CH}_3\)\(\text{CH}_3\)C(=O)) 1.45 (9H, s, OC(\(\text{CH}_3\))$_3$) 1.30 (3H, d, 6.6 Hz, CH\(\text{CH}_3\)) 0.88 (9H, s, SiC\(\text{CH}_3\)$_3$) 0.06 (3H, s, Si\(\text{CH}_3\)$_3$) 0.04 (3H, s, Si\(\text{CH}_3\)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 171.46, 166.27, 152.75, 80.90, 71.11, 67.41, 41.89, 27.82, 25.70, 24.00, 17.97, -4.91, -5.04.
Experimental Procedures for Chapter Two

5-(tert-Butyl-dimethyl-silyloxy)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (220)

To a stirring solution of β-hydroxy esters 219 (1.55 g; 4.65 mmol) in CH₂Cl₂ (80 mL) was added PCC (2 g; 9.3 mmol) and celite (2 g 1:1 w/w with PCC) in one portion at room temperature. The reaction mixture was stirred for 4 hours, then filtered through celite and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) produced the β-keto ester 220 (1.34 g; 88%) as clear oil. RF = 0.56, ¹H NMR (600MHz; CDCl₃) δ 6.24 (1H, s, C=C₆H₄) 6.06 (1H, s, C=CH₆H₄) 4.75 (1H, q, 6.2 Hz, C(=O)C₆H₄) 3.65 (1H, d, 15.0 Hz, C(=O)CH₆H₄C(=O)) 3.58 (1H, d, 15.0 Hz, C(=O)CH₆H₄C(=O)) 1.43 (9H, s, OC(CH₃)₃) 1.20 (3H, d, 6.2 Hz, CH₃) 0.88 (9H, s, Si(CH₃)₃) 0.04 (3H, s, Si(CH₃)₂) 0.01 (3H, s, Si(CH₃)) ¹³C NMR (150MHz; CDCl₃) δ 193.71, 166.67, 152.80, 125.04, 81.88, 65.90, 47.32, 27.87, 25.78, 24.67, 18.14, -4.99, -5.06.

6-Methyl-5-methylene-dihydro-pyran-2,4-dione (214)

To a solution of β-keto ester 220 (600 mg; 1.83 mmol) in CH₂Cl₂ (40 mL) and CH₃CN (40 mL) at 0°C was added 40% aqueous HF solution (8.5 mL; 0.2 mol). The mixture was stirred for 2 hours at 0°C, and then warmed to room temperature for a further 2 hours. The mixture was quenched by the addition of NaHCO₃ solution (50 mL), extracted with Et₂O (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (30% Et₂O/CH₂Cl₂) gave the unsaturated β-keto lactone 214 (210 mg; 82%) as clear oil. Data in agreement with that described above.
**Experimental Procedures for Chapter Two**

2-Methyl-butyric acid 2-methyl-3-methylene-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (221)

\[
\begin{align*}
\text{214} & \quad + \quad \text{199} \quad \xrightarrow{\text{DBU, Toluene}} \quad \text{221}
\end{align*}
\]

To a solution of unsaturated diketopyranone 214 (200 mg; 1.42 mmol) in toluene (10 mL) was added DBU (380 µL; 1.50 mmol) at room temperature and stirring continued for 20 minutes. The mixture was cooled to 0°C and 2-methylbutyryl chloride (199) (200 µL; 1.60 mmol) was added dropwise and the solution was stirred for a further two hours. A buffer solution (10 mL; pH 7) was added to quench the reaction and the mixture extracted with toluene (2*5 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the O-acylated diester product 221 (271 mg; 85%) as a clear colourless oil. Data in agreement with that described above for 204.

4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)

The diester 221 (90 mg; 0.40 mmol) was dissolved in toluene (2 mL) and PPY (3 mg; 0.02 mmol) was added in one portion at room temperature. The mixture was heated to 85°C and stirring continued for six hours at that temperature before concentrated in vacuo. Similar to use of DMAP, analysis of the crude NMR mixture indicated the loss of CR377's vinylic protons along with the decomposition of the racemic lactone 221.
4-Hydroxy-6-methyl-3-(2-methyl-butyl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)

The diester 221 (100 mg; 0.45 mmol) was added to BF$_3$-OEt$_2$ (0.2 mL; 2.22 mmol) at room temperature. The mixture was heated to 85°C and stirring continued for six hours at that temperature. The reaction was cooled by the addition of ice water (3 mL) and extracted with EtOAc (3*3 mL). The organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Analysis of the crude $^1$H NMR material revealed that some decomposition of the diester 221 had occurred but following purification by column chromatography the majority of the diester 221 material (90%) was recovered without alteration.

4-Hydroxy-6-methyl-3-(2-methyl-butyl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)

To a solution of diester 221 (100 mg; 0.45 mmol) in methylene chloride (10 mL) was added AlCl$_3$ (133 mg; 1.0 mmol) at room temperature. The mixture was heated to reflux (40°C) and stirring continued for six hours at that temperature. The reaction was quenched by the addition of a 2 M HCl (5 mL) solution and extracted with CH$_2$Cl$_2$ (3*10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Analysis of the crude $^1$H NMR material revealed that under these reaction conditions the diester 221 material had completely decomposed.
4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)

To a solution of racemic β-keto lactone 214 (20 mg; 0.14 mmol) in CH₂Cl₂ (1 mL) at 0°C was added DBU (23 µL; 0.15 mmol). The mixture was stirred for 15 minutes then TMSCl (20 µL; 0.15 mmol) was added at 0°C and the mixture was further stirred for 1 hour. The mixture was then cooled to -78°C and a solution of TiCl₄ (150 µL of a 1 M solution in CH₂Cl₂; 0.15 mmol) and 2-methylbutyryl chloride (199) (33 µL; 0.3 mmol) was added. This mixture was further stirred for 2 hours then warmed to 0°C for a further hour. The reaction was quenched with a saturated ammonium chloride solution (3 mL), extracted CH₂Cl₂ (3*3 mL), dried (Na₂SO₄) and concentrated in vacuo. Analysis of ¹H NMR showed the presence of the lactone 214 starting material, indicating that neither the TMS-enol ether 222 or the following Mukiyama aldol product, CR377 (9) had formed.

6-Methyl-4-morpholin-4-yl-5,6-dihydro-pyran-2-one (223)

To a solution of model-pyranone 214 (100 mg; 0.78 mmol) in toluene (10 mL) was added morpholine (90 µL; 1 mmol) and p-TSOH (8 mg; 0.04 mmol) at room temperature. The reaction mixture was heated to 115°C for 6 hours and the resultant water collected using dean and stark apparatus. The mixture was allowed to cool to room temperature then concentrated in vacuo. Analysis of the crude ¹H NMR indicated no enamine formation and that the model pyranone 214 had decomposed under the above conditions.
5.3 Experimental Procedures for Chapter Three

3-Hydroxy-4-methyl-pent-4-enoic acid tert-butyl ester (243)

To a solution of LiHMDS (4.50 mL; 1 M in THF 4.50 mmol) was added t-butyl acetate (130) (0.60 mL; 4.3mmol) at -78°C. The mixture was stirred for 30mins at this temperature then THF (30 mL) was added followed by methacrolein (244) (0.35 mL; 4.3mmol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was quenched with NH₄Cl (20 mL), extracted with diethyl ether (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the β-hydroxy ester 243 in (0.70 g; 88%) as a clear yellow oil. \( R_f = 0.2 \), \(^1\)H NMR (600MHz; CDCl₃) δ 4.98 (1H, d, 0.7 Hz, C=CH₂CH₃) 4.83 (1H, d, 0.7 Hz, C=CH₂CH₃) 4.39 (1H, m, C=CH₂(OH)) 3.28 (1H, d, 4.0 Hz, CH(OH)) 2.45 (2H, m, CH(OH)CH₂C(=O)) 1.71 (3H, s, CH₂=CH₂(CH₃)) 1.43 (9H, s, C(CH₃)₃) \(^{13}\)C NMR (150MHz; CDCl₃) δ 171.92, 145.50, 111.20, 81.27, 71.54, 40.92, 27.97, 18.13

2,2-Dichloro-4-methyl-3-oxo-pent-4-enoic acid tert-butyl ester (252)

To a solution of DMSO (0.34mL; 4.8x10⁻³ mol) in CH₂Cl₂ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH₂Cl₂ (1.2 mL; 2.4x10⁻³ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of β-hydroxyester 243 (0.30 g; 1.6x10⁻³ mol) in CH₂Cl₂ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.33 mL; 9.6x10⁻³ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched with NH₄Cl (20 mL), extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the α,α-dichlorinated product 252 (0.33 g; 82%) as a clear oil. \( R_f = 0.80 \), \(^1\)H NMR (600MHz; CDCl₃) δ 6.05 (1H, brs, C=CH₂CH₃) 5.92 (1H, d, 1.4, C=CH₂CH₃) 5.92 (1H, d, 1.4, C=CH₂CH₃)  5.92 (1H, d, 1.4, C=CH₂CH₃)
2HC=C(CH$_3$)$_3$) 1.47 (9H, s, C(CH$_3$)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 184.38, 162.49, 138.36, 127.90, 86.29, 82.59, 27.31, 19.44

3-[[2,4-Dinitro-phenyl]-hydrazono]-4-methyl-pent-4-enoic acid tert-butyl ester (247)

![Chemical Structure](image1)

To a premade solution of dinitrophenylhydrazine (246) (79 mg; 0.4 mmol), ethanol (4 mL) and H$_2$SO$_4$ (3 drops) was added a solution of unknown oxidation product 252 (50 mg; 0.19 mmol) in ethanol (2 mL) at room temperature. The mixture was heated to reflux for 1 hour, and then cooled and the precipitate filtered. The precipitate was washed with water (5 mL) and then recrystallised from ethyl acetate. The precipitate recovered was dinitrophenylhydrazine (246) reagent and the concentrated filtrate residue contained only decomposition products.

2,2-Dichloro-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-oxo-pentanoic acid tert-butyl ester (250)

![Chemical Structure](image2)

To a solution of phthalimide (248) (30 mg; 0.2 mmol) in THF (2 mL) at -78°C was added n-butyl lithium (0.13 mL; 0.2 mmol; 1.5 M in ether) dropwise. This mixture was stirred for 15 minutes and the unknown oxidation product 252 (50 mg; 0.19 mmol) was added via cannula (THF). The mixture was further stirred at -78°C for one hour then warmed to 0°C and quenched NH$_4$Cl (4 mL), extracted with diethyl ether (2*5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. NMR analysis showed the presence of both the unknown
Experimental Procedures for Chapter Three

Oxidation product 252 and phthalimide (248) reagents indicating no desired conjugate addition product had formed.

2,2-Dichloro-4-methyl-5-(3-nitro-phenylamino)-3-oxo-pentanoic acid tert-butyl ester (253)

To a solution of m-nitroaniline (249) (0.28 g; 2 mmol) in THF (5 mL) at -78°C was added n-butyl lithium (1.33 mL; 2 mmol; 1.5 M in ether) dropwise. This mixture was stirred for 15 minutes and the unknown oxidation product 252 (0.5 g; 1.98 mmol) was added via cannula (THF). The mixture was further stirred at -78°C for one hour then warmed to 0°C and quenched NH₄Cl (20 mL), extracted with diethyl ether (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the m-nitroaniline unknown oxidation product solid derivative 253 (0.46 g; 60%) as orange crystals. 

R_f = 0.25, ¹H NMR (600MHz; CDCl₃) δ 7.52 (1H, dd, 8.1, 1.9 Hz, ArH) 7.40 (1H, t, 2.2 Hz, ArH) 7.27 (1H, t, 8.10 Hz, ArH) 6.86 (1H, dd, 8.0, 2.2 Hz, ArH) 4.46 (1H, t, 6.2 Hz, NH) 3.59 (2H, m, CH₂NH) 3.32 (1H, m, CH(CH₃) 1.52 (9H, s, C(CH₃)₃) 1.37 (3H, d, 6.6 Hz, CH(CH₃)) ¹³C NMR (150MHz; CDCl₃) δ 197.28, 161.83, 149.34, 148.19, 129.80, 118.70, 112.14, 106.01, 86.76, 82.35, 47.01, 40.42, 27.44, 17.43, HRESIMS calculated for C₁₆H₂₀Cl₂N₂O₅⁺ [M+H]⁺: 390.0749; found 390.0725
Crystal data and Structure Refinement for 253

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3-Hydroxy-4-methyl-pentanoic acid tert-butyl ester (259)

\[
\begin{align*}
265 & \quad + \quad 130 \\
& \xrightarrow{\text{LiHMDS, THF}} 259
\end{align*}
\]

To a solution of LiHMDS (4.50 mL; 1 M in THF, 4.5 mmol) was added t-butyl acetate (130) (0.60 mL; 4.3x10$^{-3}$ mol) at -78°C. The mixture was stirred for 30 mins at this temperature then THF (30 mL) was added followed by isobutylaldehyde (265) (0.40 mL; 4.3x10$^{-3}$ mol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was quenched with NH$_4$Cl (20 mL), extracted with diethyl ether (3x50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (10% Et$_2$O/CH$_2$Cl$_2$) gave the β-hydroxy ester 259 in (0.75 g; 93%) as a clear yellow oil. R$_f$ = 0.25, $^1$H NMR (600 MHz; CDCl$_3$) δ 3.68 (1H, m, CH$_2$(OH)) 3.14 (1H, d, 3.8 Hz, CH(OH)) 2.37 (1H, dq, 5.7, 16.2 Hz, CH(OH)CH$_3$H$_9$C(=O)) 2.29 (1H, dq, 5.7, 16.2 Hz,
Experimental Procedures for Chapter Three

CH(OH)CH₃H₆C(=O)) 1.65 (1H, m, (CH₃)₂CH) 1.42 (9H, s, OC(CH₃)₃) 0.90 (3H, d, 6.8 Hz, (CH₃)₂CH) 0.87 (3H, d, 6.8 Hz, (CH₃)₂CH) ³¹C NMR (150MHz; CDCl₃) δ 172.90, 81.07, 72.70, 39.34, 33.04, 28.00, 18.25, 17.73

3-Hydroxy-pentanoic acid tert-butyl ester (260)

To a solution of LiHMDS (4.50 mL; 1 M in THF, 4.5 mmol) was added t-butyl acetate (130) (0.60 mL; 4.3x10⁻³ mol) at -78°C. The mixture was stirred for 30mins at this temperature then THF (30 mL) was added followed by propionaldehyde (266) (0.31 mL; 4.3x10⁻³ mol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was quenched with NH₄Cl (20 mL), extracted with diethyl ether (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the β-hydroxy ester 260 in (0.71 g; 95%) as a clear yellow oil. R₂ = 0.30, ¹H NMR (600MHz; CDCl₃) δ 3.87 (1H, m, (CH₃)OH) 3.13 (1H, brs, CH(OH)) 2.41 (1H, dq, 6.3, 16.4 Hz, CH(OH)CH₃H₆C(=O)) 2.30 (1H, dq, 6.3, 16.4 Hz, CH(OH)CH₃H₆C(=O)) 1.52 (2H, m, CH₂CH₃) 1.45 (9H, s, OC(CH₃)₃) 0.94 (3H, t, 7.4 Hz, CH₂CH₃) ³¹C NMR (150MHz; CDCl₃) δ 172.58, 81.13, 69.37, 41.78, 29.25, 28.04, 9.77

3-Hydroxy-3-phenyl-propionic acid tert-butyl ester (261)

To a solution of LiHMDS (4.50 mL; 1 M in THF, 4.5 mmol) was added t-butyl acetate (130) (0.60 mL; 4.3x10⁻³ mol) at -78°C. The mixture was stirred for 30mins at this temperature then THF (30 mL) was added followed by benzaldehyde (267) (0.43 mL; 4.3x10⁻³ mol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was quenched with NH₄Cl (20 mL), extracted with diethyl ether (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the β-hydroxy
ester 261 in (0.86 g; 90%) as a clear yellow oil. Rf = 0.30, $^1$H NMR (600MHz; CDCl$_3$) δ 7.36-7.24 (5H, m, ArH) 5.06 (1H, dt, 8.8, 3.7 Hz, (CH)OH) 3.60 (1H, d, 3.7 Hz, CH(OH)) 2.64 (1H, dq, 16.1, 8.8 Hz, CH(OH)CH$_3$CH$_2$C(=O)) 2.62 (1H, dq, 16.1, 8.8 Hz, CH(OH)CH$_3$CH$_2$C(=O)) 1.44 (9H, s, OC(CH$_3$)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 171.70, 142.60, 128.31, 127.50, 125.62, 81.31, 70.27, 44.23, 27.93

3-Hydroxy-4-methyl-pent-4-enolic acid ethyl ester (262)

To a solution of LiHMDS (5.7 mL; 1 M in THF, 5.7 mmol) was added ethyl acetate (119) (0.50 mL; 5.7x10$^{-3}$ mol) at -78°C. The mixture was stirred for 30 mins at this temperature then THF (30 mL) was added followed by methacrolein (244) (0.47 mL; 5.7x10$^{-3}$ mol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was quenched with NH$_4$Cl (20 mL), extracted with diethyl ether (3*50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (10% Et$_2$O/CH$_2$Cl$_2$) gave the β-hydroxy ester 262 in (0.72 g; 80%) as a clear yellow oil. Rf = 0.17, $^1$H NMR (600MHz; CDCl$_3$) δ 4.99 (1H, brs, C=C$_A$H$_B$) 4.83 (1H, brs, C=CH$_A$H$_B$) 4.44 (1H, q, 4.0 Hz, (CH)OH) 4.14 (2H, q, 7.2 Hz, OCH$_2$CH$_3$) 3.11 (1H, brs, CH(OH)) 2.52 (1H, q, 15.8, 4.0 Hz, CH(OH)CH$_3$CH$_2$C(=O)) 2.50 (1H, q, 15.8, 0.7 Hz, CH(OH)CH$_3$CH$_2$C(=O)) 1.72 (3H, s, (CH$_3$)C=CH$_3$CH$_3$) 1.23 (3H, t, 7.2 Hz, OCH$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 172.47, 145.45, 111.32, 71.43, 60.69, 40.00, 18.07, 14.05

5-Hydroxy-2,2,6-trimethyl-hept-6-en-3-one (263)

To a solution of LiHMDS (4.0 mL; 1 M in THF, 4.0 mmol) was added pinacolone (264) (0.50 mL; 4.0x10$^{-3}$ mol) at -78°C. The mixture was stirred for 30 mins at this temperature then THF (30 mL) was added followed by methacrolein (244) (0.34 mL; 4.0x10$^{-3}$ mol) dropwise. The following mixture was stirred at this temperature for a further 45 minutes then warmed to room temperature. The reaction was
Experimental Procedures for Chapter Three

quenched with NH₄Cl (20 mL), extracted with diethyl ether (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the β-hydroxy ketone 263 in (0.59 g; 81%) as a clear yellow oil. Rₚ = 0.24, ¹H NMR (600MHz; CDCl₃) δ 4.99 (1H, brs, C=CH₂H₆) 4.83 (1H, brs, C=CH₆H₂) 4.44 (1H, d, 8.8 Hz, CH(OH)) 3.29 (1H, d, 2.9 Hz, CH(OH)) 2.69 (1H, q, 17.6, 8.8 Hz, CH(OH)CH₆H₂C(=O)) 2.67 (1H, q, 17.6, 3.30 Hz, CH(OH)CH₆H₂C(=O)) 1.73 (3H, s, CH₃C=CH₆H₂) 1.12 (9H, s, C(CH₃)₃) ¹³C NMR (150MHz; CDCl₃) δ 217.04, 145.79, 110.99, 71.07, 44.38, 41.71, 26.14, 18.40

2,2-Dichloro-4-methyl-3-oxo-pentanoic acid tert-butyl ester (268)

To a solution of DMSO (0.34 mL; 4.8x10⁻³ mol) in CH₂Cl₂ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH₂Cl₂ (1.2 mL; 2.4x10⁻³ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of β-hydroxyester 259 (0.30 g; 1.6x10⁻³ mol) in CH₂Cl₂ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.33 mL; 9.6x10⁻³ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched after 12 hours with NH₄Cl (20 mL), extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the α,α-dichlorinated product 268 (0.29 g; 70%) as a clear oil. Rₚ = 0.90, ¹H NMR (600MHz; CDCl₃) δ 3.15 (1H, septet, 6.7 Hz, (CH₃)₂C) 1.47 (9H, s, OC(CH₃)₃) 1.22 (6H, d, 6.7 Hz, (CH₃)₂CH) ¹³C NMR (150MHz; CDCl₃) δ 198.42, 161.93, 86.29, 82.92, 35.93, 27.45, 20.90*2
2,2-Dichloro-3-oxo-pentanoic acid tert-butyl ester (269)

To a solution of DMSO (0.37 mL; 5.1x10⁻³ mol) in CH₂Cl₂ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH₂Cl₂ (1.28 mL; 2.6x10⁻³ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of β-hydroxyester 260 (0.30 g; 1.7x10⁻³ mol) in CH₂Cl₂ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.41 mL; 10.2x10⁻³ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched after 15 hours with NH₄Cl (20 mL), extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the α,α-dichlorinated product 269 (0.32 g; 78%) as a clear oil. Rᵣ = 0.92, ¹H NMR (600MHz; CDCl₃) δ 2.78 (1H, q, 7.2 Hz, CH₂CH₃) 1.48 (9H, s, OC(CH₃)₃) 1.16 (3H, t, 7.2 Hz, (CH₃)CH₂) ¹³C NMR (150MHz; CDCl₃) δ 195.02, 161.98, 86.24, 82.61, 29.65, 27.43, 8.64

2,2-Dichloro-3-oxo-3-phenyl-propionic acid tert-butyl ester (270)

To a solution of DMSO (0.29 mL; 4.0x10⁻³ mol) in CH₂Cl₂ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH₂Cl₂ (0.98 mL; 1.95x10⁻³ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of β-hydroxyester 261 (0.30 g; 1.3x10⁻³ mol) in CH₂Cl₂ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.1 mL; 7.8x10⁻³ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched with NH₄Cl (20 mL), extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the α,α-dichlorinated product 270 (0.32 g;
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85%) as a clear oil. $R_f = 0.85$, $^1H$ NMR (600MHz; CDCl$_3$) $\delta$ 7.99 (2H, d, 8.4 Hz, ArH) 7.58 (1H, t, 7.7 Hz, ArH) 7.44 (2H, t, 7.7 Hz, ArH) 1.33 (9H, s, OC(CH$_3$)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 183.08, 162.44, 133.97, 131.22, 129.82, 128.53, 86.39, 82.78, 27.15

2,2-Dichloro-4-methyl-3-oxo-pent-4-enoic acid ethyl ester (271)

![Chemical Structure]

To a solution of DMSO (0.40 mL; 5.7x10$^{-3}$ mol) in CH$_2$Cl$_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH$_2$Cl$_2$ (1.43 mL; 2.9x10$^{-3}$ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of $\beta$-hydroxyester 262 (0.3 g; 1.9x10$^{-3}$ mol) in CH$_2$Cl$_2$ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.58 mL; 11.4x10$^{-3}$ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched with NH$_4$Cl (20 mL), extracted with CH$_2$Cl$_2$ (3*50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave the $\alpha,\alpha$-dichlorinated product 271 (0.38 g; 89%) as a clear oil. $R_f = 0.87$, $^1H$ NMR (600MHz; CDCl$_3$) $\delta$ 6.07 (1H, s, CH$_3$C=CH$_2$A) 5.93 (1H, q, 1.5 Hz, CH$_3$C=CH$_2$B) 4.33 (2H, q, 7.0 Hz, OCH$_2$CH$_3$) 1.97 (3H, s, CH$_3$C=CH$_2$H$_3$) 1.29 (3H, t, 7.0 Hz, OCH$_2$H$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 184.37, 164.02, 138.06, 128.44, 128.44, 86.39, 82.78, 27.15

4,4-Dichloro-2,6,6-trimethyl-hept-1-ene-3,5-dione (272) and 4-Chloro-2,6,6-trimethyl-hept-1-ene-3,5-dione (273)

![Chemical Structure]

To a solution of DMSO (0.38 mL; 5.3x10$^{-3}$ mol) in CH$_2$Cl$_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in CH$_2$Cl$_2$ (1.35 mL; 2.7x10$^{-3}$ mol) dropwise and allowed to stir for 20 minutes at this
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temperature. A solution of β-hydroxyketone 263 (0.3 g; 1.8x10⁻³ mol) in CH₂Cl₂ was added and the mixture was stirred at this temperature for 30 minutes. Triethylamine (1.50 mL; 10.8x10⁻³ mol) was then added to the mixture and stirring continued at -78°C for 2 hours, then warmed to room temperature whereby the formation of the dichlorinated product was monitored by TLC analysis. The mixture was quenched after 6 hours with NH₄Cl (20 mL), extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% Hexanes/CH₂Cl₂) gave the major α,α-dichlorinated product 272 (0.19 g; 45%) as a clear oil and the minor α-chlorinated product 273 (90 mg; 25%) as a clear oil. Major 272: R_f = 0.6, ¹H NMR (600MHz; CDCl₃) δ 6.17 (1H, brs, CH₃C=C,H₆) 6.00 (1H, s, CH₃C=CH₆) 1.52 (3H, s, C(CH₃)₃) 1.17 (9H, s, C(CH₃)₃) ¹³C NMR (150MHz; CDCl₃) δ 199.65, 199.63, 136.47, 109.07, 77.98, 38.91, 27.35, 18.21 Minor 273: R_f = 0.5, ¹H NMR (600MHz; CDCl₃) δ (1H, d, 0.78 Hz, CH₃C=CH₆H₆), 5.97 (1H, m, CH₃C=CH₆H₆), 5.82 (1H, s, C(O)CHClC(O)), 1.94 (3H, brs, CH₃C=C,H₆CH₆), 1.20 (9H, s, C(CH₃)₃) ¹³C NMR (150MHz; CDCl₃) δ 204.02, 191.05, 142.00, 127.46, 58.44, 44.72, 26.90, 18.05
5.4 Experimental Procedures for Chapter Four

2,2,2-Trichloro-acetimidic acid benzyl ester (339)

\[
\begin{align*}
\text{OH} & \quad \text{KOH} \\
\text{Cl}_3\text{CCN} & \quad \text{NH} \\
\text{OH} & \quad \text{Cl}_3\text{CCN}
\end{align*}
\]

To a solution of benzyl alcohol (340) (18 mL; 0.16 mol) in CH$_2$Cl$_2$ (100 mL) was added 50% (w/w) KOH solution (50 g in 100 mL H$_2$O) and tetrabutylammonium hydrogen sulphate (200 mg) at 0°C. The reaction was stirred at this temperature for 20 minutes then trichloroacetonitrile (16 mL; 0.16 mol) was added and the reaction was stirred for a further 20 minutes. The mixture was then warmed to ambient temperature and allowed to stir for 2 hours. The solution was diluted with H$_2$O (150 mL) and extracted with CH$_2$Cl$_2$ (3*50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Distillation of the crude imidate by Kuleghor (b.p. 110°C @ 0.5 mmHg) gave the benzyl imidate 339 (38 g; 94%) as a clear colourless oil. $^1$H NMR (600MHz; CDCl$_3$) δ 8.45 (1H, brs, NH) 7.48 (2H, d, ArH) 7.43 (2H, t, ArH) 7.38 (1H, t, ArH) 5.39 (2H, s, C$_2$H$_2$Ph) $^{13}$C NMR (150MHz; CDCl$_3$) δ 207.30, 162.46, 135.37, 128.46, 128.21, 127.63, 70.64.

3-Benzylxy-2(S)-methyl-propionic acid methyl ester (338)

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{O} & \quad \text{Bn-Imidate} \\
\text{MeO} & \quad \text{OBn}
\end{align*}
\]

To a solution of (S)-methyl-3-hydroxy-2-methylpropionate (337) (5 g; 42 mmol) in cyclohexane (100 mL) and CH$_2$Cl$_2$ (50 mL) was added benzyl imidate 339 (16 g; 63 mmol). Trifluoromethanesulfonic acid (0.83 mL) was then added dropwise, giving a white precipitate, and the resulting mixture was stirred at room temperature for 18-24 hours. The crystalline residue was triturated with hexanes (3*20 mL) and removed by gravity filtration. The filtrate was washed with NaHCO$_3$ (3*20 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave the ester 338 (7.8 g; 95%) as a clear oil. $R_f = 0.50$ $^1$H NMR (600MHz; CDCl$_3$) δ 7.35-7.27 (5H, m, ArH) 7.48 (2H, d, ArH) 7.43 (2H, t, ArH) 7.38 (1H, t, ArH) 5.39 (2H, s, CH$_2$Ph) $^{13}$C NMR (150MHz; CDCl$_3$) δ 207.30, 162.46, 135.37, 128.46, 128.21, 127.63, 70.64.
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9.0, 5.9 Hz, CH₃CH₂OBn) 2.79 (1H, dq, 7.1, 6.0 Hz, CH(CH₃)CH₂OBn) 1.18 (3H, d, 7.1 Hz, CH(CH₃)CH₂OBn) 13C NMR (150MHz; CDCl₃) δ 175.30, 138.13, 128.33, 127.58, 127.56, 73.07, 71.92, 51.71, 40.15, 13.96.

3-Benzylxoy-N-methoxy-2,N-dimethyl-propionamide (341)

To a solution of benzyl ester 338 (5 g; 24 mmol) in THF (60 mL) and Et₂O (60 mL) was added N,O-dimethylhydroxylamine hydrochloride (5.85 g; 60 mmol). The mixture was cooled to -20°C and i-PrMgCl (60 mL; of a 2 M solution in THF; 120 mmol) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at -20°C for a further 30 minutes then at 0°C for a further 30 minutes before saturated NH₄Cl (200 mL) was added cautiously. The mixture was extracted with Et₂O (3*100 mL) and CH₂Cl₂ (3*100 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (20% EtOAc/hexanes) to give the amide 341 (5.20 g; 91%) as a colourless oil. Rf = 0.1, ¹H NMR (600MHz; CDCl₃) δ 7.30-7.23 (5H, m, ArH) 4.54 (1H, d, 12.1 Hz, CH₂CH₂Ph) 4.46 (1H, d, 12.1 Hz, CH₂CH₂Ph) 3.70 (1H, t, 8.6 Hz, CH₂CH₂OBn) 3.68 (3H, s, NOCH₃) 3.42 (1H, dd, 8.6, 5.8 Hz, CH₂CH₂OBn) 3.28 (1H, m, CH(CH₃)CH₂OBn) 3.19 (3H, brs, NCH₃) 1.10 (3H, d, 7.0 Hz, CH(CH₃)CH₂OBn) 13C NMR (150MHz; CDCl₃) δ 175.77, 138.25, 128.16, 127.39, 127.34, 73.06, 72.44, 61.40, 35.65, 31.91, 14.08.

1-Benzylxoy-2(S)-methyl-pentan-3-one (332)

To a solution of amide 341 (4.40 g; 18.5 mmol) in THF (75 mL) was added EtMgBr (60 mL; of a 1 M solution in THF; 60 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature for 2-3 hours then saturated NH₄Cl (100 mL) was carefully added. The mixture was extracted with Et₂O (3*100 mL) and CH₂Cl₂ (3*100 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column
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chromatography (CH$_2$Cl$_2$) gave the ketone 332 (3.7 g; 91%) as a clear oil. R$_f$ = 0.55, $^1$H NMR (600MHz; CDCl$_3$) δ 7.35-7.26 (5H, m, ArH) 4.49 (1H, d, 12.0 Hz, OCH$_3$CH$_3$Ph) 4.46 (1H, d, 12.0 Hz, OCH$_3$CH$_3$Ph) 3.63 (1H, dd, 9.1, 8.0 Hz, CH$_3$CH$_2$OBn) 3.46 (1H, dd, 9.1, 5.4 Hz, CH$_3$CH$_2$OBn) 2.88 (1H, m, CH(CH$_3$)CH$_2$OBn) 2.50 (2H, dq, 7.3, 1.2 Hz, CH$_2$CH$_3$) 1.07 (3H, d, 7.1 Hz, CH(CH$_3$)CH$_2$OBn) 1.04 (3H, t, 7.3 Hz, CH$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 213.53, 138.01, 128.21, 127.45, 127.39, 73.05, 72.23, 46.02, 35.14, 13.47, 7.40.

1-Benzyl-5(S)-hydroxy-2(S),4(R)-dimethyl-heptan-3-one (333)

![Chemical Structure](image)

To a solution of benzyl ketone 332 (5 g; 22.5 mmol) in CH$_2$Cl$_2$ (120 mL) was added a mixture of TiCl$_4$ (20.5 mL; 1 M of a solution in CH$_2$Cl$_2$; 20.5 mmol) and Ti(i-iPrO)$_4$ (2 mL; 6.8 mmol) at -78°C via cannula. The mixture was stirred for 20 minutes then iPr$_2$NET (4.3 mL; 24.7 mmol) was added and the mixture was stirred for a further 1 hour. Freshly distilled propionaldehyde (266) (2.5 mL; 34 mmol) was then added and the mixture was stirred for a further hour then warmed to room temperature over an additional hour. The reaction was then quenched by the addition of saturated NH$_4$Cl (100 mL), extracted with CH$_2$Cl$_2$ (3*100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave the major aldol adduct 333 (5.20 g; 79%) as clear colourless liquid. **Major Isomer 333:** R$_f$ = 0.3, $^1$H NMR (600MHz; CDCl$_3$) δ 7.35-7.26 (5H, m, ArH) 4.44 (1H, d, 11.8 Hz, CH$_3$CH$_3$Ph) 4.41 (1H, d, 11.8 Hz, CH$_3$CH$_3$Ph) 3.89-3.87 (1H, m, CHOH) 3.64 (1H, t, 9.0 Hz, CH$_3$CH$_2$OBn) 3.46 (1H, dd, 9.0, 5.0 Hz, CH$_3$CH$_2$OBn) 3.18-3.12 (1H, m, C(=O)CH(CH$_3$)CHOH) 2.96 (1H, d, 3.3 Hz, CHOH) 2.74 (1H, dq, 7.1, 3.0 Hz, CH(CH$_3$)CH$_2$OBn) 1.50-1.43 (1H, m, CH$_3$CH$_2$CH$_3$) 1.38-1.32 (1H, m, CH$_3$CH$_2$CH$_3$) 1.07 (3H, d, 7.1 Hz, C(=O)CH(CH$_3$)CHOH) 1.02 (3H, d, 7.1 Hz, CH(CH$_3$)CH$_2$OBn) 0.89 (3H, t, 7.6 Hz, CH$_3$CH$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 218.20, 137.47, 128.41, 127.82, 127.68, 73.45, 73.16, 72.09, 50.45, 44.77, 26.45, 13.58, 10.51, 8.67. **Minor Isomer:** R$_f$ = 0.4 $^1$H NMR (600MHz; CDCl$_3$) δ 7.34-7.26 (5H, m, ArH) 4.49 (1H, d, 11.8 Hz, CH$_3$CH$_3$Ph) 4.45 (1H, d, 11.8 Hz, CH$_3$CH$_3$Ph) 3.80-3.77 (1H, m, CHOH) 3.66 (1H, t, 9.0 Hz, CH$_3$CH$_2$OBn) 3.43 (1H, dd, 9.0, 5.0 Hz, CH$_3$CH$_2$OBn) 3.13-3.07 (1H, m, C(=O)CH(CH$_3$)CHOH) 2.92 (1H, brs, CHOH) 2.70 (1H, dq, 7.1, 2.8 Hz, CH(CH$_3$)OBn) 1.55-1.47 (1H, m, CH$_3$CH$_3$CH$_3$) 1.40-1.33 (1H, m, CH$_3$CH$_2$CH$_3$) 1.12 (3H, d, 7.1 Hz, C(=O)CH(CH$_3$)CHOH) 1.05 (3H, d, 7.1 Hz, CH(CH$_3$)2OBn) 0.92 (3H, t, 7.4
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Hz, CH$_3$CH$_2$ 13C NMR (150MHz; CDCl$_3$) δ 218.53, 137.80, 128.34, 127.65, 127.54, 73.32, 72.78, 72.28, 49.49, 45.12, 26.97, 13.79, 10.43, 8.89.

1-Benzylxoy-2(S),4(R)-dimethyl-heptane-3(S),5(S)-diol (334)

Tetramethylammonium triacetoxyborohydride (19 g; 76 mmol) was dissolved in acetonitrile (80 mL) and acetic acid (75 mL) at RT. The mixture was stirred for two hours then cooled to -20°C and alcohol 333 (2.5 g; 9.5 mmol) in acetonitrile (10 mL) was added via cannula. The mixture was stirred for a further two hours at this temperature then placed in the freezer for a further 48 hours. The reaction was quenched at 0°C with careful addition of NaHCO$_3$ (150 mL), warmed to room temperature and extracted with CH$_2$Cl$_2$ (3*100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (50% EtOAc/hexanes) gave the diol 334 (2.1 g; 83%) as a clear oil. R$_f$ = 0.5, 1H NMR (600MHz; CDCl$_3$) δ 7.37-7.26 (5H, m, ArH) 4.53 (2H, s, CH$_2$OBn) 3.90 (1H, t, 7.3 Hz, CH(OH)CH$_2$CH$_3$) 3.84 (1H, brs, CH(OH)) 3.68 (1H, dd, 9.0, 4.0 Hz, CH$_2$CH$_2$OBn) 3.66 (1H, m, CH(OH)) 3.59 (1H, dd, 8.3, 1.7 Hz, CH(CH$_3$)CH(OH)CH(CH$_3$)) 3.48 (1H, t, 9.0 Hz, CH$_2$CH$_2$OBn) 2.16-2.13 (1H, m, CH(CH$_3$)CH$_2$OBn) 1.74-1.70 (1H, qdd, 7.0, 3.7, 1.5 Hz, CH(OH)CH(CH$_3$)CH(OH)) 1.63-1.55 (1H, m, CH$_2$CH$_2$CH$_3$) 1.42-1.35 (1H, m, CH$_2$CH$_2$CH$_3$) 0.97 (3H, d, 7.2 Hz, CH$_2$CH$_2$OBn) 0.92 (3H, t, 7.4 Hz, CH$_2$CH$_3$) 0.84 (3H, d, 7.0 Hz, CH(OH)CH(CH$_3$)CH(OH)) 13C NMR (150MHz; CDCl$_3$) δ 137.29, 128.19, 127.54, 127.37, 81.40, 75.31, 73.21, 72.49, 36.62, 35.57, 26.90, 13.54, 10.69, 10.36.
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4-(2-Benzyloxy-1-methyl-ethyl)-2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan (355)

![Image of chemical structure](image1)

To a solution of diol 334 (1.60 g; 6 mmol) in CH₂Cl₂ (20 mL) was added 2,6-lutidine (2.3 mL; 19.7 mmol) and ditertbutylsilyl bistrifluoromethane sulfonate (3.3 mL; 10.1 mmol) at room temperature and stirred for 6 hours. The mixture was quenched with saturated NaHCO₃ (100 mL), extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the silyl protected ether 335 (2.20 g; 90%) as a clear oil. Rf = 0.80, ¹H NMR (600MHz; CDCl₃) δ 7.34-7.26 (5H, m, ArH) 4.52 (1H, d, 11.8 Hz, CH₂CH₂Ph) 4.47 (1H, d, 11.8 Hz, CH₂CH₂Ph) 3.85-3.82 (1H, m, CH₃CH₂C(CH(OSi)) 3.80 (1H, dd, 11.2, 1.6 Hz, CH(CH₃)CH(OSi)) 3.70 (1H, dd, 9.0, 5.4 Hz, CH₂CH₂OBn) 3.33 (1H, t, 9.0 Hz, CH₂CH₂OBn) 2.33-2.27 (1H, m, CH(OSi)CH(CH₃)CH(OSi)) 2.04-2.01 (1H, m, CH(CH₃)CH₂OBn) 1.52-1.42 (2H, m, CH₂CH₂) 1.09 (3H, d, 6.8 Hz, CH₃CH₂OBn) 1.05 (3H, t, 7.3 Hz, CH₃CH₂) 1.00 (9H, s, Si(CH₃)₃) 0.99 (9H, s, Si(CH₃)₃) 0.78 (3H, d, 7.2 Hz, CH(OSi)CH(CH₃)CH(OSi)) ¹³C NMR (150MHz; CDCl₃) δ 138.72, 128.27, 127.47, 127.36, 78.47, 76.51, 73.19, 70.98, 39.32, 36.03, 27.60, 27.25, 23.38, 21.54, 20.77, 15.82, 13.61, 10.97.

2-(2,2-Di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-propan-1-ol (336)

![Image of chemical structure](image2)

To a solution of silyl protected benzyl ether 335 (750 mg; 1.85 mmol) in ethanol (20 mL) was added Pd/C (50 mg) and H₂ gas at room temperature. The reaction mixture was stirred for 6 hours then filtered through celite and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the primary alcohol 336 (500 mg; 86%) as a clear oil. Rf = 0.32, ¹H NMR (600MHz; CDCl₃) δ 3.92-
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3.87 (3H, m, 2* CH(OSi), CH₃CH₂OH) 3.61 (1H, dd, 10.9, 4.3 Hz, CH₃CH₂OH) 2.36-2.30 (1H, m, CH(OSi)CH(CH₃)CH(OSi)) 1.80-1.74 (1H, m, CH(CH₃)CH₂OH) 1.48-1.44 (2H, m, CH₂CH₂) 1.14 (3H, d, 7.0 Hz, CH(OSi)CH(CH₃)CH(OSi)) 1.03 (3H, t, 7.3 Hz, CH₂CH₂) 1.00 (9H, s, SiC(CH₃)₃) 0.97 (9H, s, SiC(CH₃)₃) 0.82 (3H, d, 7.2 Hz, CH(OSi)CH(CH₂)CH(OSi)) 13C NMR (150MHz; CDCl₃) δ 79.06, 77.96, 63.96, 39.90, 36.38, 27.41, 27.25, 23.70, 21.59, 20.59, 14.96, 13.46, 10.83.

2-(2,2-Di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilan-4-yl)-propionaldehyde (330)

To a solution of DMSO (300 µL; 4.26 mmol) in CH₂Cl₂ (20 mL) at -78°C was added oxalyl chloride (1.06 mL of a 2 M solution in CH₂Cl₂; 2.13 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 336 (450 mg; 1.42 mmol) in CH₂Cl₂ (5 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt₃ (1.2 mL; 8.52 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH₄Cl (70 mL) then extracted with CH₂Cl₂ (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the desired aldehyde 330 (406 mg; 91%) as a colourless oil. R_f = 0.78, 1H NMR (600MHz; CDCl₃) δ 9.81 (1H, d, 3.1 Hz, CH(=O)) 4.01 (1H, dd, 9.7, 2.5 Hz, CH(OSi)CH(CH₂)CH(=O)) 3.87 (1H, dt, 9.6, 4.9 Hz, CH₃CH₂CH(OSi)) 2.49-2.42 (1H, m, CH(CH₃)CH(=O)) 2.33-2.29 (1H, m, CH(OSi)CH(CH₂)CH(OSi)) 1.48-1.44 (2H, m, CH₂CH₂) 1.25 (3H, d, 7.0 Hz, CH(CH₂)CH(=O)) 1.04 (3H, t, 7.3 Hz, CH₂CH₂) 1.00 (9H, s, SiC(CH₃)₃) 0.97 (9H, s, SiC(CH₃)₃) 0.82 (3H, d, 7.2 Hz, CH(OSi)CH(CH₂)CH(OSi)) 13C NMR (150MHz; CDCl₃) δ 205.55, 78.04, 76.23, 49.19, 39.95, 27.46, 27.14, 23.35, 21.50, 20.74, 13.49, 11.53, 10.82.
6-(2,2-Di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-5-hydroxy-2,4-dimethyl-heptan-3-one (343)

To a stirring solution of ketone 342 (130 µL; 1.05 mmol) in THF (200 µL) was added LiHMDS (1.1 mL of a 1 M solution in THF; 1.1 mmol) dropwise at -78°C. The mixture was stirred for 30 minutes, then silylaldehyde 330 (300 mg; 0.96 mmol) was added in THF (10 mL) via cannula at -78°C. The reaction continued to stir at this temperature for 1 hour then warmed to RT over another hour. The mixture was quenched with saturated NH₄Cl (30 mL), extracted with Et₂O (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the minor aldol product (30 mg; 7.5%) followed by the major aldol product 343 (300 mg; 76%) as clear oils.

**Major Isomer 343:**
- Rₚ = 0.4, ¹H NMR (600MHz; CDCl₃) δ 3.89-3.84 (3H, m, CH₃CH(CH₃)OSi), 3.74-3.71 (1H, m, C(=O)CH(CH₃)₂) 3.08 (1H, dq, 7.3, 3.1 Hz, C(=O)CH(CH₃)₂) 2.78 (1H, sept, 6.9 Hz, C(=O)CH(CH₃)₂) 2.44-2.41 (1H, m, CH(OSi)CH(CH₃)CH(OSi)) 1.86-1.82 (1H, m, CH(CH₃)CH(OH)) 1.50-1.38 (2H, m, CH₂CH₃) 1.27 (3H, d, 7.3 Hz, C(=O)CH(CH₃)₂) 1.10 (3H, d, 6.9 Hz, C(=O)CH(CH₃)₂) 1.08 (3H, d, 6.9 Hz, C(=O)CH(CH₃)₂) 1.02 (9H, s, Si(CH₃)₃) 1.00-0.98 (2H, m, CH₂CH₃) 0.98 (9H, s, Si(CH₃)₃) 0.93 (3H, d, 7.0 Hz, CH(CH₃)CH(OH)) 0.82 (3H, d, 7.1 Hz, CH(OSi)CH(CH₃)CH(OSi)) ¹³C NMR (150MHz; CDCl₃) δ 222.13, 78.84, 77.84, 76.37, 71.01, 40.78, 39.97, 27.60, 27.47, 23.97, 21.64, 20.97, 18.35, 18.21, 16.13, 15.66, 13.96, 10.93.

**Minor Isomer:**
- Rₚ = 0.45, ¹H NMR (600MHz; CDCl₃) δ 4.13 (1H, d, 9.8 Hz, CH(OH)) 3.92-3.90 (2H, m, CH₂CH₂CH(OSi), CH(OSi)CH(CH₃)CH(OH)) 3.89 (1H, s, CH(OH)) 2.93 (1H, dq, 9.8, 6.9 Hz, C(=O)CH(CH₃)₂) 2.70 (1H, sept, 6.9 Hz, C(=O)CH(CH₃)₂) 2.51-2.47 (1H, m, CH(OSi)CH(CH₃)CH(OSi)) 1.51-1.38 (3H, m, CH₂CH₃, CH(CH₃)CH(OH)) 1.21 (3H, d, 6.9 Hz, C(=O)CH(CH₃)₂) 1.11-1.08 (9H, m, 2*CH(CH₃)₂, CH₂CH₃) 1.06 (3H, d, 7.0 Hz, CH(CH₃)CH(OH)) 1.02 (9H, s, Si(CH₃)₃) 0.98 (9H, s, Si(CH₃)₃) 0.72 (3H, d, 7.1 Hz, CH(OSi)CH(CH₃)CH(OSi)) ¹³C NMR (150MHz; CDCl₃) δ 217.76, 79.85, 78.59, 71.17, 41.94, 41.48, 39.45, 35.46, 27.42, 27.21, 23.39, 21.71, 20.49, 18.03, 18.00, 15.32, 12.63, 11.39, 10.90.
To a solution of aldol product 343 (200 mg; 0.48 mmol) in THF (4.5 mL) at 0°C was added HF/Pyr/Pyr (3.42 mL of a 0.15 M solution in THF) solution dropwise. The reaction was allowed to warm to RT and stirring continued for three hours. The reaction was diluted with Et₂O (10 mL) and quenched with NaHCO₃ (20 mL) followed by CuSO₄ (10 mL). The aqueous layers were re-extracted with Et₂O (2*10 mL) dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% Et₂O/CH₂Cl₂) yielded model hemiacetal 344 (105 mg; 80%) as a clear oil. Rf = 0.35, ¹H NMR (600MHz; CDCl₃) δ 4.71 (1H, brs, CH(-O-)C(OH)) 3.90-3.85 (2H, m, CH₂CH₃CH(OH)) 3.73-3.68 (2H, m, CH(CH₃)C(OH)CH(CH₃)) 3.41 (1H, d, 5.9 Hz, CH(OH)) 1.96 (1H, sept, 6.8 Hz, CH(CH₃)₂) 1.89-1.84 (2H, m, CH₂CH₃) 1.78-1.73 (1H, m, CH(CH₃)CH(OH)) 1.63-1.56 (1H, m, CH(CH₃)CH(OH)CH(CH₃)) 1.40-1.33 (1H, m, CH(CH₃)CH(OH)CH₂CH₃) 1.06 (3H, d, 7.1 Hz, CH(CH₃)CH(OH)) 1.03 (3H, d, 7.0 Hz, CH(CH₃)CH(OH)CH₂CH₃) 0.95 (3H, d, 6.8 Hz, CH(CH₃)₂) 0.93-0.86 (6H, m, CH(CH₃)₂, CH₂CH₃) 0.84 (3H, d, 7.0 Hz, CH(CH₃)CH(OH)CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 102.07, 76.00, 74.65, 71.78, 38.21, 37.27, 34.74, 34.15, 27.18, 17.35, 14.46, 13.69, 12.76, 10.67, 10.48.

2-Hydroxy-2-isopropyl-3,5-dimethyl-6-(1-methyl-2-oxo-butyl)-tetrahydro-pyran-4-one (345)

To a solution of DMSO (165 µL; 2.22 mmol) in CH₂Cl₂ (10 mL) at -78°C was added oxalyl chloride (0.55 mL of a 2 M solution in CH₂Cl₂; 1.11 mmol) dropwise. The mixture was stirred for 20 minutes then hemiacetal 344 (100 mg; 0.37 mmol) in CH₂Cl₂ (5 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt₃ (0.62 mL; 4.44 mmol) was added and the solution was stirred for a
Further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH₄Cl (20 mL) then extracted with CH₂Cl₂ (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the diketone 345 (75 mg; 75%) as a colourless oil. 

Rf = 0.70, ¹H NMR (600MHz; CDCl₃) δ 3.83 (1H, dd, 10.3, 3.2 Hz, \(\text{CH}-(\text{OH})\text{CH}(\text{CH}_3)_2\)) 2.76 (1H, dq, 7.1, 3.4 Hz, \(\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{CH}(\text{CH}_3)\text{C}(\text{OH})\)) 2.64 (1H, q, 6.5 Hz, \(\text{C}(=\text{O})\text{CH}(\text{CH}_3)\text{C}(\text{OH})\)) 2.60 (1H, m, \(\text{CH}_5\text{CH}_3\text{CH}_3\)) 2.53 (1H, m, \(\text{CH}_5\text{CH}_3\text{CH}_3\)) 2.46 (1H, dq, 9.90, 6.6 Hz, \(\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{CH}(\text{CH}_3)\text{C}(\text{OH})\)) 1.98 (1H, sept, 6.8 Hz, \(\text{CH}(\text{CH}_3)_2\)) 1.28 (3H, d, 7.1 Hz, \(\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{CH}(\text{CH}_3)\text{C}(\text{OH})\)). ¹³C NMR (150MHz; CDCl₃) δ 213.31, 208.95, 103.35, 78.03, 49.50, 48.83, 47.35, 34.84, 34.70, 17.44, 14.67, 14.38, 9.65, 8.07, 7.36.

3-Hydroxy-2,4-dimethyl-pentanal (346)

To a solution of isobutyraldehyde (265) (7.5 mL; 83 mmol) in DMF (18 mL) and (L)-proline (450 mg; 4.1 mmol) was added freshly distilled propionaldehyde (266) (3 mL; 41.5 mmol) in DMF (20 mL) was added over 24 hours at 5°C. The mixture was diluted with Et₂O (150 mL) and washed with water (300 mL) and brine (100 mL). The aqueous layers are combined and re-extracted with Et₂O (3*50 mL) then dried (Na₂SO₄) and concentrated in vacuo. Due to stability of the final product 346 it was used in the following step without further purification. ¹H NMR (600MHz; CDCl₃) δ 9.77 (1H, d, 3.1 Hz, \(\text{CH}(=\text{O})\)) 3.54 (1H, dd, 10.9, 6.8 Hz, \(\text{CH}(\text{OH})\)) 2.54 (1H, dq, 10.9, 3.1 Hz \(\text{CH}(\text{CH}_3)\text{CH}((\text{OH})\)) 1.81-1.74 (1H, m, \(\text{CH}(\text{CH}_3)_2\)) 1.14-0.91 (9H, m, 2*\(\text{CH}(\text{CH}_3)_2\), \(\text{CH}(\text{CH}_3)\text{CH}((\text{OH})\)).
2,4-Dimethyl-pentane-1,3-diol (348)

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\text{To a stirring solution of aldehyde 346 (2 g; 15.4 mmol) in THF (30 mL) was added NaBH}_4 (1.70 g; 46 mmol) at ambient temperature. The reaction was stirred for 2-4 hours then quenched cautiously with HCl (2 M ~ 50mL) until all effervescence had ceased. The mixture was diluted with H}_2\text{O (100 mL) and extracted with CH}_2\text{Cl}_2 (3*50 mL), dried (Na}_2\text{SO}_4) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave the diol 348 (1.45 g; 71%) as a clear oil. R}_f =0.25, {^1}\text{H NMR (600MHz; CDCl}_3 \delta 3.69 (1H, dd, 10.9, 3.6 Hz, C\text{H}_A\text{CH}_B(OH)) 3.63 (1H, brs, CH(OH)) 3.55 (1H, dd, 10.9, 7.3 Hz, CH\text{A}C\text{H}_B(OH)) 3.45 (1H, brs, CH(OH)) 3.27 (1H, dd, 8.0, 3.8 Hz, CH(OH)) 1.90-1.84 (1H, m, CH(CH}_3}_2) 1.78-1.73 (1H, m, CH(CH}_3)) 0.88 (3H, d, 6.6 Hz, CH(CH}_3)) 0.84 (3H, d, 6.8 Hz, CH(CH}_3}_2) 0.80 (3H, d, 7.0 Hz, CH(CH}_3}_2) {^{13}}\text{C NMR (150MHz; CDCl}_3 \delta 81.58, 67.72, 36.88, 30.20, 19.60, 16.55, 14.98.}
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4-Isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (350)

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\text{To a solution of diol 348 (5 g; 38 mmol) in CH}_2\text{Cl}_2 (150 mL) was added anisaldehyde dimethyl acetal (6.5 mL; 38 mmol) and CSA (580 mg; 2.5 mmol) at room temperature. The reaction mixture was monitored by TLC analysis and extra acetal and acid were added as deemed required. The reaction was stirred for 48 hours at RT before being quenched with an equal amount of NaHCO}_3 (100 mL). The mixture was separated and extracted with CH}_2\text{Cl}_2 (3*100 mL), dried (Na}_2\text{SO}_4) and concentrated in vacuo. Purification by column chromatography (CH}_2\text{Cl}_2) yielded the protected acetal 350 (6.50 g; 68%) and as clear oil. R}_f = 0.6, {^1}\text{H NMR (600MHz; CDCl}_3 \delta 7.41 (2H, d, 8.6 Hz, ArH) 6.88 (2H, d, 8.6 Hz, ArH) 5.41 (1H, s, CHPMP) 4.08 (1H, dd, 11.1, 4.7 Hz, CH\text{A}CH}_3\text{O}) 3.80 (3H, s, OCH}_3) 3.47 (1H, t, 11.0 Hz, CHO) 3.29 (1H, dd, 9.9, 1.9 Hz, CH\text{A}CH}_3\text{O}) 1.95 (2H, m, CH(CH}_3), CH(CH}_3}_2) 1.05 (3H, d, 7.0 Hz, CH(CH}_3}_2) 0.96 (3H, d, 6.9 Hz, CH(CH}_3}_2)
\]
0.75 (3H, d, 6.7 Hz, CH(CH₃)) ¹³C NMR (150MHz; CDCl₃) δ 159.66, 131.68, 127.26, 113.42, 101.49, 100.90, 86.91, 73.14, 55.25, 30.96, 28.57, 20.02, 15.02, 12.13.

4-Isopropyl-5-methyl-2-phenyl-[1,3]dioxane (349)

To a solution of diol 348 (3 g; 22.7 mmol) in CH₂Cl₂ (80 mL) was added benzaldehyde dimethyl acetal (4.5 mL; 30 mmol) and CSA (580 mg; 2.5 mmol) at room temperature. The reaction mixture was monitored by TLC analysis and extra acetal and acid were added as deemed required. The reaction was stirred for 48 hours at RT before being quenched with an equal amount of NaHCO₃ (80 mL). The mixture was separated and extracted with CH₂Cl₂ (3*100 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) yielded the protected acetal 349 (4.0 g; 80%) and as clear oil. Rₚ = 0.63, ¹H NMR (600MHz; CDCl₃) δ 7.36 (2H, d, 6.0 Hz, ArH) 7.34-7.31 (3H, m, ArH) 5.49 (1H, s, CHPh) 4.11 (1H, dd, 11.4, 4.8 Hz, CH₆CH₆CH(CH₃)) 3.50 (1H, t, 10.8 Hz, CH₆CH₆CH(CH₃)) 3.31 (1H, d, 9.6, 1.8 Hz, CHO) 2.05-1.95 (2H, m, CH(CH₃), CH(CH₃)₂) 1.08 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.99 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.77 (3H, d, 6.6 Hz, CH(CH₃)) ¹³C NMR (150MHz; CDCl₃) δ 139.08, 128.47, 128.07, 126.00, 100.96, 86.93, 73.19, 31.00, 28.57, 20.03, 15.01, 12.11

3-(4-Methoxy-benzyloxy)-2,4-dimethyl-pentan-1-ol (352)

To a stirred solution of acetal 350 (2 g; 8 mmol) in CH₂Cl₂ (100 mL) was added DIBALH (13.3 mL; of a 1 M solution in toluene; 13.3 mmol) dropwise at -78°C. The mixture was stirred at this temperature for 3
hours then warmed to 0°C for a further hour. The reaction mixture was poured into a pre-cooled (0°C) of CH₂Cl₂ and 2 M HCl (200 mL; 1:1). The mixture was further diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the primary alcohol 352 (1.92 g; 95%) as a clear oil. Rₚ = 0.3, ¹H NMR (600MHz; CDCl₃) δ 7.27 (2H, d, 8.7 Hz, ArH) 6.86 (2H, d, 8.7 Hz, ArH) 4.57 (1H, d, 10.5 Hz, OCH₂CH₂PMP) 4.50 (1H, d, 10.5 Hz, OCH₂CH₂PMP) 3.79 (3H, s, OC₃H₃) 3.69 (1H, dd, 10.9, 3.1 Hz, CH₂OH) 3.58 (1H, dd, 10.9, 5.6 Hz, CH₂CH₂OH) 3.14 (1H, dd, 5.8, 5.2 Hz, CH₂OH) 1.96-1.85 (1H, m, CH(CH₃)₂, CH(CH₃)) 1.01-0.96 (9H, m, CH(CH₃), CH(CH₃)₂) ¹³C NMR (150MHz; CDCl₃) δ 159.19, 130.46, 129.34, 113.78, 89.84, 75.12, 66.01, 55.19, 37.09, 31.07, 20.17, 17.51, 15.59.

3-Benzoyloxy-2,4-dimethyl-pentan-1-ol (351)

To a stirred solution of acetal 349 (0.5 g; 2.27 mmol) in CH₂Cl₂ (50 mL) was added DIBALH (6.81 mL; of a 1 M solution in toluene; 6.81 mmol) dropwise at -78°C. The mixture was stirred at this temperature for 3 hours then warmed to 0°C for a further hour. The reaction mixture was poured into a pre-cooled (0°C) of CH₂Cl₂ and 2 M HCl (200 mL; 1:1). The mixture was further diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the primary alcohol 351 (0.47 g; 93%) as a clear oil. Rₚ = 0.35, ¹H NMR (600MHz; CDCl₃) δ 7.35-7.26 (5H, m, ArH) 4.62 (1H, d, 10.8 Hz, OCH₃CH₂Ph) 4.59 (1H, d, 10.8 Hz, OCH₃CH₂Ph) 3.73 (1H, dd, 10.9, 3.7 Hz, CH₃CH₂OH) 3.61 (1H, dd, 10.9, 5.5 Hz, CH₃CH₂OH) 3.17 (1H, t, 6.2 Hz, CHOBr) 2.73-2.69 (1H, m, CH₃CH₂(OH)) 1.98-1.90 (2H, m, CH(CH₃)₂, CH(CH₃)) 1.02-0.99 (9H, m, 2*CH(CH₃)₂, CH(CH₃)) ¹³C NMR (150MHz; CDCl₃) δ 138.29, 128.39, 127.67, 127.63, 90.20, 75.50, 66.05, 37.13, 31.12, 20.15, 17.58, 15.64.

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Experimental Procedures for Chapter Four
Experimental Procedures for Chapter Four

3-(4-Methoxy-benzyloxy)-2,4-dimethyl-pentanal (353)

![Chemical Structure](image)

To a solution of alcohol 352 (130 mg; 0.52 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added Dess-Martin periodinane (264 mg; 0.62 mmol). The reaction was stirred for 30 minutes then quenched by the addition of Na\(_2\)S\(_2\)O\(_3\) in NaHCO\(_3\) (20 mL; 1.2 g per 100 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) (3*10 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography (CH\(_2\)Cl\(_2\)) gave the aldehyde 353 (100 mg; 77%) as a clear oil. R\(_f\) = 0.55, \(^1\)H NMR (600MHz; CDCl\(_3\)) δ 9.78 (1H, d, 2.3 Hz, CH(=O)) 7.25 (2H, d, 8.7 Hz, ArH) 6.87 (2H, d, 8.7 Hz, ArH) 4.52 (1H, d, 10.8 Hz, OC\(_2\)H\(_3\)PMP) 4.48 (1H, d, 10.8 Hz, OCH\(_2\)C\(_6\)H\(_5\)PMP) 3.80 (3H, s, OC\(_3\)H\(_3\)) 3.39 (1H, t, 5.6 Hz, CHOBn) 2.67 (1H, d, 5.6 Hz, CH(CH\(_3\))CH(=O)) 1.97-1.91 (1H, m CH(CH\(_3\))\(_2\)) 1.11 (3H, d, 7.0 Hz, CH(CH\(_3\))CH(=O)) 0.99 (3H, d, 6.8 Hz, CH(CH\(_3\))\(_2\)) 0.96 (3H, d, 6.8 Hz, CH(CH\(_3\))\(_2\)\(^{13}\)C NMR (150MHz; CDCl\(_3\)) δ 204.83, 159.13, 130.36, 129.23, 113.69, 85.52, 73.78, 55.19, 48.87, 30.80, 19.47, 17.77, 11.31.

3-Benzyloxy-2,4-dimethyl-pentanal (347)

![Chemical Structure](image)

To a solution of DMSO (0.38 mL; 5.4 mmol) in CH\(_2\)Cl\(_2\) (25 mL) at -78°C was added oxalyl chloride (1.35 mL of a 2 M solution in CH\(_2\)Cl\(_2\); 2.7 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 351 (0.41 g; 1.85 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt\(_3\) (1.50 mL; 10.8 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH\(_4\)Cl (50 mL), then extracted with CH\(_2\)Cl\(_2\) (3*50 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography (CH\(_2\)Cl\(_2\)) gave the desired aldehyde 347 (0.4 g; 98%) as a colourless oil. R\(_f\) = 0.76, \(^1\)H NMR (600MHz; CDCl\(_3\)) δ 9.80 (1H, d, 2.3 Hz, CH(=O)) 7.36-7.26 (5H, m, ArH) 4.61 (1H, d, 11.3 Hz, OCH\(_2\)C\(_6\)H\(_5\)Ph) 4.56 (1H, d, 11.3 Hz, OCH\(_2\)C\(_6\)H\(_5\)Ph) 3.42 (1H, t, 5.6 Hz, CHO\(_2\)Ph) 2.74-2.69 (1H, m, CH(CH\(_3\))\(_2\)) 1.96 (1H, d, 6.8 Hz, CH(CH\(_3\))\(_2\)) 1.13 (3H, d, 7.0 Hz, CH(CH\(_3\))\(_2\)) 1.01 (3H, d, 6.8 Hz, CH(CH\(_3\))\(_2\)) 0.98.
Experimental Procedures for Chapter Four

\((3H, d, 6.8 \text{ Hz}, CH(CH_3)_2)\) \(^{13}\text{C} \text{ NMR (150MHz; CDCl}_3\) \(\delta 204.7, 138.25, 128.32, 127.60, 127.54, 85.94, 74.13, 48.87, 30.83, 19.46, 17.78, 11.36\)

\(\text{2-}(R)\text{-Hydroxy-N-methoxy-N-methylpropionamide (354)}\)

To a mixture of isobutyl\(-\)(R)\)-lactate (138) (5 g; 34 mmol) and \(N,O\)-dimethylhydroxylamine hydrochloride (8.3 g; 85 mmol) in THF (60 mL) and \(\text{Et}_2\text{O}\) (60 mL) at -20°C was added i\(\text{PrMgCl}\) (85 mL; 2 M in THF; 170 mmol) dropwise of 30 minutes. The reaction mixture was stirred at -20°C for 30 minutes then at 0°C for a further 30 minutes before saturated \(\text{NH}_4\text{Cl}\) (300 mL) was added cautiously. The mixture was extracted with \(\text{Et}_2\text{O}\) (4*100 mL) and \(\text{CH}_2\text{Cl}_2\) (4*100 mL) dried (Na\(_2\text{SO}_4\)) and concentrated in vacuo. The residue was purified by distillation (bp. 65°C @ 0.5 mmHg) to give the amide 354 (4.1 g; 91%) as a colourless oil. \(^1\text{H} \text{NMR (600MHz; CDCl}_3\) \(\delta 4.42 (1H, q, 6.4 \text{ Hz}, CH(CH_3)) 3.65 (3H, s, OCH}_3\) 3.42 (1H, brs, CH(OH)) 3.19 (3H, s, NCH}_3\) 1.29 (3H, d, 6.4 Hz, CH(CH_3)). \(^{13}\text{C} \text{ NMR (150 MHz; CDCl}_3\) \(\delta 175.49, 64.75, 61.15, 32.20, 20.77.\)

\(\text{2-}(R)\text{-Benzoyloxypentan-3-one (82)}\)

To a solution of the amide 354 (4.1 g; 31 mmol) in THF (120 mL) at 0°C was added \(\text{EtMgBr}\) (100 mL of a 1 M solution in THF; 100 mmol) and the reaction mixture was allowed to warm to room temperature. After one hour, saturated \(\text{NH}_4\text{Cl}\) (180 mL) was added with caution and the mixture was extracted with \(\text{Et}_2\text{O}\) (2*80 mL) and \(\text{CH}_2\text{Cl}_2\) (2*80 mL). The combined organic extracts were dried (Na\(_2\text{SO}_4\)) and concentrated in vacuo to approximately 75-100mL. To this solution was added benzoic anhydride (10.5 g; 46 mmol), DMAP (400 mg; 3.3 mmol) and i\(\text{Pr}_2\text{NEt}\) (10.4 mL; 76 mmol) and the resulting solution was stirred at room temperature for 15 hours. Excess benzoic anhydride was removed by the addition of
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ethylenediamine (2.3 mL; 34 mmol). H₂O (200 mL) was added and the mixture was extracted with Et₂O (4*80 mL), then the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) to afford the benzoyl protected ketone 82 (5.75 g; 90%) as a colourless oil. Rₚ = 0.40, ¹H NMR (600MHz; CDCl₃) δ 8.08 (2H, d, 6.9 Hz, ArH) 7.59 (1H, t, 6.9 Hz, ArH) 7.46 (2H, t, 6.9 Hz, ArH) 5.35 (1H, q, 7.0 Hz, BzOC(CH₃)) 2.66 (1H, dq, 18.3, 7.2 Hz, CH₂CH₂CH₃) 2.52 (1H, dq, 18.3, 7.2 Hz, CH₃CH₂CH₃) 1.53 (3H, d, 7.0 Hz, BzOCH(CH₃)) 1.09 (3H, t, 7.2 Hz, CH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 208.53, 165.88, 133.34, 129.74, 129.47, 128.46, 75.10, 31.43, 16.46, 7.18.

Dicyclohexylboron chloride (355)

To a solution of freshly distilled cyclohexene (356) (20 mL; 207 mmol) in Et₂O (100 mL) at 0°C was added monochloroborane-methyl sulphide complex (9.8 mL; 94 mmol) dropwise and the resulting mixture was warmed to ambient temperature and stirred for 2 hours. The solvent was removed in vacuo and the residue was distilled under reduced pressure to give dicyclohexylboron chloride (355) (18 g; 90%) as a clear viscous liquid. b.p. 80-86°C @ 0.15 mmHg. ¹³C NMR (150MHz; CDCl₃) δ 208.53, 165.88, 133.34, 129.74, 129.47, 128.46, 75.10, 31.43, 16.46, 7.18.

Benzoic acid 4-hydroxy-6-(4-methoxy-benzyloxy)-1,3,5,7-tetramethyl-2-oxo-octyl ester (357)

To a solution of dicyclohexylboron chloride (355) (0.5 mL; 2.3 mmol) in Et₂O (5 mL) at -78°C was added NEt₃ (380 µL; 2.8 mmol) followed by ketone 82 (100 mg; 0.5 mmol) in Et₂O (2 mL). The reaction was warmed to 0°C and stirred for 2 hours, before being re-cooled to -78°C. Aldehyde 353 (100 mg; 0.4 mmol) was added and stirring continued for a further 2 hours then at -23°C overnight in the freezer.
reaction was warmed to 0°C and stirred for 30 minutes then quenched by the addition of MeOH (1 mL), pH 7 buffer solution (1 mL) and 30% H₂O₂ solution (1 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between H₂O (30 mL) and extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave the *anti*-aldol product 357 (101 mg; 55%) as a clear oil. Rₖ = 0.25, ¹H NMR (600MHz; CDCl₃) δ 8.06 (2H, d, 8.2 Hz, Bz-ArH) 7.56 (1H, t, 7.4 Hz, Bz-ArH) 7.44 (2H, t, 8.0 Hz, Bz-ArH) 7.23 (2H, d, 8.6 Hz, PMB-ArH) 6.83 (2H, d, 8.6 Hz, PMB-ArH) 5.36 (1H, q, 7.0 Hz, BzOC(CH₃)) 4.53 (1H, d, 11.0 Hz, OCH₃(CH₂PMP)) 4.52 (1H, d, 11.0 Hz, OCH₃CH₂PMP) 3.79 (3H, s, OCH₃) 3.75 (1H, q, 6.5 Hz, CH(OH)) 3.37 (1H, d, 6.7 Hz, CH(OH)) 3.31 (1H, dd, 6.2, 4.7 Hz, CHOPMB) 3.19 (1H, qn, 7.1 Hz, CH(CH₃)CHOPMB, CH(CH₃)₂) 1.95 (1H, dsept, 6.9, 2.0 Hz, CH(CH₃)₂) 1.48 (3H, d, 6.9 Hz, CH(CH₃)₂) 1.32 (3H, d, 7.1 Hz, CH(CH₃)₂) 0.90 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.96 (3H, d, 7.1 Hz, CH(CH₃)₂) 0.95 (1H, d, 7.1 Hz, CH(CH₃)₂) ¹³C NMR (150MHz; CDCl₃) δ 212.18, 165.92, 159.20, 133.41, 131.03, 129.92, 129.71, 128.57, 113.89, 87.30, 77.66, 74.76, 74.00, 55.41, 46.36, 37.98, 31.14, 20.88, 17.63, 16.60, 16.06, 14.92.

Benzoic acid 3-[6-isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-1-methyl-2-oxo-butyl ester (358)

To a solution of aldol product 357 (100 mg; 0.22 mmol) in CH₂Cl₂ (10 mL) and pH 7 buffer solution (1 mL) was added DDQ (60 mg; 0.26 mmol) at ambient temperature. The reaction was stirred for 3 hours then quenched by the addition of saturated NaHCO₃ solution (15 mL). The mixture was extracted with CH₂Cl₂ (3*20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the desired PMP-acetal adduct 358 (86 mg; 86%) as a clear oil. Rₖ = 0.7, ¹H NMR (600MHz; CDCl₃) δ 8.08 (2H, d, 8.2 Hz, Bz-ArH) 7.56 (1H, t, 7.4 Hz, Bz-ArH) 7.43 (2H, t, 8.1 Hz, Bz-ArH) 7.26 (2H, d, 8.8 Hz, PMB-ArH) 6.83 (2H, d, 8.8 Hz, PMB-ArH) 5.56 (1H, q, 6.8 Hz, BzOCH(CH₃)) 5.34 (1H, s, CHPMP) 3.79 (3H, s, OCH₃) 3.73 (1H, dd, 10.0, 4.1 Hz, CHOCHPMP) 3.29 (1H, m, C(=O)CH(CH₃)) 3.25 (1H, dd, 9.8, 2.0 Hz, CHOCHPMP) 1.95 (1H, dsept, 6.9, 2.0 Hz, CH(CH₃)₂) 1.92-1.85 (1H, m, CH(CH₃)) 1.48 (3H, d, 6.9 Hz, BzOCH(CH₃)) 1.32 (3H, d, 7.1 Hz, C(=O)CH(CH₃)) 1.02 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.90 (3H, d, 7.0 Hz,
CH(CH$_3$)$_2$) 0.78 (3H, d, 6.6 Hz, CH(CH$_3$)) $^{13}$C NMR (150MHz; CDCl$_3$) δ 208.58, 165.65, 159.57, 133.23, 131.40, 129.76, 129.56, 128.42, 127.26, 113.24, 100.43, 85.67, 82.68, 74.63, 55.20, 47.65, 34.12, 28.10, 20.26, 16.28, 14.69, 13.39, 11.93.

2-[6-Isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-pentan-3-one (359)

To a solution of PMP acetal adduct 358 (85 mg; 0.19 mmol) in THF (2.5 mL) and MeOH (1.5 mL) at 0°C was added SmI$_2$ (7.4 mL of a 0.1 M solution in THF, 0.74 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0°C with the addition of saturated K$_2$CO$_3$ (15 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et$_2$O (3*20 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (50% CH$_2$Cl$_2$/hexanes) afforded ethyl ketone 359 (53 mg; 83%) as a colourless oil. R$_f$ = 0.48, $^1$H NMR (600MHz; CDCl$_3$) δ 7.38 (2H, d, 8.8 Hz, ArH) 6.88 (2H, d, 8.8 Hz, ArH) 5.44 (1H, s, CHPMP) 3.80 (3H, s, OCH$_3$) 3.58 (1H, dd, 10.0, 3.3 Hz, CHO) 3.27 (1H, dd, 9.8, 2.0 Hz, CHO) 2.86 (1H, dq, 7.2, 3.4 Hz, C(=O)CH(CH$_3$)) 2.61 (1H, dq, 18.4, 7.1 Hz, CH$_3$CH$_2$CH$_3$) 2.50 (1H, dq, 18.4, 7.1 Hz, CH$_3$CH$_2$CH$_3$) 2.50 (1H, dq, 18.4, 7.1 Hz, CH$_3$CH$_2$CH$_3$) 1.97 (1H, dsept, 6.9, 1.9 Hz, CH(CH$_3$)$_2$) 1.70-1.65 (1H, m, CH(CH$_3$)) 1.29 (3H, d, 7.2 Hz, C(=O)CH(CH$_3$)) 1.04 (3H, d, 6.9 Hz, CH(CH$_3$)$_2$) 1.00 (3H, t, 7.1 Hz, C(=O)CH$_2$CH$_3$) 0.88 (3H, d, 6.9 Hz, CH(CH$_3$)$_2$) 0.80 (3H, d, CH(CH$_3$)) $^{13}$C NMR (150MHz; CDCl$_3$) δ 213.68, 159.60, 131.73, 127.21, 113.35, 100.53, 85.70, 83.78, 55.23, 49.71, 34.04, 28.23, 20.26, 14.71, 13.68, 11.61, 7.61.
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Benzoic acid 6-benzyloxy-4-hydroxy-1,3,5,7-tetramethyl-2-oxo-octyl ester (361)

To a solution of dicyclohexylboron chloride (355) (970 µL; 4.48 mmol) in Et₂O (15 mL) at -78°C was added NEt₃ (750 µL; 5.38 mmol) followed by ketone 82 (605 mg; 2.93 mmol) in Et₂O (5 mL). The reaction was warmed to 0°C and stirred for 2 hours, before being re-cooled to -78°C. Aldehyde 347 (430 mg; 1.95 mmol) was added and stirring continued for a further 2 hours then at -23°C overnight in the freezer. The reaction was warmed to 0°C and stirred for 30 minutes then quenched by the addition of MeOH (10 mL), pH 7 buffer solution (10 mL) and 30% H₂O₂ solution (10 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between H₂O (80 mL) and extracted with Et₂O (3*50 mL), CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the anti aldol product 361 (515 mg; 62%) as a clear oil. R_f = 0.20 , ¹H NMR (600MHz; CDCl₃) δ 8.05 (2H, d, 9.5 Hz, Bz-ArH) 7.55 (1H, t, 7.4 Hz, Bz-ArH) 7.43 (2H, t, 7.9 Hz, Bz-ArH) 7.33-7.24 (5H, m, Bn-ArH) 5.32 (1H, q, 7.0 Hz, BzOC(CH₃)) 4.61 (2H, s, OC₆H₅Ph) 3.78 (1H, q, 6.6 Hz, CH(OH)) 3.36 (1H, dd, 6.6, 4.2 Hz, CHO_Bn) 3.31 (1H, d, 6.6 Hz, CH(OH)) 3.19 (1H, qn, 7.1 Hz, C(=O)CH(CH₃)) 2.06-1.94 (2H, m, CH(CH₃)₂, CH(CH₃)CHOBn) 1.36 (3H, d, 7.0 Hz, BZOC(CH₃)) 1.28 (3H, d, 7.1 Hz, C(=O)CH(CH₃)) 1.01 (3H, d, 6.9 Hz, CH(CH₃)CHOBn) 0.99-0.96 (6H, m, 2* CH(CH₃)₂) ¹³C NMR (150MHz; CDCl₃) δ 212.14, 165.74, 138.75, 133.23, 129.70, 129.40, 128.36, 128.25, 127.33, 127.05, 86.83, 77.36, 74.43, 73.97, 46.13, 37.57, 30.82, 30.04, 25.64, 23.62, 20.74, 17.18, 16.35, 15.74, 14.75.

Benzoic acid 6-benzyloxy-4-(4-methoxy-benzyloxy)-1,3,5,7-tetramethyl-2-oxo-octyl ester (362)

To a solution of NaH (6 mg; 0.15 mmol) in dry DMF (0.25 mL) and THF (0.12 mL) at 0°C was added alcohol 361 (50 mg; 0.12 mmol) in THF (0.12 mL) and PMB-Cl (23 µL; 0.17 mmol). The reaction mixture was stirred for 4 hours at 0°C and for a further 2 hours at room temperature. The mixture was quenched with saturated NH₄Cl solution (5 mL), extracted with ether (3*5 mL), dried (Na₂SO₄) and concentrated in vacuo.
Analysis of the crude $^1$H NMR spectrum indicated the alcohol 361 had decomposed to the enone through $\beta$-elimination under the above reaction conditions.

**Benzoic acid 6-benzyloxy-1,3,5,7-tetramethyl-2-oxo-4-triethylsilanyloxy-octyl ester (364)**

To a solution of alcohol 361 (430 mg; 1 mmol) in CH$_2$Cl$_2$ (10 mL) at -78°C was added 2,6-lutidine (265 µL; 2.28 mmol) and TESOTf (1.86 mmol). The reaction was stirred for 2 hours then warmed to room temperature. The reaction was quenched with the addition of NaHCO$_3$ solution (20 mL), extracted with CH$_2$Cl$_2$ (3*40 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification of column chromatography (50% CH$_2$Cl$_2$/hexanes) gave the protected adduct 364 (512 mg; 94%) as a colourless oil. R$_f$ = 0.5, $^1$H NMR (600MHz; CDCl$_3$) δ 8.04 (2H, d, 8.4 Hz, Bz-ArH) 7.55 (1H, t, 7.2 Hz, Bz-ArH) 7.42 (2H, t, 7.8 Hz, Bz-ArH) 7.35 (2H, d, 7.8 Hz Bn-ArH) 7.30 (2H, t, 7.2 Hz, Bn-ArH) 7.23 (1H, t, 7.8 Hz, Bn-ArH) 5.27 (1H, q, 7.2 Hz, BzOC(H(CH$_3$))) 4.79 (1H, d, 12.0 Hz, OCH$_2$CH$_2$Ph) 4.65 (1H, d, 12.0 Hz, OCH$_2$CH$_2$Ph) 4.28 (1H, dd, 9.6, 1.2 Hz, C(=O)C(H$_3$)CHOBn) 3.35 (1H, dd, 9.6, 1.8 Hz, C(=O)CH(C$_3$H$_7$)) 2.02-1.98 (1H, m, C(H$_3$)(CH$_3$)CHOBn) 1.92-1.88 (1H, m, CH(CH$_3$)$_3$) 1.34 (3H, d, 7.2 Hz, BzOCH(CH$_3$)) 1.20 (3H, d, 7.2 Hz, CH(CH$_3$)$_3$) 0.96-0.93 (12H, m, CH(CH$_3$)CHOBn, 3*OSi(CH$_3$)$_3$) 0.60 (6H, q, 8.4 Hz, 3*OSi(CH$_3$)$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 209.29, 165.66, 139.37, 133.02, 129.74, 129.69, 128.26, 128.07, 126.89, 126.41, 84.72, 76.20, 74.60, 73.92, 47.18, 31.56, 30.40, 22.62, 21.03, 15.04, 15.00, 14.93, 7.00, 5.22.

**7-Benzyl-4,6,8-trimethyl-5-triethylsilanyloxy-nonan-3-one (363)**

To a solution of protected adduct 364 (700 mg; 1.3 mmol) in THF (15 mL) and MeOH (7.5 mL) at 0°C was added Sml$_2$ (52 mL of a 0.1 M solution in THF; 5.2 mmol) until a deep green colour persisted in the
reaction mixture. The reaction was quenched at 0°C with the addition of saturated K$_2$CO$_3$ (80 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et$_2$O (3*70 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (50% CH$_2$Cl$_2$/hexanes) afforded ethyl ketone 363 (521 mg; 92%) as a colourless oil. R$_f$ = 0.52, $^1$H NMR (600MHz; CDCl$_3$) δ 7.37-7.24 (5H, m, ArH) 4.74 (1H, d, 11.6 Hz, OCH$_A$CH$_B$Ph) 4.62 (1H, d, 11.6 Hz, OCH$_A$CH$_B$Ph) 4.09 (1H, dd, 8.3, 1.9 Hz, CHOTES) 3.33 (1H, dd, 9.7, 2.2 Hz, CHOBN) 2.96 (1H, qn, 7.1 Hz, C(=O)CH(CH$_3$)) 2.36 (1H, dq, 18.5, 7.3 Hz, CH$_B$CH$_3$CH$_3$) 2.27 (1H, dq, 18.5, 7.3 Hz, CH$_B$CH$_3$CH$_3$) 1.95-1.91 (2H, m, C$_H$(CH$_3$)$_2$, C$_H$(CH$_3$)CHOBn) 1.05 (3H, d, 7.1 Hz, CH(CH$_3$)$_2$) 0.96-0.89 (21H, m, CH$_2$CH$_3$, C(=O)CH(CH$_3$), CH(CH$_3$)CHOBN, CH(CH$_3$)$_2$, 3*OSiCH$_2$CH$_3$) 0.56 (6H, q, 8.0 Hz, 3*OSiCH$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 215.61, 139.57, 128.13, 126.98, 126.86, 84.92, 77.30, 74.06, 50.13, 39.68, 36.46, 30.39, 21.13, 15.23, 14.76, 14.51, 7.33, 7.02, 5.19.

9-Benzylxoy-2-(2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-3-hydroxy-4,6,8,10-tetramethyl-7-triethylsilanyloxy-undecan-5-one (365)

To a solution of ketone 363 (250 mg; 0.57 mmol) in THF (80 µL) at -78°C was added LiHMDS (0.68 mL of a 1 M solution in THF; 0.68 mmol) dropwise. The resulting yellow solution was stirred for one hour at -78°C then warmed to -50°C for a further hour. The mixture was re-cooled to -78°C and the aldehyde 330 (170 mg; 0.54 mmol) was added as a solution in THF (5 mL) via cannula. After two hours the solution was diluted with Et$_2$O (10 mL) and quenched with pH 7 buffer (20 mL) and allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et$_2$O (3*15 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (20% Et$_2$O/hexanes) gave the aldol product 365 (310 mg; 77%) as a clear oil. R$_f$ = 0.7, $^1$H NMR (600MHz; CDCl$_3$) δ 7.37-7.23 (5H, m, ArH) 4.82 (1H, d, 12 Hz, OCH$_A$CH$_B$Ph) 4.63 (1H, d, 12 Hz, OCH$_A$CH$_B$Ph) 4.14 (1H, dd, 9.2, 1.3 Hz, CHOTES) 4.01 (1H, dd, 9.3, 1.3 Hz, CH(OH)) 3.89-3.86 (1H, m, CH$_3$CH$_2$CH(OSi)) 3.77 (1H, dd, 7.9, 4.0 Hz, CH(CH$_3$)CH(OSi)CH(CH$_3$)) 3.55 (1H, brs, CH(OH)) 3.33 (1H, dd, 10.0, 2.0 Hz, CHOBN) 3.16 (1H, dq, 9.0, 7.1 Hz, C(=O)CH(CH$_3$)CHOTES) 2.48 (1H, dq, 7.0, 1.3 Hz, CH(OH)CH(CH$_3$)C(=O)) 2.37-2.31 (1H, m,
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CH(OSiCH(CH₃)CH(OSi)) 2.00-1.94 (1H, m, CH(CH₃)CH(OBn)) 1.90-1.85 (1H, m, CH(CH₃)₂) 1.73-1.68 (1H, m, CH(CH₃)CH(OH)) 1.54-1.47 (1H, m, CH₂CH₂CH₃) 1.47-1.38 (1H, m, CH₄CH₂CH₃) 1.04 (3H, d, 7.0 Hz, CH(CH₃)CH(OBn)) 1.02-0.99 (21H, m, 2* SiC(CH₃)₃, CH₂CH₃) 0.95-0.85 (24H, m, 3*OSiCH₂CH₃, 2*C(CH₃)₂, C(=O)CH(CH₃), CH(OSi)CH(CH₃)CH(OSi), CH(OH)CH(CH₃)C(=O)) 0.70 (3H, d, 6.9 Hz, CH(CH₃)CH(OH)) 0.57 (6H, q, 7.9 Hz, 3*OSiCH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 218.87, 139.65, 128.11, 126.89, 126.41, 84.69, 80.04, 77.44, 77.10, 73.78, 71.62, 49.43, 48.17, 40.25, 39.27, 30.40, 27.67, 27.62, 26.89, 24.37, 22.65, 21.59, 21.13, 21.08, 15.07, 14.75, 14.24, 14.01, 10.97, 7.12, 7.06, 5.30.

3-Benzylxoy-9,11,13-trihydoxy-2,4,6,8,10,12-hexamethyl-5-triethylsilyloxy-pentadecan-7-one (367)

To a solution of aldol product 365 (20 mg; 0.03 mmol) in THF (1.5 mL) and H₂O (20 µL) at 0°C was added HF/Pyr/Pyr (0.2 mL of a 0.15 M solution in THF; 0.03 mmol) solution dropwise. The reaction was allowed to warm to RT and stirring continued for three hours. The reaction was diluted with Et₂O (3 mL) and quenched with NaHCO₃ (2 mL) followed by CuSO₄ (2 mL). The aqueous layers were re-extracted with Et₂O (2*5 mL) dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (50% Et₂O/hexanes) yielded triol 367 (13mg; 90%) as a clear oil. Rf = 0.15, ¹H NMR (600MHz; CDCl₃) δ 7.37-7.25 (5H, m, ArH) 5.46 (1H, brs, CH(OH)) 4.75 (1H, d, 12 Hz, OCH₂CH₂Ph) 4.68 (1H, d, 12 Hz, OCH₃CH₂Ph) 4.66 (1H, brs, CH(OH)) 4.16 (1H, d, 8.6 Hz, CHOTES) 4.05 (1H, brs, CH(OH)) 3.86 (1H, t, 7.3 Hz, CH₃CH₂CH(OH)) 3.80 (1H, dd, 9.5, 1.3 Hz, CH(OH)CH(CH₃)C(=O)) 3.57 (1H, dd, 9.1, 1.9 Hz, CH₃CH₂CH(OH)CH(CH₃)CH(OH)) 3.33 (1H, dd, 10.1, 2 Hz, CHOBn) 3.16 (1H, dq, 9.3, 7.2 Hz, C(=O)CH(CH₃)CH(CH₃)CH(OH)) 2.52 (1H, q, 6.0, 1.2 Hz, CH(OH)CH(CH₃)C(=O)) 1.97-1.94 (1H, m, CH(CH₃)CH(OBn)) 1.93-1.79 (2H, m, CH₂(CH₃)₂, CH(CH₃)CH(OH)CH(CH₃)C(=O)) 1.70 (1H, q, 7.1, 7.1 Hz, CH₃CH₂CH(OH)CH(CH₃)C(=O)) 1.61-1.56 (1H, m, CH₃CH₂CH₃) 1.39-1.34 (1H, m, CH₃CH₂CH₃) 1.07 (3H, d, 7.1 Hz, CH₃CH₂CH(OH)CH(CH₃)) 1.06 (3H, d, 6.9 Hz, CH(CH₃)CH(OH)CH(CH₃)C(=O)), 1.00 (3H, d, 7.1 Hz, CH(CH₃)CH(OBn)) 0.96-0.91 (21H, m, 3*OSiCH₂CH₃, 2* CH(CH₃)₂, CH(OH)CH(CH₃)C(=O), C(=O)CH(CH₃)CHOTES) 0.60-0.55 (9H, m, 3*OSiCH₂CH₃, CH₃CH₂CH(OH)CH(CH₃)) ¹³C NMR (150MHz;
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CDCl$_3$ δ 219.70, 139.53, 128.14, 126.94, 126.42, 84.74, 83.05, 77.78, 77.10, 73.85, 72.09, 49.35, 46.76, 37.36, 36.01, 30.43, 27.62, 21.08, 15.27, 15.12, 15.11, 15.02, 12.30, 10.68, 10.46, 7.47, 7.02, 5.26.


To a solution of triol 367 (12 mg; 0.025 mmol) in CDCl$_3$ (0.7 mL) was added a single crystal of PPTS and the reaction mixture was monitored by $^1$H NMR spectroscopy. After 1 hour the reaction mixture was purified by column chromatography (20% EtOAc/hexanes) gave the two dehydrated hemiacetal products 369 and 370. Hemiaclatal 369, R$_f$ = 0.40, $^1$H NMR (600MHz; CDCl$_3$) δ 7.37 (2H, d, 7.3 Hz, ArH) 7.30 (2H, t, 7.3 Hz, ArH) 7.22 (1H, t, 7.3 Hz, ArH) 5.74 (1H, d, 5.2 Hz, CH=CCH$_3$) 4.72 (1H, d, 12.0 Hz, OCH$_3$CH$_2$Ph) 4.42 (1H, t, 3.3 Hz, CH-O-COH) 4.37 (1H, d, 12.0 Hz, OCH$_3$CH$_2$Ph) 4.05 (1H, t, 6.7 Hz, CHOTES) 3.63 (1H, m, CHOH) 3.53 (1H, s, CHO$_2$H) 2.71 (1H, m, CH(CH$_2$)CHOBn) 2.19 (1H, dq, 6.9, 2.2 Hz, CH(CH$_3$)$_2$) 2.09 (1H, dq, 7.3, 3.3 Hz, CH(CH$_3$)CH-O-) 1.92 (1H, m, CH(CH$_3$)CH=CCCH$_3$) 1.64-1.48 (2H, m, CH$_2$CH$_2$CH$_3$, CH(CH$_3$)CHOTES) 1.53 (3H, s, CH=CCCH$_3$) 1.38-1.30 (1H, m, CH$_2$CH$_2$CH$_3$) 1.09 (3H, d, 6.9 Hz, CH(CH$_3$)CHOBn) 1.07 (3H, d, 6.9 Hz, CH(CH$_3$)CH=CCCH$_3$) 1.05 (3H, d, 7.3 Hz, CH(CH$_3$)CHOTES) 0.98-0.95 (15H, m, 3*O$\text{CH}_2$CH$_3$, CH(CH$_3$)CH$_3$, CH(CH$_3$)CH-O-) 0.91 (3H, d, 6.9 Hz, CH(CH$_3$)CHOTES) 0.86 (3H, t, 7.2 Hz, CH$_2$CH$_3$) 0.62 (6H, dq, 7.7, 3.3 Hz, 3*O$\text{CH}_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 140.52, 130.92, 130.50, 127.97, 127.46, 126.77, 98.91, 83.83, 74.96, 71.41, 71.08, 64.43, 44.85, 38.23, 36.46, 34.66, 29.95, 29.69, 25.46, 22.84, 20.39, 18.35, 17.66, 15.37, 13.80, 10.09, 7.02, 5.16. 

Hemiaclatal 370, R$_f$ = 0.20, $^1$H NMR (600MHz; CDCl$_3$) δ 7.33 (2H, d, 7.3 Hz, ArH) 7.27 (2H, t, 7.3 Hz, ArH) 7.18 (1H, t, 7.3 Hz, ArH) 5.61 (1H, d, 5.1 Hz, CH=CCH$_3$) 5.00 (1H, s, C-OH) 4.90 (1H, d, 12.1 Hz,
Experimental Procedures for Chapter Four

OCH₃CH₂Ph 4.63 (1H, d, 12.1 Hz, OCH₃CH₂Ph) 4.05 (1H, d, 8.8 Hz, CHOH) 3.86 (1H, td, 8.3, 5.2, 2.9 Hz, CH₃CH₂CHOH) 3.61 (1H, s, CH(CH₃)CH-O-COH) 3.54 (1H, dd, 9.5, 2.1 Hz, CHOBN) 2.19 (1H, dq, 8.8, 7.0 Hz, CH(CH₃)CHOH) 2.06 (1H, m, CH(CH₃)CHOBN) 1.91 (1H, m, CH(CH₃)₂) 1.57 (3H, brs, CH=CHCH₃) 1.54 (1H, m, CH₃CH₂CHOH) 1.35-1.26 (3H, m, CH₃CH₂CH₃, CH(CH₃)CH-O-COH, CH(CH₃)CH=C(CH₃)) 1.13 (3H, d, 6.9 Hz, CH(CH₃)CH-O-COH) 1.05-1.02 (6H, m, CH(CH₃)CH₃, CH(CH₃)CHOBN) 0.96 (3H, d, 6.9 Hz, CH(CH₃)CH₃) 0.89-0.82 (6H, m, CH₂CH₃, CH(CH₃)CH=C(CH₃)) 0.77 (3H, d, 7.0 Hz, CH(CH₃)CHOH) ¹³C NMR (150MHz; CDCl₃) δ 139.42, 128.13, 126.53, 84.74, 78.78, 76.47, 75.85, 73.97, 61.12, 52.78, 50.10, 40.49, 30.39, 27.72, 27.63, 25.33, 21.59, 21.15, 21.00, 15.08, 14.71, 14.01, 12.70, 11.46, 10.90, 7.00, 5.18.

9-Benzylxoy-2-(2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-4,6,8,10-tetramethyl-7-triethyilsilanyloxy-undecane-3,5-dione (371)

To a solution of aldol product 365 (40 mg; 0.05 mmol) in CH₂Cl₂ (1 mL) at room temperature was added NaHCO₃ (45 mg) and DMP (50 mg; 0.12 mmol). The reaction mixture was stirred for 2 hours at ambient temperature. The mixture was loaded directly onto silica and purified by column chromatography (50% CH₂Cl₂/hexanes) to give diketone 371 (33 mg; 88%) as a clear oil. Rf = 0.25. ¹H NMR (600MHz; CDCl₃) δ 7.36-7.22 (5H, m, ArH) 4.78 (1H, d, 11.8 Hz, OCH₃CH₂Ph) 4.61 (1H, d, 11.8 Hz, OCH₃CH₂Ph) 4.16 (1H, dd, 9.4, 1.1 Hz, CHOTES) 3.93-3.88 (3H, m, C(=O)CH(CH₃)C(=O), CH₃CH₂CHOsi, CH(CH₃)CH(OSi)CH(CH₃) 3.31 (1H, dd, 10.1, 2.0 Hz, CHOBN) 3.03 (1H, dq, 9.4, 7.0 Hz, C(=O)CH(CH₃)CHOTES) 2.72 (1H, qn, 7.3, 6.8 Hz, CH(CH₃)C(=O)CH(CH₃)C(=O)) 1.98-1.93 (2H, m, CH(CH₃)CHOBN, CH(OSi)CH(CH₃)CH(OSi)) 1.91-1.86 (1H, dqn, 6.8, 1.9 Hz, CH(CH₃)₂) 1.54-1.46 (1H, m, CH₃CH₂CH₃) 1.41-1.34 (1H, m, CH₃CH₂CH₃) 1.09-1.07 (6H, m, C(=O)CH(CH₃)CHOTES, CH(CH₃)C(=O)CH(CH₃)C(=O)) 1.04 (3H, d, 7.0 Hz, C(=O)CH(CH₃)C(=O), 1.01-0.89 (39H, m, 6*SiC(CH₃)₃, 3*OSiCH₂CH₃, 2*CH(CH₃)₂, CH₂CH₃, CH(CH₃)CHOBN ) 0.83 (3H, d, 7.2 Hz, CH(OSi)CH(CH₃)CH(OSi)) 0.55 (6H, q 7.9 Hz, 3*OSiCH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 210.96, 210.53, 139.42, 128.13, 126.94, 126.53, 84.74, 78.78, 76.47, 75.85, 73.97, 61.12, 52.78, 50.10, 40.49, 30.39, 27.72, 27.63, 25.33, 21.59, 21.15, 21.00, 15.08, 14.71, 14.01, 12.70, 11.46, 10.90, 7.00, 5.18.
3-Benzylxylo-11,13-dihydroxy-2,4,6,8,10,12-hexamethyl-5-triethylsilanyloxy-pentadecane-7,9-dione (373)

To a solution of dione 371 (30 mg; 0.04 mmol) in THF (2.5 mL) and H₂O (30 µL) at 0°C was added HF/Pyr/Pyr (0.33 mL of a 0.15 M solution in THF; 0.05 mmol) solution dropwise. The reaction was allowed to warm to RT and stirring continued for three hours. The reaction was diluted with Et₂O (5 mL) and quenched with NaHCO₃ (4 mL) followed by CuSO₄ (4 mL). The aqueous layers were re-extracted with Et₂O (2*10 mL) dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) yielded diol 373 (16 mg; 85%) as a clear oil. **Crude Compound:** ¹H NMR (600MHz; CDCl₃) δ 7.35-7.24 (5H, m, ArH) 4.72 (1H, d, 11.6 Hz, OCH₂CH₃Ph) 4.63 (1H, d, 11.6 Hz, OCH₂CH₈Ph) 4.12 (1H, dd, 9.4, 1.0 Hz, CHO(Bn)) 3.88 (1H, q, 7.1 Hz, C(=O)CH(CH₃)C(=O)) 3.83 (1H, t, 6.7 Hz, CH₂CH₂CH(OH)) 3.69 (1H, brs, CH(OH)) 3.44 (1H, brs, CH(OH)) 3.28 (1H, dd, 8.0, 2.0 Hz, CHO(Bn)) 2.99-2.94 (3H, m, CH(CH₃)C(=O)CH(CH₃)C(=O), CH(OH)CH(CH₃)C(=O), C(=O)CH(CH₃)CHOTES) 1.95-1.87 (2H, m, CH(CH₃)₂, CH(CH₃)CHOBn) 1.65-1.60 (1H, m, CH(OH)CH(CH₃)CH(OH)) 1.59-1.53 (1H, m, CH₃CH₂CH₃) 1.40-1.35 (1H, m, CH₃CH₂CH₃) 1.15 (3H, d, 7.1 Hz, C(=O)CH(CH₃)C(=O)) 1.07-1.03 (9H, m, CH(CH₃)₂, C(=O)CH(CH₃)CHOTES, CH(CH₃)C(=O)CH(CH₃)C(=O), 0.98 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.94-0.88 (18H, m, 3*OSiCH₂CH₃, CH₃CH₃, CH(CH₃)CHOBn, CH(OH)CH(CH₃)CH(OH)) 0.54 (6H, q, 8.0 Hz, 3*OSiCH₂CH₃)

**Purified Compound:** Rf = 0.3, ¹H NMR (600MHz; CDCl₃) δ 7.37-7.24 (5H, m, ArH) 4.74 (1H, d, 11.8 Hz, OCH₂CH₃Ph) 4.66 (1H, d, 11.8 Hz, OCH₂CH₈Ph) 4.20 (1H, d, 9.0 Hz, CHO(Bn)) 4.13 (1H, d, 10.2 Hz, CH₂CH₂CH(OH)) 3.73-3.69 (1H, m, CH(OH)CH(CH₃)C(=O)) 3.53 (1H, d, 7.3 Hz, CH(OH)) 3.33 (1H, dd, 9.6, 1.7 Hz CHO(Bn)) 3.18 (1H, brs, CH(OH)) 3.09 (1H, qn, 8.9, 7.2 Hz, C(=O)CH(CH₃)CHOTES) 2.99-2.92 (1H, m, CH(CH₃)C(=O)CH(CH₃)C(=O)) 2.61-2.51 (3H, m, CH₃CH₂CH₃, CH₃CH₂CH₃, C(=O)CH(CH₃)C(=O)) 2.00-1.86 (2H, m, CH(CH₃)₂, CH(CH₃)CHOBn) 1.69-1.67 (1H, m, CH(OH)CH(CH₃)CH(OH)) 1.16-0.88 (30H, m, 3*OSiCH₂CH₃, 2*CH(CH₃)₂, CH₃CH₃, CH(CH₃)CHOBn, CH(OH)CH(CH₃)CH(OH), C(=O)CH(CH₃)CHOTES, CH(CH₃)C(=O)CH(CH₃)C(=O)) 0.72 (3H, d, 7.3 Hz, C(=O)CH(CH₃)C(=O)) 0.58 (6H, q, 7.9 Hz, 3*OSiCH₂CH₃)

¹³C NMR (150MHz; CDCl₃) δ 216.73, 216.01, 139.55, 128.08, 126.90, 126.52, 84.78, 78.59, 76.53, 75.96, 73.85, 71.82, 50.69, 48.92, 48.63, 36.20, 33.30, 30.39, 21.14, 15.20, 13.99, 13.91, 12.34, 10.29, 7.48, 7.11, 7.05, 5.30.
2-(6-Benzylxy-1,3,5,7-tetramethyl-2-oxo-4-triethylsilanyloxy-octyl)-6-ethyl-2-hydroxy-3,5-dimethyl-tetrahydro-pyran-4-one (374)

To a solution of diol 373 (7 mg; 0.015 mmol) in CH₂Cl₂ (1 mL) at room temperature was added NaHCO₃ (15 mg) and DMP (10 mg; 0.024 mmol). The reaction mixture was stirred for 2 hours at ambient temperature. The mixture was loaded directly onto silica and purified by column chromatography (CH₂Cl₂) to give hemiacetal 374 (5.9 mg; 84%) as a clear oil. Rf = 0.7, ¹H NMR (600MHz; CDCl₃) δ 7.36-7.24 (5H, m, ArH) 4.76 (1H, d, 11.9 Hz, OCH₂CH₂Ph) 4.67 (1H, d, 11.9 Hz, OCH₂CH₂Ph) 4.34 (1H, dd, 10.4, 2.6 Hz, CH₃CH₂CH-O) 4.13 (1H, dd, 9.0, 1.4 Hz, CH₂OTES) 3.35 (1H, dd, 9.5, 2.1 Hz, CH₂OBn) 3.01 (1H, dq, 9.0, 7.2 Hz, C(=O)CH(CH₃)CHOTES) 2.65 (1H, q, 6.7 Hz, C(=O)CH₂C-OH) 2.50 (1H, m, HO-CCH(CH₃)C(=O)) 2.37 (1H, dq, 7.0, 2.6 Hz, C(=O)CH(CH₃)C-O-) 2.27 (1H, d, 1.4 Hz, C-OH) 1.99 (1H, m, CH(CH₃)CHOBn) 1.89 (1H, m, CH(CH₃)CH₂) 1.71 (1H, m, CH₃CH₂CH₃) 1.58 (1H, m, CH₃CH₂CH₃) 1.05 (3H, m, CH₃) 0.95-0.92 (15H, m, 3*OSiCH₂CH₃, CH(CH₃)CH₂, CH(CH₃)CHOBn) 0.98 (3H, d, 7.2 Hz, C(=O)CH(CH₃)C-O-) 0.88 (3H, t, 7.4 Hz, CH₃CH₂) 0.67 (3H, d, 7.0 Hz, HO-CCH(CH₃)C(=O)) 0.60 (6H, q, 7.9 Hz, 3*OSiCH₂CH₃) ¹³C NMR (150MHz; CDCl₃) δ 213.79, 211.61, 139.83, 128.15, 126.95, 126.57, 101.90, 84.92, 73.85, 71.16, 65.96, 52.15, 46.13, 45.99, 45.58, 32.76, 30.54, 29.80, 21.31, 15.43, 14.22, 13.22, 11.53, 10.66, 8.29, 7.64, 7.24, 5.50.

9-Benzylxy-2-(2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-7-hydroxy-4,6,8,10-tetramethyl-undecane-3,5-dione (375)

To a solution of diketone 371 (20 mg; 0.03 mmol) in CH₂Cl₂ (3 mL) and MeOH (0.5 mL) at 0°C was added PPTS (9 mg; 0.03 mmol). The reaction was warmed to room temperature and monitored by TLC analysis.
for 48 hours. The mixture was quenched with pH 7 buffer solution (10 mL) and extracted with CH$_2$Cl$_2$ (3*10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (10% EtOAc/hexanes) gave an alcohol-like product 375 (12 mg; 65%) as a clear oil. $R_f = 0.3$, $^1$H NMR (600MHz; CDCl$_3$) δ 7.33-7.27 (5H, m, ArH) 4.59 (1H, d, 11.3 Hz, OCH$_3$CH$_2$Ph) 4.53 (1H, d, 11.3 Hz, OCH$_2$CH$_2$Ph) 4.08 (1H, dd, 11.9, 2.2 Hz, CH(OH)) 4.02-3.97 (3H, m, C(=O)C(=O)(CH$_3$)C(=O), 2*C(=O)(OSi)) 3.42 (1H, dd, 9.0, 2.3 Hz, C$_A$H$_B$OBn) 2.99 (1H, qd, 8.1, 6.8 Hz, CH(CH$_3$)C(=O)CH(CH$_3$)C(=O)) 2.60-2.54 (1H, m, C(=O)CH(CH$_3$)CHOH) 2.25 (1H, qd, 7.1, 2.1 Hz, CH(CH$_3$)$_2$) 1.99-1.95 (1H, m, CH(CH$_3$)CHOBn) 1.92-1.87 (1H, m, CH(OSi)CH(CH$_3$)CH(OSi)) 1.60-1.53 (1H, m, CH$_2$CH$_2$CH$_3$) 1.39-1.34 (1H, m, CH$_2$CH$_2$CH$_3$) 1.16-0.92 (42H, m, 2*SiC(CH$_3$)$_3$, 2*CH(CH$_3$)$_2$, CH$_2$CH$_3$, CH(OSi)CH(CH$_3$)CH(OSi), CH(CH$_3$)C(=O)CH(CH$_3$)C(=O), C(=O)CH(CH$_3$)C(=O), C(=O)CH(CH$_3$)CHOH, CH(CH$_3$)CHOBn).

3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propionic acid methyl ester (379)

$$\text{MeO-OH} \xrightarrow{\text{TBS-Cl, Imidazole}} \text{MeO-OTBS}$$

To a solution of ester 337 (3 g; 25.4 mmol) in CH$_2$Cl$_2$ (100 mL) at 0°C was added imidazole (2.1 g; 30.5 mmol) followed by TBS-Cl (4.25 g; 28 mmol). The reaction was warmed to ambient temperature and stirring continued for 15 hours. The reaction was filtered through celite and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave TBS-protected roche ester 379 (5.5 g; 93%) as a clear oil. $R_f = 0.73$, $[\alpha]_D^{20} = +18.9$ (c 1.0, CHCl$_3$), $^1$H NMR (600MHz; CDCl$_3$) δ 3.76 (1H, dd, 9.8, 7.0 Hz, C$_A$H$_B$OTBS) 3.67 (3H, s, OCH$_3$) 3.64 (1H, dd, 9.8, 7.0 Hz, CH$_2$CH$_2$OTBS) 2.64 (1H, sex, 6.8 Hz, C(=O)CH(CH$_3$)) 1.13 (3H, d, 6.8 Hz, CH(CH$_3$)) 0.86 (9H, s, SiC(CH$_3$)$_3$) 0.03 (3H, s, SiCH$_3$) 0.02 (3H, s, SiCH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 175.48, 65.21, 51.50, 42.49, 25.74, 18.18, 13.42, -5.53*2.
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3-(tert-Butyl-dimethyl-silanyloxy)-N-methoxy-N-methyl-propionamide (380)

\[ \text{MeO} \text{O} \text{OTBS} \xrightarrow{\text{MeONH(Me)}_2\text{HCl}, \text{THF}} \text{MeO} \text{N} \text{OTBS} \]

To a solution of TBS-protected roche ester 379 (1.0 g; 4.24 mmol) in THF (12 mL) and Et₂O (12 mL) was added \( N,O \)-dimethylhydroxylamine hydrochloride (1.05 g; 10.6 mmol). The mixture was cooled to -20°C and \( \text{^iPrMgCl} \) (10.6 mL; of a 2 M solution in THF; 21.2 mmol) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at -20°C for a further 30 minutes then at 0°C for a further 30 minutes before saturated NH₄Cl (80 mL) was added cautiously. The mixture was extracted with Et₂O (3*50 mL) and CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo to give Weinreb amide 380 (1.10 g; 98%) as a clear oil. \( ^1H \) NMR (600MHz; CDCl₃) \( \delta \) 3.82 (1H, dd, 9.4, 8.3 Hz, \( \text{CH} \text{A} \text{CH} \text{B} \text{OTBS} \)) 3.70 (1H, s, \( \text{NOC} \text{H} \text{3} \)) 3.51 (1H, dd, 9.5, 6.1 Hz, \( \text{CH} \text{A} \text{C} \text{H} \text{B} \text{OTBS} \)) 3.22-3.16 (4H, m, \( \text{NC} \text{H} \text{3} \), \( \text{CH} \text{(CH₃)} \text{CH}₂ \text{OTBS} \)) 1.06 (3H, d, 7.0 Hz, \( \text{CH} \text{(CH₃)} \text{CH}₂ \text{OTBS} \)) 0.86 (9H, s, \( \text{SiC} \text{(CH₃)} \text{3} \)) 0.03 (3H, s, \( \text{SiC} \text{H} \text{3} \)) 0.02 (3H, s, \( \text{SiC} \text{H} \text{3} \)) 13C NMR (150MHz; CDCl₃) \( \delta \) 175.90, 65.49, 61.25, 37.79, 31.72, 25.64, 18.04, 13.54, -5.69, -5.70.

1-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-pentan-3-one (378)

\[ \text{MeO} \text{N} \text{OTBS} \xrightarrow{\text{EtMgBr}, \text{THF}} \text{MeO} \text{C} \text{OTBS} \]

To a solution of amide 380 (1.0 g; 3.77 mmol) in THF (20 mL) was added EtMgBr (13.5 mL; of a 1 M solution in THF; 13.5 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature for 2-3 hours then saturated NH₄Cl (50 mL) was carefully added. The mixture was extracted with Et₂O (3*50 mL) and CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the ketone 378 (720 mg; 82%) as a clear oil. \( R_f = 0.65, [\alpha]^{20}_D = +18.9 \) (c 1.0, CHCl₃). \( ^1H \) NMR (600MHz; CDCl₃) \( \delta \) 3.71 (1H, dd, 9.8, 5.5 Hz, \( \text{CH} \text{A} \text{CH} \text{B} \text{OTBS} \)) 3.59 (1H, dd, 9.8, 5.5 Hz, \( \text{CH} \text{A} \text{C} \text{H} \text{B} \text{OTBS} \)) 2.77 (1H, m, \( \text{C}(=O)\text{CH(\text{CH}₃)} \)) 2.56-2.45 (2H, m, \( \text{C}(=O)\text{CH₃CH₃}, \text{C}(=O)\text{CH₆OTBS} \)) 1.04 (3H, t, 7.2 Hz, \( \text{C}(=O)\text{CH₃CH₃} \)) 1.01 (3H, d, 7.0 Hz, \( \text{C}(=O)\text{CH(\text{CH}₃)} \)) 0.86 (9H, s, \( \text{SiC(\text{CH}₃)} \)) 0.02 (3H, s, \( \text{SiCH}₃ \)) 0.01 (3H, s, \( \text{SiCH}₃ \)) 13C NMR (150MHz; CDCl₃) \( \delta \) 214.49, 65.71, 48.26, 35.97, 25.77, 18.16, 13.07, 7.44, -5.59, -5.60.
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1-(tert-Butyl-dimethyl-silyloxy)-5-hydroxy-2,4-dimethyl-heptan-3-one (381)

\[
\text{O} \quad \text{TiCl}_4, \text{Ti}(\text{i-PrO})_4 \quad \text{Pr}_2\text{NEt} \\
\begin{array}{c}
\text{OTBS} \\
\text{378} \\
\end{array} \\
\text{O} \quad \text{OH} \\
\begin{array}{c}
\text{OTBS} \\
\text{381} \\
\end{array} \\
\text{O} \\
\begin{array}{c}
\text{381} \\
\text{OH} \\
\end{array}
\]

To a solution of TBS-protected ketone 378 (500 mg; 2.14 mmol) in CH\(_2\)Cl\(_2\) (15 mL) was added a mixture of TiCl\(_4\) (2 mL; 1 M of a solution in CH\(_2\)Cl\(_2\); 2 mmol) and Ti(\text{i-PrO})\(_4\) (0.2 mL; 0.65 mmol) at -78°C via cannula. The mixture was stirred for 20 minutes then \text{iPr}_2\text{NEt} (0.41 mL; 2.35 mmol) was added and the mixture was stirred for a further 1 hour. Freshly distilled propionaldehyde (266) (0.23 mL; 3.2 mmol) was then added and the mixture was stirred for a further hour then warmed to room temperature over an additional hour. The reaction was then quenched by the addition of saturated NH\(_4\)Cl (50 mL), extracted with CH\(_2\)Cl\(_2\) (3*50 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/hexanes) gave the major aldol adduct 381 (0.5 g; 77%) followed by the minor aldol adduct (55 mg; 8.4%) and a clear colourless oils. **Major Isomer** 381 \(R_F = 0.35\), \(^1\)H NMR (600MHz; CDCl\(_3\)) \(\delta 3.93-3.89 (1H, m, CH(OH)) 3.75 (1H, t, 9.2 Hz, CH\(_A\)CH\(_B\)OTBS) 3.58 (1H, dd, 9.5, 4.8 Hz, CH\(_A\)C\(_H\)B OTBS) 3.08-3.02 (1H, m, CH\(_H\)(CH\(_3\))CH\(_2\)OTBS) 2.99 (1H, d, 3.2 Hz, CH(OH)) 2.74 (1H, dq, 7.2, 2.6 Hz, C(=O)CH(CH\(_3\))CH(OH)) 1.56-1.49 (1H, m, CH\(_A\)CH\(_B\)CH\(_3\)) 1.40-1.33 (1H, m, CH\(_A\)CH\(_B\)CH\(_3\)) 1.08 (3H, d, 7.2 Hz, , C(=O)CH(CH\(_3\))CH(OH)) 0.97 (3H, d, 6.9 Hz, CH(CH\(_3\))CH\(_2\)OTBS) 0.94 (3H, t, 7.4 Hz, CH\(_2\)CH\(_3\)) 0.86 (9H, s, SiC(CH\(_3\))\(_3\)) 0.04 (3H, s, SiCH\(_3\)) 0.02 (3H, s, SiCH\(_3\)) \(^{13}\)C NMR (150MHz; CDCl\(_3\)) \(\delta 219.10, 71.83, 66.52, 50.43, 46.96, 26.50, 25.81, 18.26, 13.29, 10.58, 8.53, -5.62, -5.67.** **Minor Isomer** 381 \(R_F = 0.30\), \(^1\)H NMR (600MHz; CDCl\(_3\)) \(\delta 3.81-3.78 (2H, m, CH(OH), CH\(_A\)CH\(_B\)OTBS) 3.55 (1H, dd, 9.6, 5.0 Hz, CH\(_A\)CH\(_B\)OTBS) 3.04-2.98 (1H, m, CH(CH\(_3\))CH\(_2\)OTBS) 2.95 (1H, d, 2.6 Hz, CH(OH)) 2.68 (1H, dq, 7.2, 2.8 Hz, , C(=O)CH(CH\(_3\))CH(OH)) 1.57-1.50 (1H, m, CH\(_A\)CH\(_B\)CH\(_3\)) 1.41-1.34 (1H, m, CH\(_A\)CH\(_B\)CH\(_3\)) 1.11 (3H, d, 7.2 Hz, C(=O)CH(CH\(_3\))CH(OH)) 1.00 (3H, d, 7.0 Hz, CH(CH\(_3\))CH\(_2\)OTBS) 0.95 (3H, t, 7.5 Hz, CH\(_2\)CH\(_3\)) 0.86 (9H, s, SiC(CH\(_3\))\(_3\)) 0.04 (3H, s, SiCH\(_3\)) 0.02 (3H, s, SiCH\(_3\)) \(^{13}\)C NMR (150MHz; CDCl\(_3\)) \(\delta 218.97, 72.70, 65.58, 49.69, 47.27, 26.97, 26.79, 18.21, 13.48, 10.46, 8.58, -5.61, -5.66.**
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1-(tert-Butyl-dimethyl-silylloxy)-2,4-dimethyl-heptane-3,5-diol (382)

\[
\text{OH} \quad \text{OTBS} \quad \text{(Me)}_4\text{NBH(OAc)}_3 \quad \text{CH}_3\text{COOH} \quad \text{CH}_3\text{CN} \quad \text{OH} \quad \text{OTBS}
\]

Tetramethylammonium triacetoxyborohydride (2.60 g; 9.8 mmol) was dissolved in acetonitrile (10.5 mL) and acetic acid (10 mL) at RT. The mixture was stirred for two hours then cooled to -20°C and alcohol 381 (375 mg; 1.23 mmol) in acetonitrile (5 mL) was added via cannula. The mixture was stirred for a further two hours at this temperature then placed in the freezer for a further 48 hours. The reaction was quenched at 0°C with careful addition of NaHCO\textsubscript{3} (50 mL), warmed to room temperature and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x50 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography (50% EtOAc/hexanes) gave the diol 382 (2.1 g; 83%) as a clear oil. R\textsubscript{f} = 0.45, \textsuperscript{1}H NMR (600MHz; CDCl\textsubscript{3}) δ 4.90 (1H, brs, CH(OH)) 4.02 (1H, brs, CH(OH)) 3.87 (1H, t, 6.7 Hz, CH(OH)CH\textsubscript{2}CH\textsubscript{3}) 3.83 (1H, dd, 10.0, 3.8 Hz, CHCH\textsubscript{3}OTBS) 3.62-3.57 (2H, m, CHCH\textsubscript{3}OTBS, CH(OH)CH\textsubscript{2}OTBS) 2.06-2.00 (1H, m, CHCH\textsubscript{3}CH(OH)CH\textsubscript{2}CH\textsubscript{3}) 1.72-1.68 (1H, m, CH(CH\textsubscript{3})CH\textsubscript{2}OTBS) 1.65-1.55 (1H, m, CH\textsubscript{2}CH\textsubscript{3}CH\textsubscript{3}) 1.43-1.34 (1H, m, CH\textsubscript{2}CH\textsubscript{3}CH\textsubscript{3}) 1.03 (3H, d, 7.1 Hz, CH(CH\textsubscript{3})CH(CH\textsubscript{3})CH\textsubscript{3}) 0.93 (3H, t, 7.6 Hz, CH\textsubscript{2}CH\textsubscript{3}) 0.89 (9H, s, Si(CH\textsubscript{3})\textsubscript{3}) 0.77 (3H, d, 6.9 Hz, CH(CH\textsubscript{3})CH(CH\textsubscript{3})CH\textsubscript{2}OTBS) 0.09 (6H, s, 2*SiCH\textsubscript{3}) \textsuperscript{13}C NMR (150MHz; CDCl\textsubscript{3}) δ 83.43, 72.71, 69.74, 36.98, 36.75, 27.18, 25.77, 18.04, 13.12, 10.86, 10.62, -5.64, -5.70.

1-(tert-Butyl-dimethyl-silylloxy)-5-(4-methoxy-benzyloxy)-2,4-dimethyl-heptan-3-ol (383)

To a solution of the alcohol 382 (70 mg; 0.22 mmol) in Et\textsubscript{2}O (5 mL) at 0°C was added via cannula PMB-imidate 147 (95 mg; 0.33 mmol) in Et\textsubscript{2}O (3 mL). The solution was then treated with trifluoromethanesulfonic acid (10 µL; 0.1 M of a solution in Et\textsubscript{2}O) and the resulting yellow solution was warmed to room temperature and stirred for one hour. The reaction was quenched with the addition of NaHCO\textsubscript{3} solution (20 mL) and the mixture was extracted with Et\textsubscript{2}O (3x20 mL). The combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo. Purification by column chromatography
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(CH₂Cl₂) gave the PMB-protected ether 383 (20 mg; 21%) as a clear oil. Rₗ = 0.60, ¹H NMR (600MHz; CDCl₃) δ 7.25 (2H, d, 8.6 Hz, ArH) 6.86 (2H, d, 8.6 Hz, ArH) 4.52 (1H, d, 11.0 Hz, OCH₃CH₂PMP) 4.49 (1H, d, 11.0 Hz, OCH₃CH₂PMP) 3.80 (3H, s, OCH₃) 3.79-3.76 (1H, m, CH₂CH₃OTBS) 3.73-3.66 (3H, m, CH₂CH₂OTBS, CH(OH), CHOPMB) 3.42 (1H, q, 7.2, 5.3 Hz, CH₂OH) 1.96-1.91 (1H, m, CH₂(CH₃)CHOPMB) 1.80-1.72 (2H, m, CH(CH₃)CH₂OTBS, CH₂CH₂CH₃) 1.52-1.46 (1H, m, CH₂CH₂CH₃, CH(CH₃)CHOPMB) 0.07 (6H, brs, 2*SiC₃H₃) ¹³C NMR (150MHz; CDCl₃) δ 159.06, 130.85, 129.31, 113.71, 81.83, 77.32, 71.49, 65.11, 55.24, 37.27, 37.12, 25.90, 23.51, 18.22, 15.23, 11.27, 10.69, -5.50, -5.52.

1-[3,5-Bis-(tert-butyl-dimethyl-silanyloxy)-1-ethyl-2,4-dimethyl-pentyloxymethyl]-4-methoxy-benzene (384)

To a solution of alcohol 383 (20 mg; 0.05 mmol) in CH₂Cl₂ (3 mL) at -78°C was added 2,6-lutidine (12 µL; 0.10 mmol) followed by TBSOTf (20 µL; 0.08 mmol). The reaction was stirred for 30 minutes at -78°C, warmed to ambient temperature and quenched with NaHCO₃ (5 mL). The mixture was extracted with CH₂Cl₂ (3*5 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/hexanes) gave the protected tri-protected adduct 384 (24 mg; 92%) as a clear oil. Rₗ = 0.6, ¹H NMR (600MHz; CDCl₃) δ 7.26 (2H, d, 8.5 Hz, ArH) 6.86 (2H, d, 8.5 Hz, ArH) 4.43 (1H, d, 11.0 Hz, OCH₃CH₂PMP) 4.36 (1H, d, 11.0 Hz, OCH₃CH₂PMP) 3.80 (3H, s, OCH₃) 3.74-3.69 (2H, m, CH₂CH₃OTBS, CHOTBS) 3.50-3.47 (1H, m, CHOPMB) 3.39 (1H, dd, 9.8, 7.9 Hz, CH₂CH₂OTBS) 2.07 (1H, CH(CH₃)CHOPMB) 1.93-1.86 (1H, m, CH(CH₃)CH₂OTBS) 1.63-1.56 (1H, m, CH₂CH₂CH₃) 1.43-1.37 (1H, CH₂CH₂CH₃) 0.95-0.86 (18H, m, 2*SiC(CH₃)₃, CH₂CH₂CH₃, CH(CH₃)CHOPMB, CH(CH₃)CH₂OTBS) 0.05 (3H, s, SiCH₃) 0.04 (3H, s, SiCH₃) 0.03 (3H, s, SiCH₃) 0.02 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 158.90, 131.43, 129.14, 113.61, 80.65, 75.38, 70.58, 65.24, 55.25, 42.00, 39.75, 39.54, 26.12, 25.96, 22.32, 18.30, 14.86, 11.12, 9.53, -4.07, -4.08, -5.32, -5.36.
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3-(tert-Butyl-dimethyl-silyloxy)-2-methyl-propan-1-ol (386)

\[
\begin{align*}
\text{MeO} & \quad \text{OTBS} \quad \text{379} \\
\text{DIBALH} & \quad \text{CH}_2\text{Cl}_2 \\
\text{HO} & \quad \text{OTBS} \quad \text{386}
\end{align*}
\]

To a solution of TBS-protected roche ester 379 (3.4 g; 14.5 mmol) in CH\(_2\)Cl\(_2\) (150 mL) was added DIBALH (43 mL; 1.0 M of a solution in CH\(_2\)Cl\(_2\); 43 mmol) at -78°C. The mixture was stirred for three hours at -78°C then warmed to room temperature for a further hour. The reaction was quenched with NH\(_4\)Cl (100 mL), extracted with CH\(_2\)Cl\(_2\) (3*100 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography (10% Et\(_2\)O/CH\(_2\)Cl\(_2\)) gave the TBS-protected alcohol 386 (2.86 g; 95%) as a clear oil. R\(_f\) = 0.3, \(^1\)H NMR (600MHz; CDCl\(_3\)) \(\delta \) 3.73 (1H, dd, 9.9, 4.4 Hz, CH\(_A\)CH\(_B\)OTBS) 3.65-3.58 (2H, m, CH\(_A\)C\(_H\)B OTBS, CH\(_A\)CH\(_B\)OH) 3.53 (1H, dd, 9.8, 8.0 Hz, CH\(_A\)CH\(_B\)OH) 2.90 (1H, brs, CH\(_2\)O) 1.96-1.91 (1H, m, CH\(_H\)CH\(_3\)) 0.89 (9H, s, SiC(CH\(_3\))\(_3\)) 0.83 (3H, d, 7.0 Hz, CHC\(_H\)3) 0.78 (6H, s, 2*SiC(CH\(_3\))\(_2\)) \(^{13}\)C NMR (150MHz; CDCL\(_3\)) \(\delta \) 68.82, 68.37, 36.95, 25.82, 18.14, 13.04, -5.57, -5.64.

3-(tert-Butyl-dimethyl-silyloxy)-2-methyl-propionaldehyde (385)

\[
\begin{align*}
\text{HO} & \quad \text{OTBS} \quad \text{386} \\
\text{Swern [O]} & \quad \text{385}
\end{align*}
\]

To a solution of DMSO (2.3 mL; 32.3 mmol) in CH\(_2\)Cl\(_2\) (60 mL) at -78°C was added oxalyl chloride (8.07 mL of a 2 M solution in CH\(_2\)Cl\(_2\); 16.16 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 386 (2.25 g; 10.77 mmol) in CH\(_2\)Cl\(_2\) (15 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt\(_3\) (8.9 mL; 64.6 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH\(_4\)Cl (100 mL) then extracted with CH\(_2\)Cl\(_2\) (3*50 mL), dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. Purification by column chromatography (CH\(_2\)Cl\(_2\)) gave the desired aldehyde 385 (2.0 g; 90%) as a colourless oil. R\(_f\) = 0.79, \(^1\)H NMR (600MHz; CDCl\(_3\)) \(\delta \) 9.73 (1H, d, 1.5 Hz, CH(=O)) 3.85 (1H, dd, 10.2, 5.2 Hz, CH\(_A\)CH\(_B\)OTBS) 3.79 (1H, dd, 10.2, 5.2 Hz, CH\(_A\)CH\(_B\)OH) 2.55-2.49 (1H, m, CHCH\(_3\)) 1.08 (3H, d, 7.0 Hz, CHCH\(_3\)) 0.87 (9H, s, SiC(CH\(_3\))\(_3\)) 0.04 (6H, s, 2*SiCH\(_3\)) \(^{13}\)C NMR (150MHz; CDCl\(_3\)) \(\delta \) 204.78, 63.40, 48.78, 25.76, 18.20, 10.26, -5.54, -5.57.
**Experimental Procedures for Chapter Four**

**Benzoic acid 6-(tert-butyl-dimethyl-silanyloxy)-4-hydroxy-1,3,5-trimethyl-2-oxo-hexyl ester (388)**

![Chemical structure](image)

To a solution of dicyclohexylboron chloride (355) (2.5 mL; 11.6 mmol) in Et₂O (30 mL) at -78°C was added NEt₃ (1.95 mL; 13.9 mmol) followed by ketone 82 (1.6 g; 7.73 mmol) in Et₂O (30 mL). The reaction was warmed to 0°C and stirred for two hours, before being re-cooled to -78°C. The aldehyde 385 (2.0 g; 9.70 mmol) in Et₂O (10 mL) was added via cannula and stirring continued at -78°C for 2 hours then at -25°C for 15 hours. The reaction was quenched at 0°C with the addition of MeOH (30 mL), pH 7 buffer solution (30 mL) and 30% H₂O₂ solution (30 mL) and stirring maintained for one hour at ambient temperature. The mixture was extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography gave the anti-aldol adduct 388 (2.40 g; 75%) as a clear oil. R_f = 0.1, ¹H NMR (600MHz; CDCl₃) δ 8.00 (2H, m, ArH) 7.57 (1H, m, ArH) 7.45 (2H, m, ArH) 5.45 (1H, q, 7.0 Hz, BzOCH(CH₃)) 3.81 (1H, dd, 10.2, 4.0 Hz, CH₃CH₂OTBS) 3.72 (1H, td, 8.0, 4.0 Hz, CH₂OH) 3.66 (1H, dd, 10.2, 4.0 Hz, CH₃CH₂OTBS) 3.42 (1H, d, 7.7 Hz, CHOH) 3.17 (1H, dqn, 7.1, 1.4 Hz, CH(CH₃)C(OH)) 1.83 (1H, m, CH(CH₃)CH₂OTBS) 1.56 (3H, d, 7.0 Hz, BzOCH(CH₃)) 1.18 (3H, d, 7.0 Hz, CH(CH₃)CHOH) 1.06 (3H, d, 7.1 Hz, CH(CH₃)CH₂OTBS) 0.88 (9H, s, Si(CH₃)₃) 0.05 (3H, s, SiCH₂) 0.60 (3H, d, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 211.02, 165.85, 133.26, 129.80, 129.57, 128.41, 77.55, 75.16, 65.12, 46.77, 35.52, 25.78, 18.08, 15.52, 15.24, 14.19, -5.66, -5.72.

**Benzoic acid 4,6-bis-(tert-butyl-dimethyl-silanyloxy)-1,3,5-trimethyl-2-oxo-hexyl ester (389)**

![Chemical structure](image)

To a solution of alcohol 388 (1.60 g; 3.88 mmol) in CH₂Cl₂ (40 mL) at -78°C was added 2,6-lutidine (0.9 mL; 7.74 mmol) followed by TBSOTf (1.30 mL; 5.68 mmol). The reaction was stirred for 30 minutes at -78°C, warmed to ambient temperature and quenched with NaHCO₃ (70 mL). The mixture was extracted with CH₂Cl₂ (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography gave the bis-TBS-protected adduct 389 (1.97 g; 96%) as a clear oil. R_f = 0.85, ¹H NMR...
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(600MHz; CDCl$_3$) $\delta$ 8.07 (2H, d, 7.0 Hz, ArH) 7.57 (1H, t, 7.5 Hz, ArH) 7.45 (2H, t, 7.5 Hz, ArH) 5.45 (1H, q, 7.0 Hz, BzOCH(CH$_3$)) 4.08 (1H, dd, 8.5, 2.5 Hz, CHOTBS) 3.69 (1H, dd, 10.0, 7.4 Hz, CH$_3$CH$_2$OTBS) 3.40 (1H, dd, 7.0 Hz, CH(CH$_3$)CHOTBS) 1.99-1.92 (1H, m, CH$_2$(CH$_3$)CH$_2$OTBS) 1.52 (3H, d, 7.0 Hz, BzOCH(CH$_3$)) 1.15 (3H, d, 7.0 Hz, CH(C$_3$H$_3$)CHOTBS) 1.01 (3H, s, SiC(CH$_3$)$_3$) 1.00 (3H, s, SiC(CH$_3$)$_3$) 0.06 (3H, s, SiCH$_3$) 0.04 (3H, s, SiCH$_3$) 0.03 (3H, s, SiCH$_3$) -0.06 (3H, SiCH$_3$)

$^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 208.97, 165.68, 133.18, 129.79, 128.35, 75.42, 74.83, 64.33, 46.27, 39.57, 26.15, 26.87, 18.36, 18.17, 15.41, 14.19, 13.99, -3.85, -4.84, -5.48, -5.52.

5,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,6-dimethyl-heptan-3-one (390)

![Chemical Structure]

To a solution of protected adduct 389 (1.60 g; 3.02 mmol) in THF (30 mL) and MeOH (15 mL) at 0°C was added SmI$_2$ (120 mL of a 0.1 M solution in THF; 12 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0°C with the addition of saturated aqueous K$_2$CO$_3$ (180 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et$_2$O (3*100 mL), and the combined organic extracts dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (CH$_2$Cl$_2$) gave ketone 390 (1.14 g; 92%) as a clear colourless oil. R$_f$ = 0.87, $^1$H NMR (600MHz; CDCl$_3$) $\delta$ 3.99 (1H, dd, 7.1, 3.8 Hz, CHOTBS) 3.67 (1H, dd, 9.9, 6.5 Hz, CH$_3$CH$_2$OTBS) 2.86 (1H, qn, 7.0 Hz, CH(CH$_3$)CHOTBS) 2.57-2.43 (2H, m, CH$_3$CH$_2$CH$_3$, CH$_3$CH$_2$CH$_2$CH$_3$) 1.91-1.84 (1H, m, CH(CH$_3$)CH$_2$OTBS) 1.01 (6H, m, CH(CH$_3$)CHOTBS, CH$_2$CH$_3$) 0.89 (9H, s, SiC(CH$_3$)$_3$) 0.86 (12H, m, SiC(CH$_3$)$_3$, CH(CH$_3$)CH$_2$OTBS) 0.06 (3H, s, SiCH$_3$) 0.04 (3H, s, SiCH$_3$) 0.03 (3H, s, SiCH$_3$) -0.04 (3H, s, SiCH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) $\delta$ 214.21, 75.76, 64.44, 50.15, 39.56, 36.41, 26.03, 25.89, 18.26, 18.21, 13.91, 13.45, 7.40, -4.41, -4.58, -5.42, -5.49.
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5,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,6-dimethyl-heptan-3-ol (391/392)

![Chemical Structure](image)

To a solution of the ketone 390 (800 mg; 1.96 mmol) in EtOH (15 mL) at 0°C was added NaBH₄ (150 mg; 3.92 mmol) and the resulting mixture was warmed to room temperature. After six hours H₂O (50 mL) was added and the mixture was extracted with Et₂O (3*100 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (25% Et₂O/hexanes) gave the alcohol 391/392 (752 mg; 93%) as an inseparable mixture of isomers (4:1). R_f = 0.7, ¹H NMR (600MHz; CDCl₃) δ 3.77 (1H, t, 4.9 Hz, 5.0 Hz, CHOTBS) 3.58 (1H, dd, 10.2, 7.3 Hz, CH₂CH₆OTBS) 3.47 (1H, d, 1.5 Hz, CHO) 3.47-3.44 (1H, m, CHOH) 3.40 (1H, dd, 10.2, 6.7 Hz, CH₂CH₆OTBS) 1.95-1.89 (1H, m, CH(CH₃)CH₂OTBS) 1.76-1.71 (1H, m, CH(CH₃)CHOTBS) 1.64-1.50 (1H, m, CH₂CH₆CH₃) 0.96 (3H, t, 7.3 Hz, CH₂CH₃) 0.91 (9H, s, Si(CH₃)₃) 0.89-0.87 (12H, m, Si(CH₃)₃, CH(CH₃)CH₂OTBS) 0.84 (3H, d, 7.0 Hz, CH(CH₃)CHOTBS) 0.10 (3H, s, SiCH₃) 0.09 (3H, s, SiCH₃) 0.04 (3H, s, SiCH₃) 0.03 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 78.77, 74.76, 64.84, 42.23, 39.78, 26.66, 25.93, 25.86, 18.17, 18.12, 16.05, 12.60, 9.40, -4.36, -4.52, -5.42, -5.50.

1-[3,5-Bis-(tert-butyl-dimethyl-silanyloxy)-1-ethyl-2,4-dimethyl-pentyloxy)methyl]-4-methoxy-benzene (393)

![Chemical Structure](image)

To a solution of alcohols 391/392 (700 mg; 1.70 mmol) in Et₂O (30 mL) was added PMB-imidate 147 (0.71 mL; 3.4 mmol) and TfOH (40 µL of a 0.9 M solution in Et₂O; 3.4 µmol) at 0°C. The mixture was warmed to ambient temperature and stirred for 24 hours. The reaction was quenched with NaHCO₃ (50 mL), extracted with Et₂O (3*50 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/hexanes) gave the protected PMB-ether adduct 393 (520 mg; 58%) as a clear oil. Data in agreement with that described above for 384.
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3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2,4-dimethyl-heptan-1-ol (394)

![Chemical structure](image)

To the protected adduct 393 (450 mg; 0.85 mmol) was added a 1% solution of HCl in EtOH (28 mL) at 0°C. The reaction was stirred at room temperature for 30 minutes, then quenched with NaHCO₃ (50 mL), extracted with Et₂O (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) gave the primary alcohol 394 (300 mg; 85%) as a clear oil. Rₖ = 0.55, ¹H NMR (600MHz; CDCl₃) δ 7.24 (2H, d, 8.7 Hz, ArH) 6.87 (2H, d, 8.7 Hz, ArH) 4.44 (1H, d, 11.1 Hz, OCH₂ClPMP) 4.31 (1H, d, 11.1 Hz, OCH₃PMP) 3.96 (1H, dd, 5.3, 3.8 Hz, CHOTBS) 3.80 (3H, s, OCH₃) 3.73 (1H, dd, 10.8, 3.9 Hz, CH₃CH₂OH) 3.57 (1H, dd, 10.8, 5.4 Hz, CH₃CH₂OH) 3.40-3.37 (1H, m, CHOPMB) 2.87 (1H, brs, CH₂OH) 2.08 (1H, qdd, 7.2, 6.0, 5.4 Hz, CH(CH₃)CHOPMB) 1.93-1.86 (1H, m, CH(CH₃)CH₂OH) 1.73-1.63 (1H, m, CH₃CH₂CH₃) 1.51-1.44 (1H, m, CH₃CH₂CH₃) 0.99 (3H, d, 7.1 Hz, CH(CH₃)CH₂OH) 0.93-0.90 (15H, m, Si(CH₃)₃, CH₂CH₃, CH(CH₃)CHOPMB) 0.11 (3H, s, SiCH₃) 0.07 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 158.93, 131.08, 128.93, 113.65, 80.18, 78.12, 70.07, 66.38, 55.26, 41.12, 35.90, 25.99, 22.00, 18.12, 16.88, 10.69, 8.16, -4.27, -4.38.

3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2,4-dimethyl-heptanal (377)

![Chemical structure](image)

To a solution of DMSO (155 µL; 2.19 mmol) in CH₂Cl₂ (20 mL) at -78°C was added oxalyl chloride (0.55 mL of a 2 M solution in CH₂Cl₂; 1.10 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol 394 (300 mg; 0.73 mmol) in CH₂Cl₂ (5 mL) was added via cannula. This mixture was stirred for a further 30 minutes then NEt₃ (606 µL; 4.38 mmol) was added and the solution was stirred for a further hour then warmed to room temperature over 30 minutes. The mixture was quenched with NH₄Cl (50 mL) then extracted with CH₂Cl₂ (3*30 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the desired aldehyde 377 (280 mg; 93%) as a colourless oil. Rₖ = 0.6, ¹H
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NMR (600MHz; CDCl$_3$) δ 9.77 (1H, d, 2.8 Hz, CH(=O)) 7.24 (2H, d, 8.7 Hz, ArH) 6.87 (2H, d, 8.7 Hz, ArH) 4.44 (1H, d, 11.2 Hz, OCH$_A$CH$_B$PMP) 4.32 (1H, d, 11.2 Hz, OCH$_A$CH$_B$PMP) 4.10 (1H, dd, 5.6, 2.6 Hz, C$_A$H$_{OTBS}$) 3.80 (3H, s, OC$_3$H$_3$) 3.37 (1H, td, 6.4, 3.5 Hz, C$_A$H$_{OPMB}$) 2.50 - 2.46 (1H, m, C$_A$H$_{OTBS}$) 2.06 - 2.01 (1H, m, C$_A$H$_{OTBS}$) 1.68 - 1.62 (1H, m, C$_A$H$_{CH}_3$CH$_B$CH$_3$) 1.49 - 1.42 (1H, m, CH$_A$C$_H$B$_{CH}_3$) 1.07 (3H, d, 7.1 Hz, C$_A$H$_{CH}_3$CH$_B$CH$_3$) 0.92 (3H, t, 7.4 Hz, CH$_2$C$_3$H$_3$) 0.89 (9H, s, SiC(C$_3$H$_3$)$_3$) 0.81 (3H, d, 7.2 Hz, C$_A$H$_{CH}_3$CH$_B$CH$_3$) 0.07 (3H, s, SiC$_3$H$_3$) 0.05 (3H, s, SiC$_3$H$_3$)

$^{13}$C NMR (150MHz; CDCl$_3$) δ 205.41, 159.01, 130.90, 129.14, 113.67, 80.16, 75.15, 70.45, 55.23, 49.32, 40.68, 25.81, 22.08, 18.08, 12.21, 10.92, 8.53, -4.36, -4.64.

Benzoic acid 4-hydroxy-1,3,5-trimethyl-2-oxo-hexyl ester (395)

To a solution of dicyclohexylboron chloride (355) (1.6 mL; 7.4 mmol) in Et$_2$O (20 mL) at -78°C was added NEt$_3$ (1.2 mL; 8.7 mmol) followed by ketone 82 (1.0 g; 4.85 mmol) in Et$_2$O (10 mL). The reaction was warmed to 0°C and stirred for 2 hours, before being re-cooled to -78°C. Isobutyraldehyde (265) (1.35 mL; 14.8 mmol) was added and stirring continued for a further 2 hours then at -23°C overnight in the freezer. The reaction was warmed to 0°C and stirred for 30 minutes then quenched by the addition of MeOH (15 mL), pH 7 buffer solution (15 mL) and 30% H$_2$O$_2$ solution (15 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3*100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo gave the anti-aldol product 395 (1.35 g; 99%) as a white solid. $^1$H NMR (600MHz; CDCl$_3$) δ 8.08 (2H, d, 5.4 Hz, ArH) 7.57 (1H, t, 7.3 Hz, ArH) 7.44 (2H, d, 7.7 Hz, ArH) 5.44 (1H, q, 7.1 Hz, BzOCH(CH$_3$)) 3.60-3.56 (1H, m, CH(OH)) 3.00 (1H, dq, 7.2 Hz, C(=O)CH(CH$_3$)) 2.28 (1H, brs, CH(OH)) 1.80-1.75 (1H, m, CH(CH$_3$)$_2$) 1.56 (3H, d, 7.1 Hz, BzOCH(CH$_3$)) 1.22 (3H, d, 7.2 Hz, C(=O)CH(CH$_3$)) 0.96 (3H, d, 6.8 Hz, CH$(CH_3)_2$) 0.89 (3H, d, 6.8 Hz, CH$(CH_3)_2$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 212.03, 165.86, 133.33, 129.77, 129.43, 128.44, 77.69, 74.70, 45.42, 29.78, 20.00, 15.87, 15.20, 14.40.
Benzoic acid 4-benzyloxy-1,3,5-trimethyl-2-oxo-hexyl ester (396)

\[
\begin{align*}
\text{BzO} & \quad \text{Bn-imidate} \quad \text{TiOH} \quad \text{BzO} \\
\text{395} & \quad \text{396}
\end{align*}
\]

To a solution of the alcohol 395 (1.3 g; 4.7 mmol) in cyclohexane (8 mL) at 0°C was added \textit{via} cannula benzyl-imidate 338 (2.35 g; 9.4 mmol) in CH$_2$Cl$_2$ (4 mL). The solution was then treated with trifluoromethanesulfonic acid (0.1 mL) and the resulting solution was warmed to room temperature and stirred for three hours. The reaction was filtered/triturated with hexane (2*20 mL) quenched with the addition of NaHCO$_3$ solution (50 mL), and brine (50 mL), dried (Na$_2$SO$_4$) and concentrated \textit{in vacuo}.

Purification by column chromatography (50% CH$_2$Cl$_2$/hexanes) gave the benzyl protected ether 396 (1.31 g; 76%) as a clear oil. R$_f$ = 0.8, $^1$H NMR (600MHz; CDCl$_3$) δ 8.07 (2H, d, 7.1 Hz, Bz-$\text{Ar}$H) 7.57 (1H, t, 7.5 Hz, Bz-$\text{Ar}$H) 7.44 (2H, t, 8.0 Hz, Bz-$\text{Ar}$H) 7.32-7.29 (2H, m, Bn-$\text{Ar}$H) 7.26-7.23 (3H, m, Bn-$\text{Ar}$H) 5.38 (1H, q, 7.1 Hz, BzOC$_2$H(C$_3$H$_7$)) 4.52 (1H, d, 11.2 Hz, CH$_3$A CH$_2$PMP) 4.43 (1H, d, 11.2 Hz, CH$_3$B CH$_2$PMP) 3.69 (1H, dd, 9.8, 2.2 Hz, CHOBN) 3.02 (1H, dq, 9.8, 7.0 Hz, C(=O)CH(CH$_3$)) 1.93-1.88 (1H, m, CH(CH$_3$)$_2$) 1.42 (3H, d, 7.1 Hz, BzOCH(CH$_3$)) 4.52 (1H, d, 11.2 Hz, CH$_3$A CH$_2$PMP) 4.43 (1H, d, 11.2 Hz, CH$_3$B CH$_2$PMP) 3.69 (1H, dd, 9.8, 2.2 Hz, CHOBN) 3.02 (1H, dq, 9.8, 7.0 Hz, C(=O)CH(CH$_3$)) 1.93-1.88 (1H, m, CH(CH$_3$)$_2$) 1.42 (3H, d, 7.1 Hz, BzOCH(CH$_3$)) 1.14 (3H, d, 7.0 Hz, C(=O)CH(CH$_3$)) 1.07 (3H, d, 7.0 Hz, CH(CH$_3$)$_2$) 0.94 (3H, d, 7.0 Hz, CH(CH$_3$)$_2$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 210.00, 165.79, 138.93, 133.16, 129.77, 129.60, 128.35, 128.10, 127.32, 127.19, 84.95, 75.06, 45.72, 29.61, 20.54, 15.17, 15.02, 14.37.

5-Benzylxy-4,6-dimethyl-heptane-2,3-diol (397)

\[
\begin{align*}
\text{BzO} & \quad \text{LiBH}_4 \quad \text{THF} \quad \text{HO} \\
\text{396} & \quad \text{397}
\end{align*}
\]

To a solution of benzyl-protected adduct 396 (1.0 g; 2.72 mmol) in THF (30 mL) at -78°C was added LiBH$_4$ (50 mL of a 2 M solution in THF; 50 mmol). The reaction mixture was warmed to room temperature slowly and stirred for 24 hours, then cooled to 0°C and carefully quenched with the addition of H$_2$O (50 mL). The mixture was partitioned between H$_2$O (150 mL) and Et$_2$O (4*100 mL), dried (Na$_2$SO$_4$) and concentrated \textit{in vacuo}. Purification by column chromatography (50% Et$_2$O/hexanes) gave the diol 397 (654 mg; 90%) as a clear oil. R$_f$ = 0.1, $^1$H NMR (600MHz; CDCl$_3$) δ 7.35-7.29 (5H, m, ArH) 4.67 (1H, d, 10.9 Hz, BzOCH(C$_3$H$_7$)).
3-Hz, OCH₃CH₆Ph) 4.64 (1H, d, 10.9 Hz, OCH₃CH₆Ph) 3.80-3.75 (1H, m, (CH₃)CH(OH)) 3.71 (1H, dd, 7.8, 4.2 Hz, CH(OH)) 3.24 (1H, dd, 6.6, 4.5 Hz, CHOBN) 2.04-1.87 (1H, m, CH(CH₃)₂) 1.88-1.81 (1H, m, CH(CH₃)) 1.16 (3H, d, 6.3 Hz, (CH₃)CH(OH)) 1.05 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.99 (3H, d, 7.0 Hz, CH(CH₃)₂) 0.88 (3H, d, 7.0 Hz, CH(CH₃)₂) 13C NMR (150MHz; CDCl₃) δ 137.73, 128.48, 127.88, 127.69, 90.13, 76.98, 75.43, 67.94, 38.49, 31.33, 20.48, 17.25, 16.54, 14.47.

3-Benzyloxy-2,4-dimethyl-pentanal (347)

To a stirred solution of diol 397 (550 mg; 2.07 mmol) in MeOH (25 mL) and H₂O (12.5 mL) was added NaIO₄ (2.64 g; 12.4 mmol) at room temperature. The reaction was stirred for 15 minutes, then diluted with H₂O (90 mL) and extracted with Et₂O (3*70 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the aldehyde 347 (430 mg; 96%) as a clear oil. Data in agreement with that described above.

3-Benzyloxy-11-(tert-butyldimethylsilyloxy)-9-hydroxy-13-(4-methoxy-benzyloxy)-2,4,6,8,10,12-hexamethyl-5-triethylsilanyloxy-pentadecan-7-one (398)

To a solution of ketone 363 (140 mg; 0.32 mmol) in THF (50 µL) at −78°C was added LiHMDS (0.33 mL of a 1 M solution in THF; 0.33 mmol) dropwise. The resulting yellow solution was stirred for one hour at −78°C then warmed to −50°C for a further hour. The mixture was re-cooled to −78°C and the aldehyde 377 (120 mg; 0.29 mmol) was added as a solution in THF (2 mL) via cannula. After two hours the solution was diluted with Et₂O (5 mL) and quenched with pH 7 buffer (10 mL) and allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et₂O (3*10 mL),
dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/hexanes) gave the aldol product 398 (152 mg; 62%) as a clear oil. Rᵣ = 0.1, ¹H NMR (600MHz; CDCl₃) δ 7.37-7.21 (7H, m, 5*Bn-ArH, 2*PMB-ArH) 4.80 (1H, d, 11.8 Hz, OCH₃CH₈Ph) 4.60 (1H, d, 11.8 Hz, OCH₃CH₈Ph) 4.40 (1H, d, 11.2, OCH₃CH₈PMP) 4.35 (1H, d, 11.2 Hz, OCH₃CH₈PMP) 4.16 (1H, dd, 9.4, 1.4 Hz, CHOTES) 3.98 (1H, dd, 6.1, 4.2 Hz, CHOTBS) 3.93 (1H, d, 10.3 Hz, CHO) 3.80 (3H, s, OCH₃) 3.57 (1H, brs, CHO) 3.43 (1H, td, 7.0, 2.9 Hz, CHOPMB) 3.31 (1H, dd, 10.0, 1.9 Hz, CHOBn) 3.19 (1H, dq, 9.2, 6.9 Hz, PH(CH₃)CHOTES) 2.55 (1H, qd, 6.9, 1.5 Hz, CH(OH)CH(CH₃)C(=O)) 2.08-2.03 (1H, m, CH(OPMB)CH(CH₃)CHOTES) 1.97-1.80 (3H, m, CH(OTBS)CH(CH₃)CH(OH), CH(CH₃)CHOBn, CH(CH₃)₂) 1.66-1.60 (1H, m, CH₃CH₈CH₃) 1.46-1.39 (1H, m, CH₃CH₈CH₃) 1.04 (3H, d, 6.9 Hz, CH(CH₃)CHOTES) 1.04 (3H, d, 6.9 Hz, CH(OH)CH(CH₃)C(=O)) 0.96-0.86 (33H, m, 3*SiCH₃, 2*Si(CH₃)₃, 2*CH(CH₃)₂, CH₂CH₃, CH(CH₃)CHOTES, CH(OTBS)CH(CH₃)CHOH, CH(OTES)CH(CH₃)CHOBn) 0.73 (3H, d, 7.0 Hz, CH(CH₃)CHOBn) 0.53 (6H, q, 7.8 Hz, 3*SiCH₂CH₃) 0.08 (3H, s, SiCH₃) 0.06 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 217.36, 158.89, 139.50, 131.40 128.88, 128.11, 126.92, 126.70, 113.63, 84.98, 80.40, 77.20, 76.26, 74.16, 72.46, 69.89, 55.24, 49.04, 47.86, 40.67, 40.12, 38.53, 30.39, 29.57, 25.93, 25.83, 21.74, 21.03, 18.04, 14.82, 12.12, 10.54, 8.98, 6.96, 6.71, 5.19, -4.28, -4.67.

3-Benzylxy-11-( tert-buty1-dimethyl-silanyloxy)-9,13-dihydroxy-2,4,6,8,10,12-hexamethyl-5-triethylsilanyloxy-pentadecan-7-one (399)

To a solution of aldol adduct 398 (80 mg; 0.09 mmol) in CH₂Cl₂ (4.5 mL) at 0°C was added pH 7 buffer (0.9 mL) followed by DDQ (30 mg; 0.13 mmol). The resulting suspension was stirred at 0°C for 30 minutes before being diluted with CH₂Cl₂ (10 mL) and quenched with NaHCO₃ (15 mL). The layers were separated and the aqueous phase extracted with CH₂Cl₂ (3*10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/hexanes) gave the diol 399 (63 mg; 96%) as a clear oil. Rᵣ = 0.9, ¹H NMR (600MHz; CDCl₃) δ 7.37-7.24 (5H, m, ArH) 4.76 (1H, d, 11.9 Hz, OCH₃CH₈Ph) 4.65 (1H, d, 11.9 Hz, OCH₃CH₈Ph) 4.15 (1H, d, 8.4 Hz, CHOTES) 4.08 (1H, t, 5.0 Hz, CHOTBS) 3.71 (1H, d, 9.6 Hz, CH(OH)CH(CH₃)C(=O)) 3.42 (1H, td, 8.6, 2.8 Hz, CH₃CH₂CHOH) 3.33 (1H, dd, 10.1, 1.9 Hz, CHOBn) 3.13 (1H, qd, 9.1, 7.1 Hz, C(=O)CH(CH₃)CHOTES) 2.50 (1H, q, 7.9, 7.0 Hz, CH(OH)CH(CH₃)C(=O)) 1.95 (1H, D398 D399
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qd, 7.5, 7.3 Hz, CH(CH₃)CHOBn) 1.87 (1H, qdd, 6.8, 5.0, 1.8 Hz, CH(CH₃)₂) 1.79-1.73 (1H, m, CH(CH₃)CHOTBS) 1.70-1.59 (2H, m, CH(OTBS)CH(CH₃)CHOH, CH₃CH₆CH₃) 1.35-1.27 (1H, m, CH₂CH₆CH₃) 1.05 (3H, d, 7.0 Hz, CH(CH₃)₂) 1.00 (3H, d, C(=O)CH(CH₃)CHOTES) 0.96-0.89 (30H, m, 3*SiCH₂CH₃, 2*Si(CH₃)₃, CH(CH₃)₂, CH₂CH₃, CH(CH₃)CHOTBS, CH(OTBS)CH(CH₃)CHOH) 0.85 (3H, d, 6.9 Hz, CH(CH₃)CHOTBS) 0.72 (3H, d, 7.0 Hz, CH(OH)CH(CH₃)C(=O)) ¹³C NMR (150MHz; CDCl₃) δ 219.19, 139.49, 128.11, 126.97, 126.53, 84.83, 76.79, 76.61, 74.49, 74.02, 71.74, 49.20, 46.72, 41.09, 40.40, 30.40, 26.67, 26.14, 25.90, 25.84, 21.09, 17.96, 15.36, 15.01, 14.91, 11.26, 9.33, 7.02, 6.83, 5.24, -4.62, -4.73.

13-Benzylflox-5-(tert-butyl-dimethyl-silanyloxy)-4,6,8,10,12,14-hexamethyl-11-triethylsilanyloxy-pentadecane-3,7,9-trione (400)

To a solution of DMSO (37 µL; 0.52 mmol) in CH₂Cl₂ (1 mL) at -78°C was added oxalyl chloride (131 µL of a 2 M solution in CH₂Cl₂, 0.26 mmol) dropwise. After 30 minutes, the diol 399 (60 mg; 0.08 mmol) was added via cannula and the resulting mixture stirred at -78°C for 30 minutes. Triethylamine (145 µL; 1.04 mmol) was added and the mixture continued stirring for a further 30 minutes before being warmed to 0°C for 10 minutes. The reaction mixture was quenched with NH₄Cl (5 mL) and extracted with CH₂Cl₂ (3*10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (CH₂Cl₂) gave the trione 400 (41 mg; 68%) as a clear oil. Rf = 0.7, ¹H NMR (600MHz; CDCl₃) δ 7.35-7.23 (5H, m, ArH) 4.74 (1H, d, 11.8 Hz, OCH₂CH₆Ph) 4.62 (1H, d, 11.8 Hz, OCH₂CH₆Ph) 4.38 (1H, dd, 8.3, 5.0 Hz, CHOTBS) 4.13 (1H, d, 9.4 Hz, CHOTES) 3.74 (1H, q, 7.1 Hz, C(=O)CH(CH₃)C(=O)) 3.29 (1H, dd, 12.3, 2.0 Hz, CHOBn) 2.95 (1H, dq, 9.3, 7.0 Hz, C(=O)CH(CH₃)CHOTES) 2.76 (1H, qn, 7.3 Hz, CH(OTBS)CH(CH₃)C(=O)) 2.66 (1H, qd, 7.0, 6.9 Hz, C(=O)CH(CH₃)CHOTBS) 2.56 (1H, dq, 18.1, 7.2 Hz, CH₂CH₆CH₃) 2.45 (1H, dq, 18.1, 7.2 Hz, CH₂CH₆CH₃) 1.95-1.85 (2H, m, CH(CH₃)CHOBn, CH(CH₃)₂) 1.09-0.99 (15H, m, C(=O)CH(CH₃)C(=O), C(=O)CH(CH₃)CHOTES, C(=O)CH(CH₃)CHOTBS, CH₂CH₃, CH(CH₃)₂, CH(CH₃)CHOBn) 0.93-0.83 (18H, m, 3*SiOCH₂CH₃, CH(OTBS)CH(CH₃)C(=O), CH(CH₃)₂, CH(CH₃)CHOBn) 0.54 (6H, q, 7.9 Hz, 3*SiCH₂CH₃) 0.07 (3H, s, SiCH₃) -0.05 (3H, s, SiCH₃) ¹³C NMR (150MHz; CDCl₃) δ 211.62, 210.66, 209.76, 139.30, 128.10, 126.97, 126.55, 84.69, 76.36, 74.10, 73.98, 60.27, 51.80, 50.16, 50.07, 40.40, 35.15, 30.36, 25.71, 20.97, 17.83, 14.98, 14.54, 14.22, 12.02, 11.27, 9.71, 7.59, 6.94, 5.12, -4.68, -5.11.
To a solution of trione 400 (38 mg; 0.05 mmol) in DMF (0.4 mL) and H₂O (20 µL) was added a solution of TAS-F (70 mg; 0.25 mmol) in DMF (0.2 mL) and the resultant yellow mixture was stirred at room temperature for two hours. The reaction mixture was diluted with EtOAc (5 mL) and washed with pH 7 buffer (3*3 mL). The combined aqueous layer was washed with EtOAc (3*2 mL) and the organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (10% Et₂O/CH₂Cl₂) produced a mixture of isomeric products which were treated with DBU (minimal amount in C₆D₆) to give trioxaadamantane 403 (22 mg; 94%) as a clear oil. Rf = 0.5, ¹H NMR (600MHz; C₆D₆) δ 7.40 (2H, d, 7.5 Hz, ArH) 7.21 (2H, t, 7.6 Hz, ArH) 7.10 (1H, t, 7.4 Hz, ArH) 5.07 (1H, d, 12.0 Hz, OCH₃CH₃) 4.67 (1H, d, 12.0 Hz, OCH₃CH₃) 4.43 (1H, s, CHO₃CH₃) 4.31 (1H, d, 8.3 Hz, CHOH) 3.78 (1H, dd, 9.3, 1.9 Hz, CHOBn) 3.37 (1H, s, CH(CH₃)C) 2.62 (1H, brs COH) 2.30-2.21 (2H, m, CH(OH)CH(CH₃)CHOBn, CH(CH₃)CHOH) 1.94-1.88 (2H, m, CH(CH₃)₂, C(OH)CH(CH₃)C) 1.58-1.51 (2H, m, CH₂CH₃CH₃, C(-O-)_2CH(CH₃)CH(-O-)) 1.38-1.31 (1H, m, CH₂CH₃CH₃) 1.22 (3H, d, 6.9 Hz, CH(OH)CH(CH₃)CHOBn) 1.22-1.18 (1H, m, C(-O-)_2OHCH(CH₃)CH(-O-)) 1.07 (3H, d, 6.9 Hz, CH(CH₃)₂) 1.06 (3H, d, 6.9 Hz, CH(CH₃)₂) 1.03 (3H, d, 6.9 Hz, C(-O-)_2OHCH(CH₃)CH(-O-)) 0.99-0.95 (6H, m, CH(CH₃)CHOH, C(-O-)_2CH(CH₃)CH(-O-)) 0.91 (3H, t, 7.4 Hz, CH₂CH₃) 0.60 (3H, d, 6.7 Hz, C(OH)CH(CH₃)C) ¹³C NMR (150MHz; C₆D₆) δ 140.52, 128.34, 126.96, 126.76, 106.16, 102.47, 97.59, 84.43, 78.47, 77.20, 73.98, 43.12, 41.92, 37.94, 37.48, 35.03, 30.97, 30.19, 21.54, 18.10, 15.78, 13.46, 13.26, 10.94, 6.25, 6.03.
3-Hydroxy-2,4-dimethyl-5-oxo-heptanoic acid 3-benzyloxy-2,4-dimethyl-1-(1-methyl-2-oxo-butyl)-pentyl ester (405)

The trioxaadamantane 403 (22 mg; 0.047 mmol) was taken up in deuterated benzene (1 mL) and a minimal amount of DBU was added. The reaction was allowed to proceed for 10 hours with ester formation monitored by $^1$H NMR spectroscopy. After optimum conversion was achieved the solvent was removed and the residue purified by column chromatography (10% Et₂O/CH₂Cl₂) to obtain the ester 405 (18 mg; 81%) over two steps as a clear oil. $R_f = 0.47$, $^1$H NMR (600MHz, C₆D₆) $\delta$ 7.40 (2H, d, 7.7 Hz, ArH) 7.20 (2H, t, 7.8 Hz, ArH) 7.10 (1H, t, 7.4 Hz, ArH) 5.45 (1H, dd, 7.7, 4.1 Hz, CHO(=O)) 4.66 (1H, d, 11.3 Hz, OCH₂CH₆Ph) 4.53 (1H, d, 11.3 Hz, OCH₂CH₆Ph) 3.77 (1H, brs, CHO) 3.70 (1H, brs, CHO) 3.19 (1H, dd, 7.1, 3.9 Hz, CHOBn) 3.08 (1H, qn, 7.1 Hz, C(=O)CH(CH₃)CHOC(=O)) 2.67-2.62 (2H, m, C(=O)CH(CH₃)CHOH, CH(OH)CH(CH₃)) 2.22-2.10 (5H, m, 2*CH₂CH₃, CH(CH₃)CHOBn) 2.02 (1H, dq, 18.2, 7.2 Hz, CH₂CH₃) 1.82 (1H, qnd 6.9, 4 Hz, CH(CH₃)₂) 1.14 (3H, d, 7.1 Hz, CH(OH)CH(CH₃)) 1.00 (3H, d, 6.9 Hz, CH(CH₃)₂) 0.98 (3H, d, 7.2 Hz, C(=O)CH(CH₃)CHOH) 0.97 (3H, d, 6.9 Hz, CH(CH₃)₂) 0.95 (3H, t, 7.3 Hz, CH₂CH₃) 0.94 (3H, d, 7.1 Hz, CH(CH₃)CHOBn) 0.92 (3H, t, 7.3 Hz, CH₂CH₃) 0.88 (3H, d, 7.1 Hz, C(=O)CH(CH₃)CHO(=O)) $^{13}$C NMR (150MHz, C₆D₆) $\delta$ 214.39, 212.07, 174.11, 139.41, 128.56, 127.92, 127.67, 85.98, 78.04, 76.62, 74.59, 48.66, 48.60, 43.98, 37.03, 36.02, 34.67, 31.09, 23.01, 22.75, 21.17, 20.79, 19.57, 18.89, 17.01, 15.84, 14.99, 14.55, 14.31, 14.04, 11.62, 7.71, 7.57.
7-Benzylxoy-4,6,8-trimethyl-non-4-en-3-one (407)

\[ \text{DBU} \rightarrow \text{O} \]

β-elimination product from the esterification and retro-Claisen reactions. Purified by column chromatography (CH\(_2\)Cl\(_2\)) gave the elimination product 407. R\(_f\) = 0.55, \(^1\)H NMR (600MHz: CDCl\(_3\)) \(\delta\) 7.35-7.26 (5H, m, ArH) 6.75 (1H, dd, 9.8, 1.3 Hz, CH\(_3\)C=CH) 4.63 (1H, d, 11.2 Hz, CH\(_3\)CH\(_8\)Ph) 4.57 (1H, d, 11.2 Hz, CH\(_3\)CH\(_8\)Ph) 3.09 (1H, dd, 6.7, 4.0 Hz, CHOBn) 2.91-2.85 (1H, m, CH(CH\(_3\))CHOBn) 2.67 (2H, qd, 7.3 Hz, CH\(_2\)CH\(_3\)) 1.82-1.76 (1H, m, CH(CH\(_3\))\(_3\)) 1.78 (3H, d, 1.3 Hz, CH\(_2\)C=CH), 1.08 (3H, d, 6.9 Hz, CH(CH\(_3\))CHOBn), 1.07 (3H, t, 7.3 Hz, CH\(_2\)CH\(_3\)) 0.99 (3H, d, 6.7 Hz, CH(CH\(_3\))CH\(_3\)), 0.88 (3H, d, 6.7 Hz, CH(CH\(_3\))CH\(_3\))

Dolabriferol (10)

\[ \text{H}_2, \text{Pd/C} \]

To a solution of ester 405 (18 mg; 0.038 mmol) in EtOH (1 mL) was added Pd/C (3 mg) and H\(_2\) at room temperature. The reaction mixture was stirred for 12 hours, then filtered through celite and concentrated \textit{in vacuo}. Purification by column chromatography (10% Et\(_2\)O/CH\(_2\)Cl\(_2\)) gave dolabriferol (10) (13.4 mg; 92%) as a white powder. R\(_f\) = 0.35, \(^1\)H NMR (600MHz; CDCl\(_3\)) \(\delta\) 5.24 (1H, t, 2.7 Hz, C(=O)CH\(_3\)) 3.76 (1H, m, C(CH\(_3\))OH) 3.61 (1H, brs, CHOCH\(_3\)) 3.60 (1H, dd, 10.5, 2.2 Hz, (CH\(_3\))\(_2\)CHCHO) 3.46 (1H, brs, COCH\(_3\)) 2.79 (1H, dq, 7.2, 7.2 Hz, C(=O)CH\(_3\)) 2.73 (1H, dq, 7.1, 4.8 Hz, OC(=O)CH\(_3\)) 2.57 (1H, dq, 14.5, 7.2 Hz, C(=O)CH\(_4\)CH\(_8\)CH\(_3\)) 2.46 (1H, dq, 14.5, 7.2 Hz, C(=O)CH\(_4\)CH\(_8\)CH\(_3\)) 1.91 (1H, dq, 7.2, 2.8 Hz, CH(CH\(_3\))COH) 1.83 (1H, dqq, 6.9, 2.2 Hz, CH(CH\(_3\))\(_2\)) 1.79 (1H, dqd, 10.5, 6.9, 2.7 Hz, CH(CH\(_3\))CHO) 1.62 (2H, m, CH\(_4\)CH\(_8\)CH\(_3\), CH\(_4\)CH\(_8\)CH\(_3\)) 1.33 (3H, d, 7.1 Hz, OC(=O)CH\(_3\)) 1.15 (3H, d, 7.2 Hz, C(=O)CH\(_3\)) 1.04 (3H, t, 7.2 Hz, C(=O)CH\(_3\)) 1.01 (3H, d, 6.9 Hz, CH(CH\(_3\))CH\(_3\)) 1.00 (3H, d, 7.2 Hz, CH(CH\(_3\))COH) 0.91 (3H, t, 7.3 Hz, C(=O)CH\(_3\))
Hz, CH₂CH₃) 0.83 (3H, d, 6.9 Hz, CH(CH₃)CH₃) 0.78 (3H, d, 6.9 Hz, CH(CH₃)CHO), **HRESIMS** calculated for C₂₁H₃₈O₆ [M+H]⁺: 387.2668; found 387.2611