# 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**

Faculty of Science and Engineering

School of Chemistry and Physical Sciences

Adelaide, Australia

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# 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

# Acknowledgements

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.

Oral Presentation delivered at the Adelaide Synthetic Chemistry Symposium, Adelaide, SA, 2011.

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

Poster Presentation at the International Conference of Organic Synthesis, ICOS 19, Melbourne, Vic, 1$^{st}$-6$^{th}$ July, 2012.

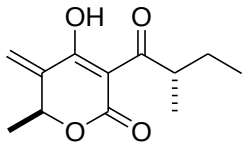
A Retro-Claisen Approach towards the Total Synthesis of Dolabriferol.

Poster Presentation at the 13$^{th}$ Tetrahedron Symposium (Asia) Challenges in Bioorganic & Organic Medicinal Chemistry Taipei, Taiwan, 27$^{th}$-30$^{th}$ November 2012.

# Abstract

Natural product chemistry has been at the forefront of organic chemistry since the late 20$^{th}$ 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.

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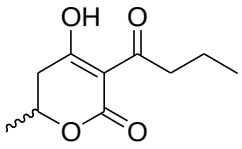


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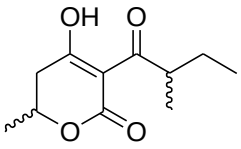


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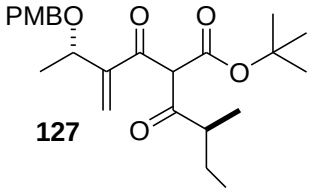


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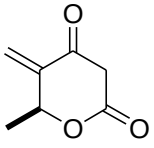


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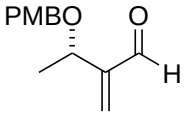


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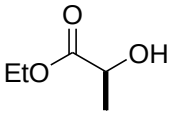
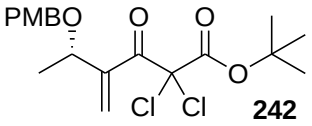



**132**

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.

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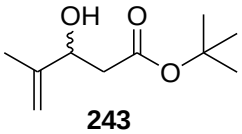


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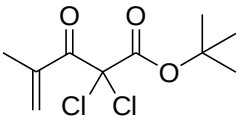


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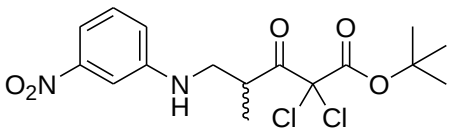
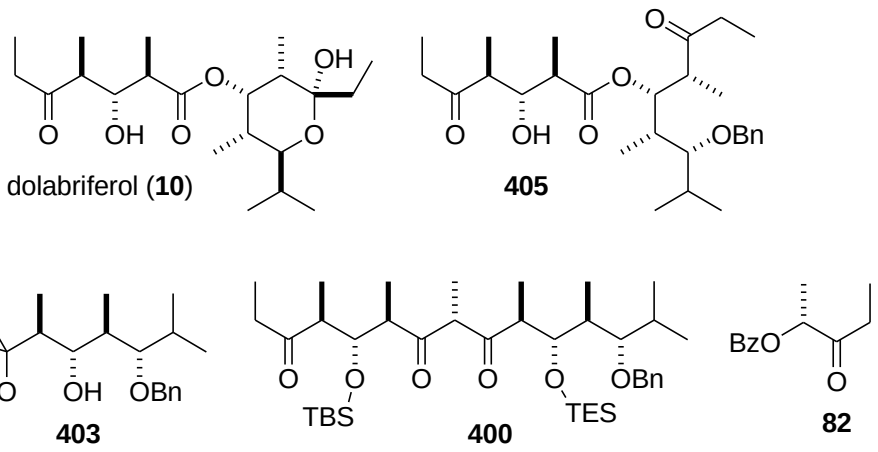



**253**

Chapter four describes an unrefined total synthesis of marine polypropionate dolabriferol (**10**), which ultilised 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.

| | |
|---|---|
| °C | degrees Celsius |
| APT | attached proton test |
| $BF_3.OEt_2$ | boron trifluoride-diethyl ether complex |
| $BH_3.SMe_2$ | borane-dimethyl sulfide complex |
| Bn | benzyl |
| b.p. | boiling point |
| *t*-BuOH | tertiary-butanol |
| *n*-BuLi | butyl lithium |
| $Bz_2O$ | benzoic anhydride |
| cat. | catalytic |
| $CDCl_3$ | deuterated chloroform |
| $C_6D_6$ | deuterated benzene |
| $CH_2Cl_2$ | dichloromethane |
| $CH_3CO_2H$ | acetic acid |
| COSY | $^1H$-$^1H$ correlation spectroscopy |
| CSA | camphor sulfonic acid |
| δ | chemical shift (ppm) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| $^cHex_2BCl$ | dicyclohexylboron chloride |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |

| | |
|---|---|
| DIBALH | diisobutylaluminium hydride |
| DMAP | 4-(*N*,*N*-dimethylamino)pyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMP | Dess-Martin Periodinane |
| | 1,1,1-triacetoxy-1,1-dihydro-1,1-benziodoxol-3-(1H)-one |
| DMSO | dimethylsulfoxide |
| eq | equivalents |
| *et al* | et alia (and others) |
| Et | ethyl |
| EtOAc | ethyl acetate |
| $Et_2O$ | diethyl ether |
| EtMgBr | ethylmagnesium bromide |
| EtOH | ethanol |
| $H_2SO_4$ | sulfuric acid |
| HCl | hydrochloric acid |
| HF | hydrofluoric acid |
| HMQC | $^{1}H$-$^{13}C$ correlation spectroscopy |
| Hz | hertz |
| $^{i}PrMgCl$ | isopropylmagnesium chloride |
| $^{i}Pr_2Net$ | *N*,*N*-diisopropylethylamine |
| J | coupling constant (Hz) |
| $KBrO_3$ | potassium bromate |
| $K_2CO_3$ | potassium carbonate |
| $KMnO_4$ | potassium permanganate |
| LDA | lithium diisopropylamine |

| | |
|---|---|
| LiHMDS | lithium hexamethyldisilazide |
| lit. | literature |
| $LiBH_4$ | lithium borohydride |
| Me | methyl |
| MeOH | methanol |
| $MgBr_2.OEt_2$ | magnesium bromide diethyl ether complex |
| MHz | megahertz |
| mmol | millimole |
| mol | mole |
| m.p. | melting point |
| $NaBH_4$ | sodium borohydride |
| NaOH | sodium hydroxide |
| $NEt_3$ | triethylamine |
| NMR | nuclear magnetic resonance |
| OTf | trifluoromethanesulfonate (triflate) |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PMB | *para*-methoxybenzyl |
| PMB-Cl | *para*-methoxybenzyl chloride |
| PMP | *para*-methoxyphenyl |
| $PPh_3$ | triphenylphosphine |
| ppm | parts per million |
| PPTS | pyridinium para-toluenesulfonate |
| pyr | pyridine |
| $R_F$ | retention factor |

| | |
|---|---|
| RT | room temperature |
| $SmI_2$ | samarium(II) iodide |
| $Sn(OTf)_2$ | tin(II) trifluoromethanesulfonate |
| TAS-F | tris(dimethylamino)sulfur (trimethylsilyl)difluoride |
| TBS | tert-butyldimethylsilyl |
| TBS-Cl | tert-butyldimethylsilyl chloride |
| TBSOTf | tert-butyldimethylsilyl trifluoromethanesulfonate |
| TES | triethylsilyl |
| TESOTf | triethylsilyl trifluoromethanesulfonate |
| TFA | trifluoroacetic acid |
| TfOH | triflic acid |
| THF | tetrahydrofuran |
| $TiCl_4$ | titanium tetrachloride |
| $Ti(^{i}PrO)_4$ | titanium tetraisopropoxide |
| tlc | thin layer chromatography |
| TMSCl | trimethylsilyl chloride |
| *p*-TsOH | *para*-toluenesulfonic acid |

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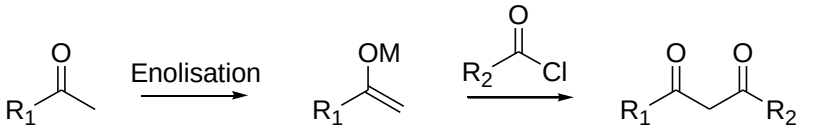
# Chapter One

## Introduction to Polyketide Natural Products:

## Formation, Biological Applications and Current Synthetic Approaches

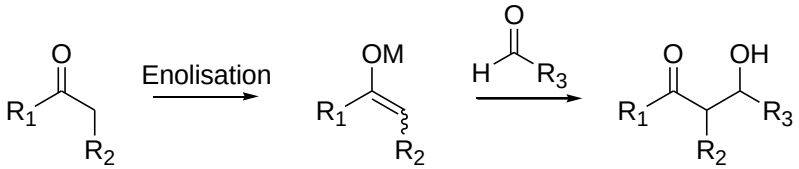
This chapter introduces polyketide natural products, their biosynthesis and potent biological activities. The chapter also details the post condensation reaction transformations that lead to the formation of active secondary metabolites. Also discussed are the current strategies employed by the modern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

**Acylation Reaction**




Ketone Metal Enolate Acylated Product

**Aldol Reaction**




Ketone Metal Enolate Aldol Product

## 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$^{th}$ century with natures' seemingly endless supply of structurally complex terrestrial and marine polyketide natural products.[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.[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 stereochemical 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$^{th}$ 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.[3] Currently, there are over 100 natural product based drugs in clinical development particularly in the area of anticancer agents.[3,4]

The increase in the number of severely immunosuppressed patients over the last 10 years has resulted from the AIDS epidemic[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,[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).

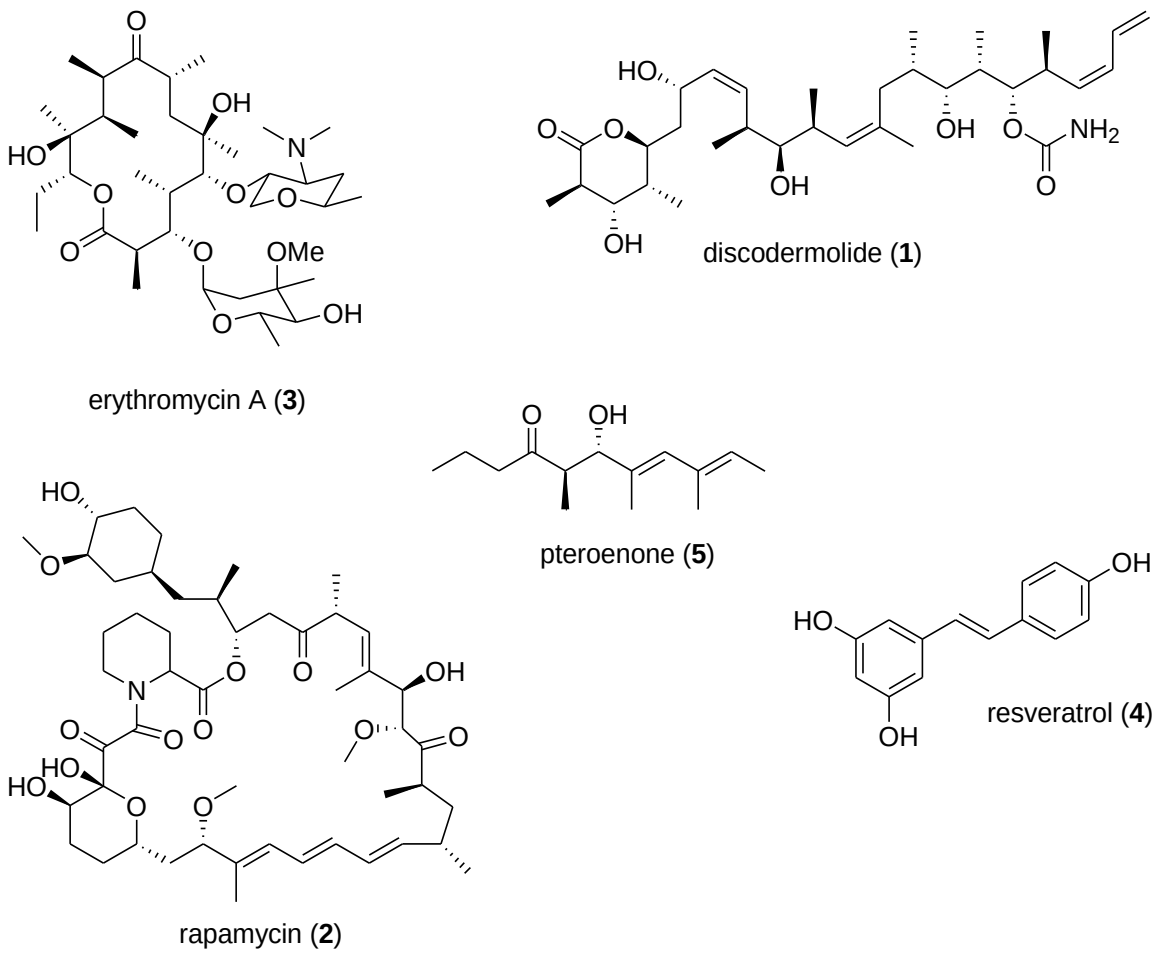



***Figure 1.1:*** *The different levels of complexity of polyketide natural products*

### 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.[12,13] 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.[14,15]

A generalised schematic of polyketide biosynthesis[16] (Figure 1.2) shows the loading of a short chain carboxylic acid thioester "starter unit" and a thioester of an "extender unit" using an acyl tranferase (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.

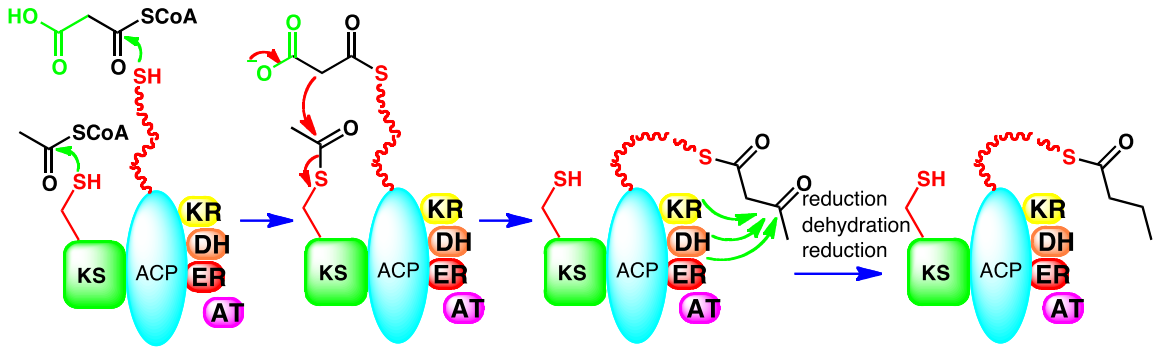



***Figure 1.2:*** *A schematic of PKS facilitated polyketide biosynthesis*

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.[17] 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**)[18] shows an example of reduced, eliminated, and completely reduced functionality, as well as a hemiacetal moiety.

Diemenensin A (**7**)[19] also displays evidence of eliminated and completely reduced functionality, as well as a β-pyrone ring system. While siphonarin A (**8**)[20] contains a γ-pyrone ring and a complex spiroacetal.

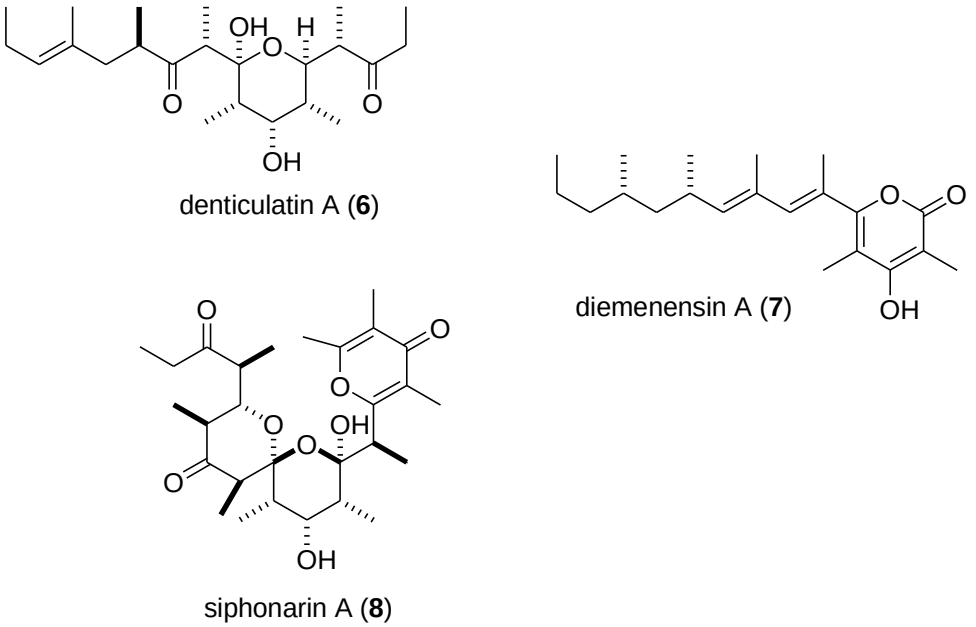



***Figure 1.3:*** *Polyketide natural products displaying the high levels of functionalisation formed by PKS*

### 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.[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,[22] for example CR377 (**9**)[23] and dolabriferol (**10**),[24] (Figure 1.4) which arise from the nucleophilic attack of an alcohol onto a carbonyl further down an acyclic precursor.[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.

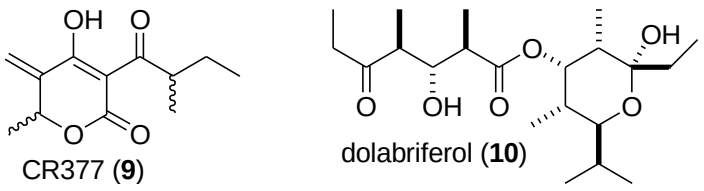



***Figure 1.4:*** *Pyrone and ketal functionality shown by polyketide natural products CR377* (**9**) *and dolabriferol* (**10**)

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**)[20] and caloundrin B (**12**)[25] are metabolites isolated from *Siphonaria. zelandica*,[22] 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 $C_8$) using cascade reactions (Figure 1.5).

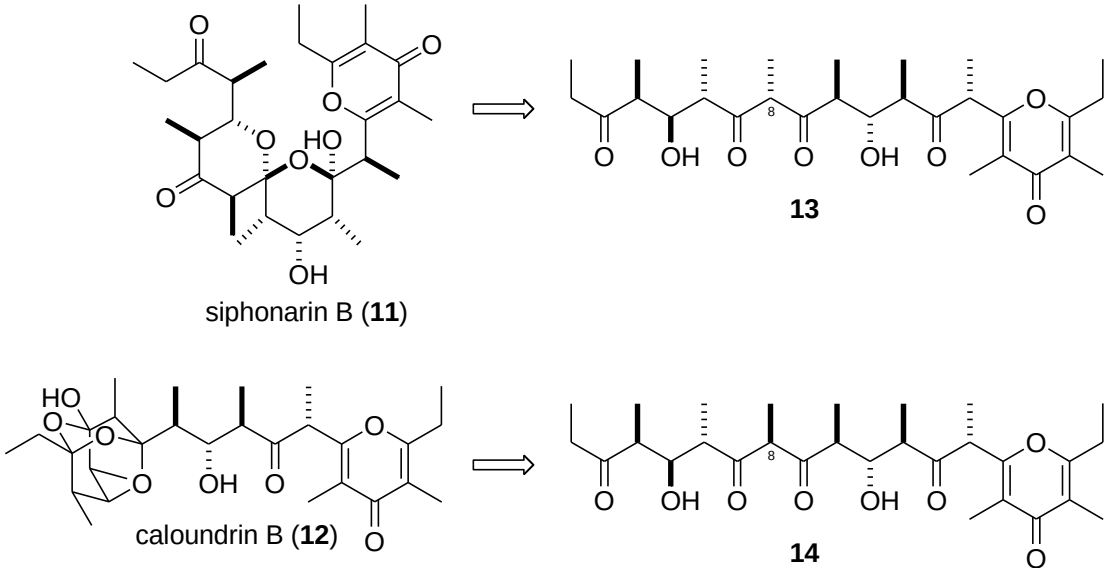



***Figure 1.5:*** *Thermodynamic cyclisation modes of two diastereomeric acyclic precursors*

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*,[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 *Dolabrifera dolabrifera*[24] is one of the rare marine polypropionates not to possess a contiguous backbone.[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-pyrone 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.

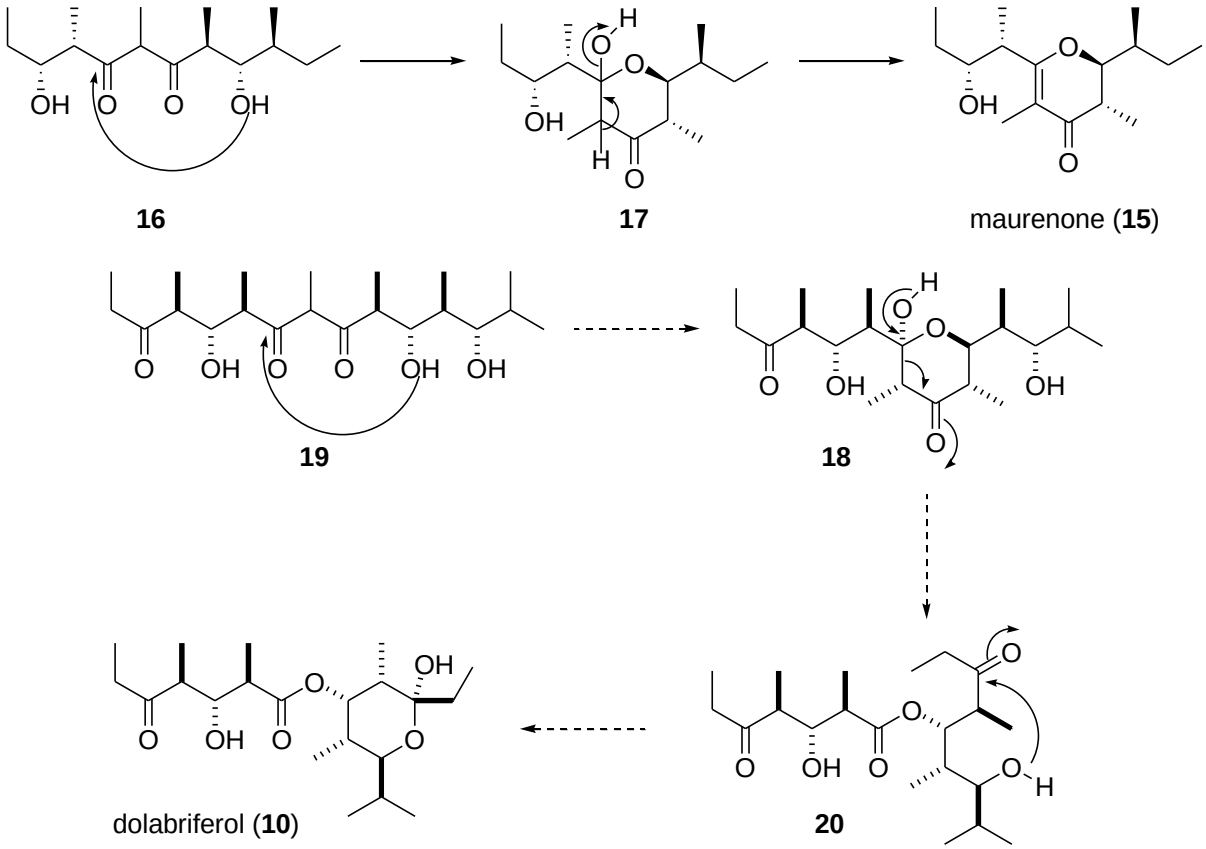



***Figure 1.6:*** *The different cyclisation modes of maurenone* (**15**) *and dolabriferol* (**10**)

### 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[29] 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.[30,31] This required structural precision has led to a resurgence in the asymmetric synthesis of polyketide natural products.[16,32,33] 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[34,35] 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[36,37] and nucleophilic[38] 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 acetylating reaction for chain extension during polyketide biosynthesis.[16,39] The current synthetic chemist often tries to develop synthetic approaches that closely mimic natures' 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[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 ($AlCl_3$). The most common example of Friedel-Crafts acylation is the acetylation of benzene (**21**)[40] with acetyl chloride (**22**) in the presence of $AlCl_3$ to form acetophenone (**23**) (Figure 1.7). Friedel-Crafts acylation has also been successfully employed towards the synthesis of numerous natural products.[41-44]

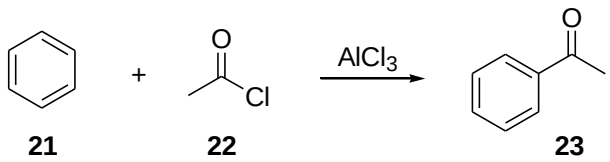



***Figure 1.7:*** *Friedel-Crafts acylation of benzene* (**21**) *with acetyl chloride* (**22**)

### 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.

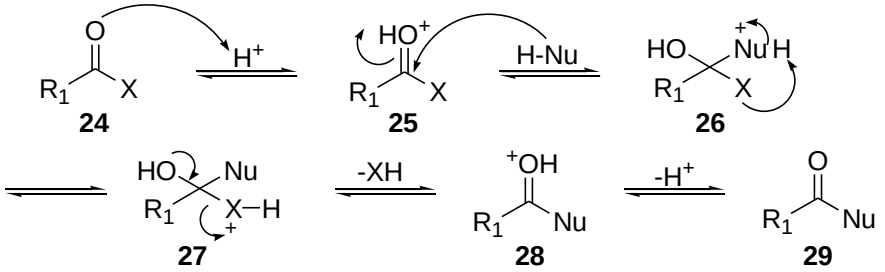



***Figure 1.8:*** *Nucleophilic acyl substitution mechanism in acidic conditions*

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.

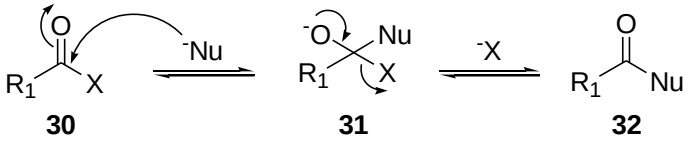



***Figure 1.8:*** *Nucleophilic acyl substitution mechansim in basic conditions*

### 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.[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.

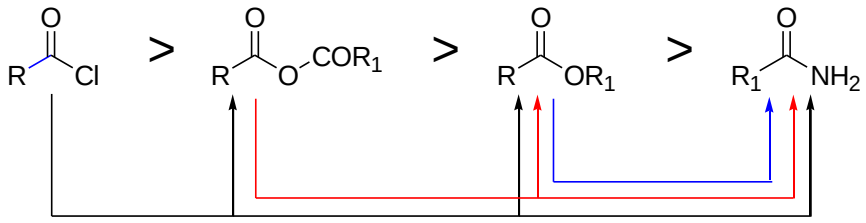



***Figure 1.10:*** *Reactivity of acyl derivatives*

Although alcohols[53,54] and amines[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 **33** and ketone **34** tautomers.[57] Enolates **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).[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 ($NaNH_2$) and 1,8-diazabicycloundec-7-ene (DBU) are all commonly employed for the preparation of such enolates. Alkyl lithiums and

Grignard reagents can be used but are often avoided as they can rapidly and irreversibly add directly to carbonyl groups.

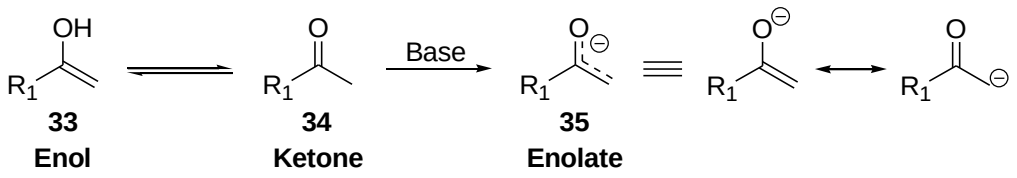



***Figure 1.11:*** *Keto-enol tautomerisation and preparation of reactive enolates*

An enolate **35** is an extremely nucleophilic substrate that can undergo nucleophilic alkylation[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[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.

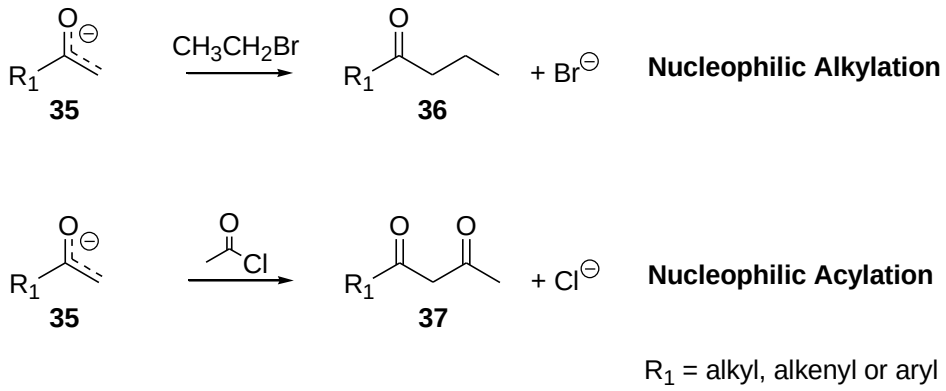



***Figure 1.12:*** *Nucleophilic alkylation and acylation of enolates*

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

1,3-Dicarbonyls are important compounds in synthetic organic chemistry.[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 LDA; a strong non-nucleophilic base to generate the enolate followed by addition of an acid chloride **41**.

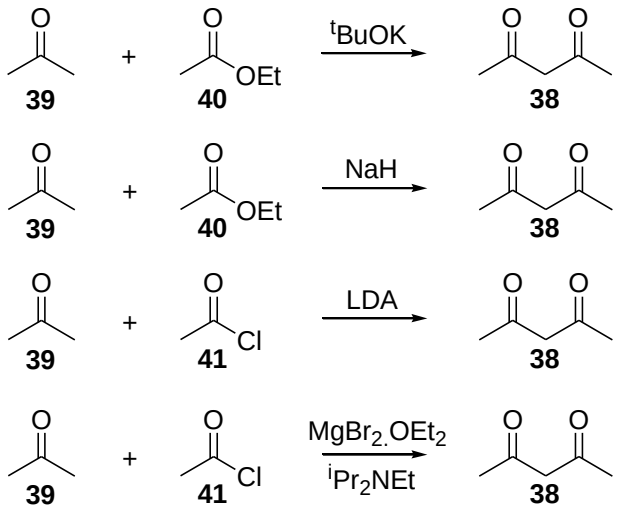



***Figure 1.13:*** *The main* syn*thetic methods for the preparation of 1,3-dicarbonyls* **38**

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 $MgBr_2.OEt_2$, $CH_2Cl_2$ and $^{i}Pr_2NEt$ under atmospheric conditions have been used to achieve robust formation of 1,3-diketones. These acylation methodologies can be extended to the formation of tricarbonylmethane 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).

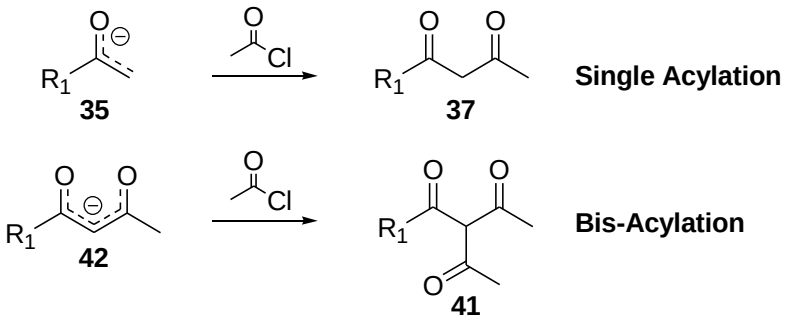



***Figure 1.14:*** *Extension of acylation methods to the* synthesis *of tricarbonylmethane systems.*

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 ($R_1$ to $R_3$) are achiral then the reaction can produce two sets of enantiomeric pairs (**45**/**46** or **47**/**48**), or if any of the R groups are chiral then all four potential products will be diastereomers.

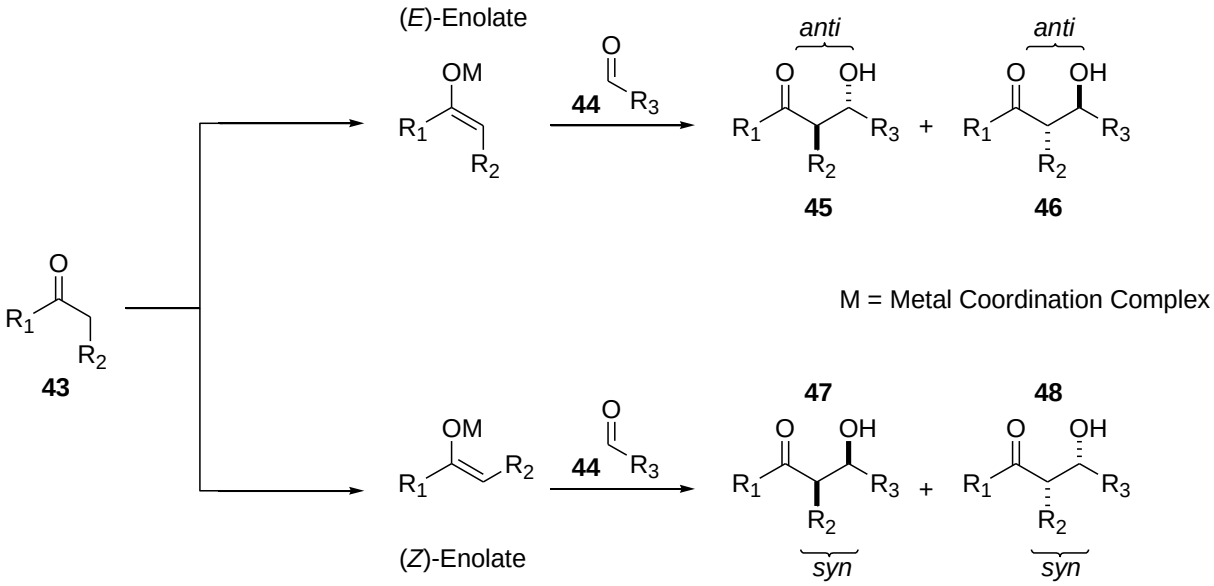



***Figure 1.15:*** *The four possible products from reaction of ketone **49** enolate with aldehyde **50***

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.[74-81] 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[82] (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 ($R_3$) 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 ($R_1$) and the aldehyde alkyl group ($R_3$). 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 ($R_1$) and alkyl group of the aldehyde ($R_3$).

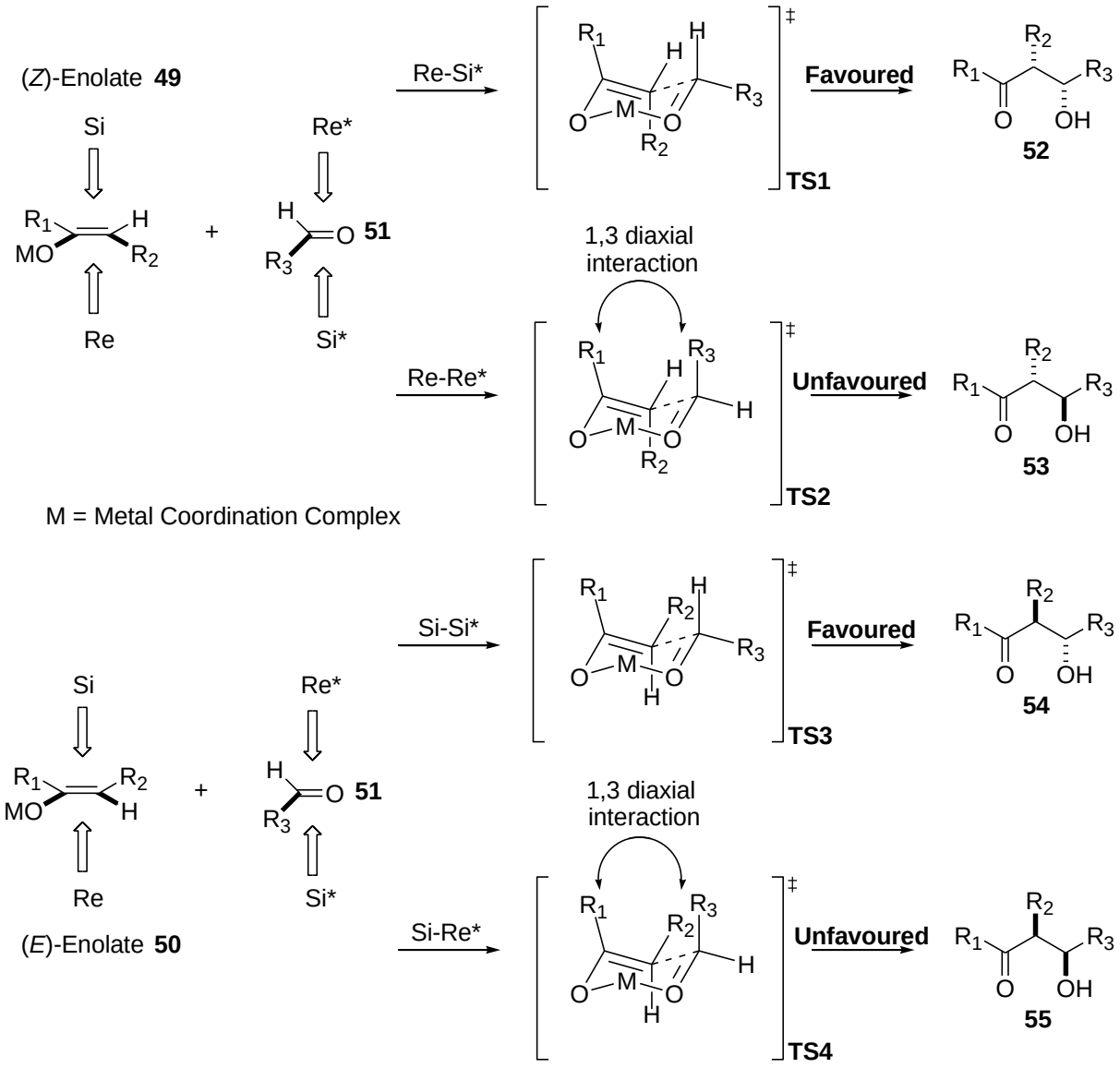



***Figure 1.16:*** *Stereochemistry of aldol products resultant from (Z)-and (E)-enolates with aldehydes.*

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 substitutents; 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.

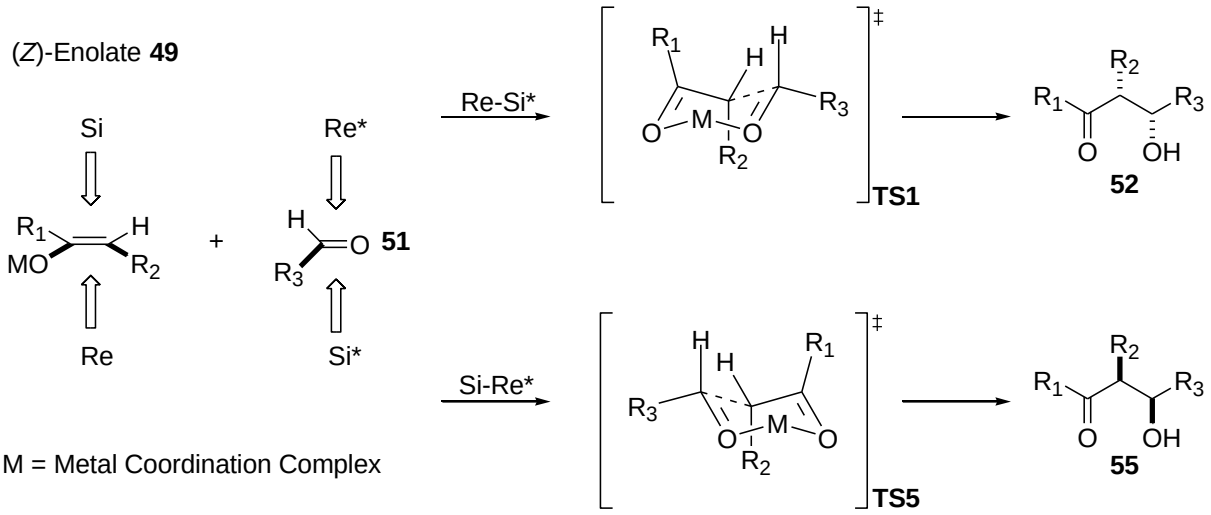



***Figure 1.17:*** *The enantiomeric pair of products* **52** *and* **55** *following reaction of aldehyde* **51** *with (Z)-enolate* **49**

To preferentially form one enantiomeric product over the other requires π-facial selectivity displayed by either the enolate or the aldehyde involved. π-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 π-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[98,99] for the purposes of asymmetric aldol additions towards natural product synthesis.

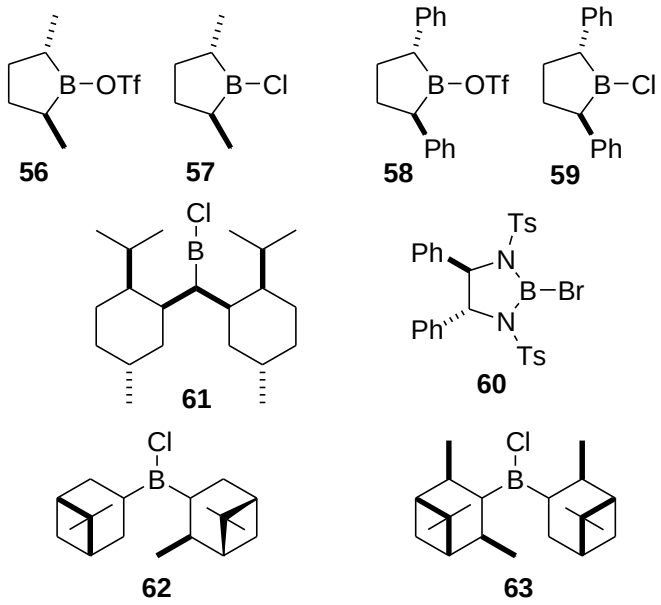



***Figure 1.18:*** *Common asymmetric boron reagents for aldol reactions*

### 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 *et al*[100] when he employed α-methyl chiral ketones (*S*)-**64** (used in Chapter 4) to react with aldehydes to give highly selective *anti-anti*-aldol adducts (Figure 1.19).

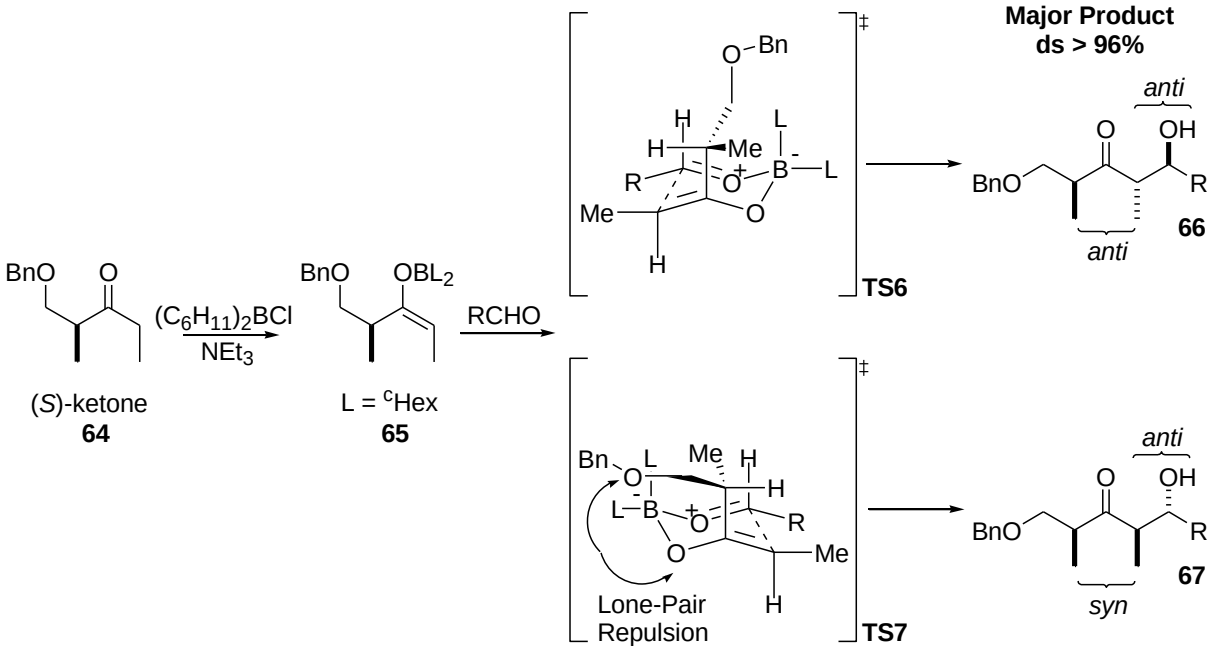



***Figure 1.19:*** *Paterson's α-methyl chiral (S)-ketone **70** to give highly selective anti-anti-aldol adducts*

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 oygen 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 titianium (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 diastereocontrol 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[102] developed a soft titanium Lewis acid ($^{i}$PrO)$TiCl_3$ 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.

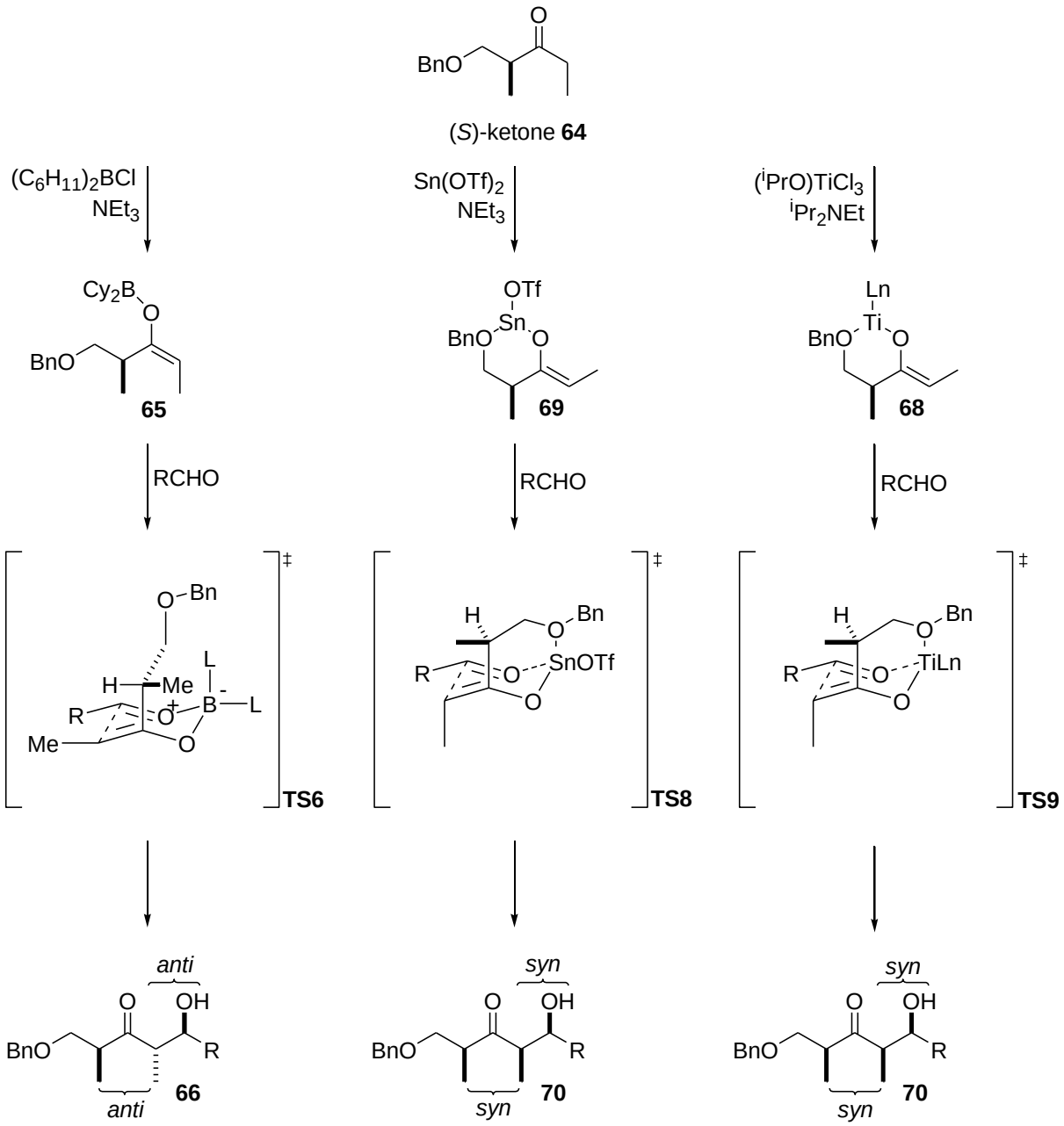



***Figure 1.20:*** *Anti vs. Syn aldol additions of α-methyl chiral (S)-ketone* **64**

Around the same time that Paterson and coworkers[100] discovered the *anti-anti*-aldol adduct **66**, Evans[103,104] had decided to extend his previous research on oxazolidinones **79-82** to create β-ketoimides **71**[105] as chiral auxiliaries for highly selective aldol reactions (Figure 1.21). While the result of using dicyclohexylboron chloride with triethylamine furnished the *anti-anti*-aldol product **72** similar to Paterson's studies,[100] it was the variants seen during the *syn*-aldol reactions that generated significant interest. Evans and coworkers[106] were able to show that the titanium (IV) and tin (II) enolates of β-ketoimide **71** have an opposing sense of stereoinduction. 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.

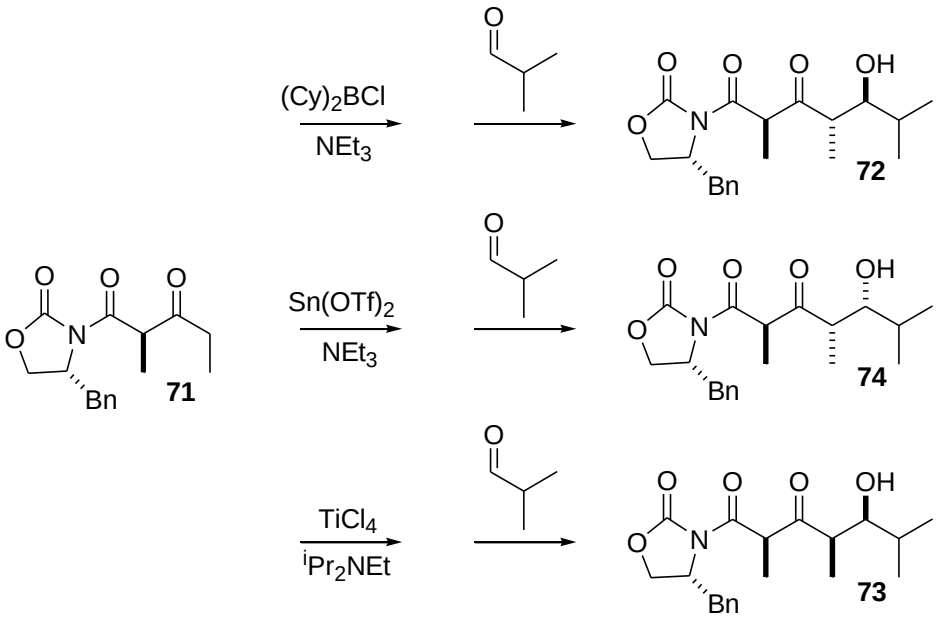



***Figure 1.21:*** *Evans' β-ketoimides* **71** *as chiral auxiliaries for highly selective aldol reactions*

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.[114-116]

### 1.3.6 Felkin-Anh Model

The Felkin-Anh model[114-116] was designed to predict the preferred addition of a nucleophile (the enolate) to the most sterically favoured face of the electophilic 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: sterics, electronics and chelation interactions.

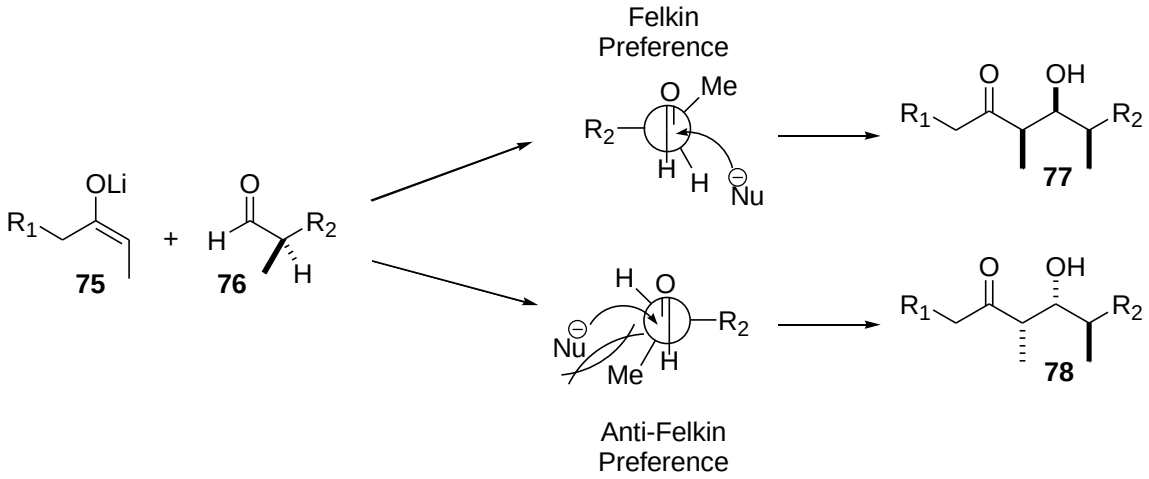



***Figure 1.22:*** *The competing Felkin and anti-Felkin preferences of chiral α-methyl aldehydes* **76**

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.

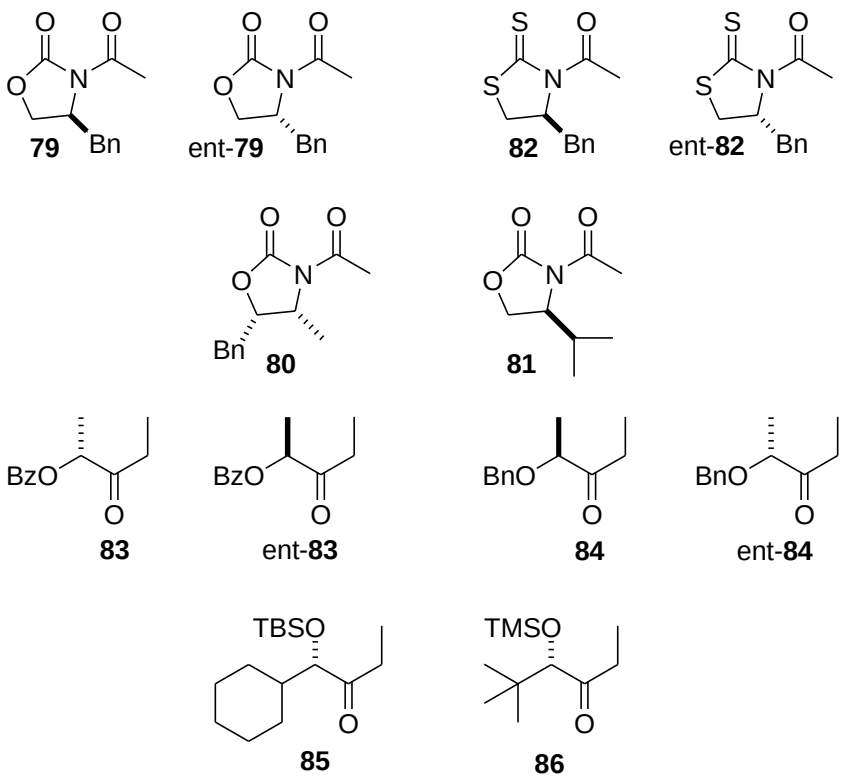



***Figure 1.23:*** *α-chiral auxiliaries used in asymmetric aldol reactions*

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.[103,104] These auxiliaries have been widely used in organic synthesis for *syn*-aldol carbon-carbon bond forming reactions. In Chapter Two the thiazolidine thione auxiliary **82** was used to selectively produce the *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[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 **87** to give amide **88**, which in turn can reacted using a variety of nucleophilic reagents including Grignards, hydrides and alkyllithiums to give ketones **89**.[123] The auxiliary **87** can also be effectively reduced using DIBALH or $LiBH_4$ to the corresponding alcohol **90**,[123] oxidation to the aldehyde **91** can then continue chain elongation through further aldol couplings.

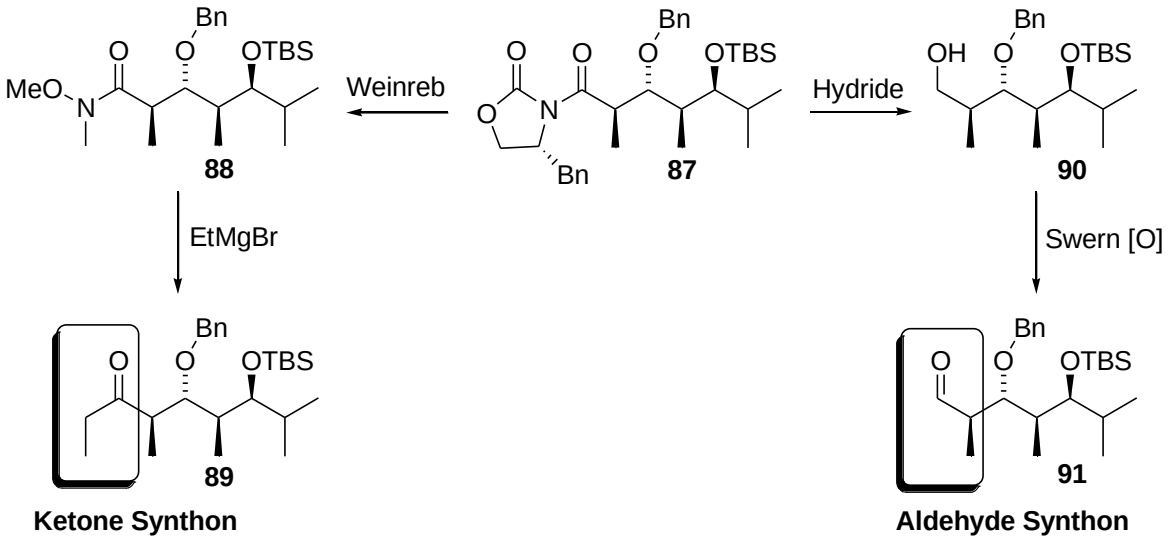



***Figure 1.24:*** *Versatility of Evans' oxazolidinone auxiliary*

Similarly Paterson's lactate derived ketones (**83**, ent-**83**) (Figure 1.23) are also easily synthesised in two linear steps from commercially available (*S*)-ethyl lactate (**98**) or (*R*)-isobutyl lactate (**99**).[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

form *anti-anti* adducts and *anti-syn* adducts.[117] 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[117,118,124] makes them an appealing synthon for construction of polyketide natural products.[125,126] 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**,[118,124] 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**.[118,124]

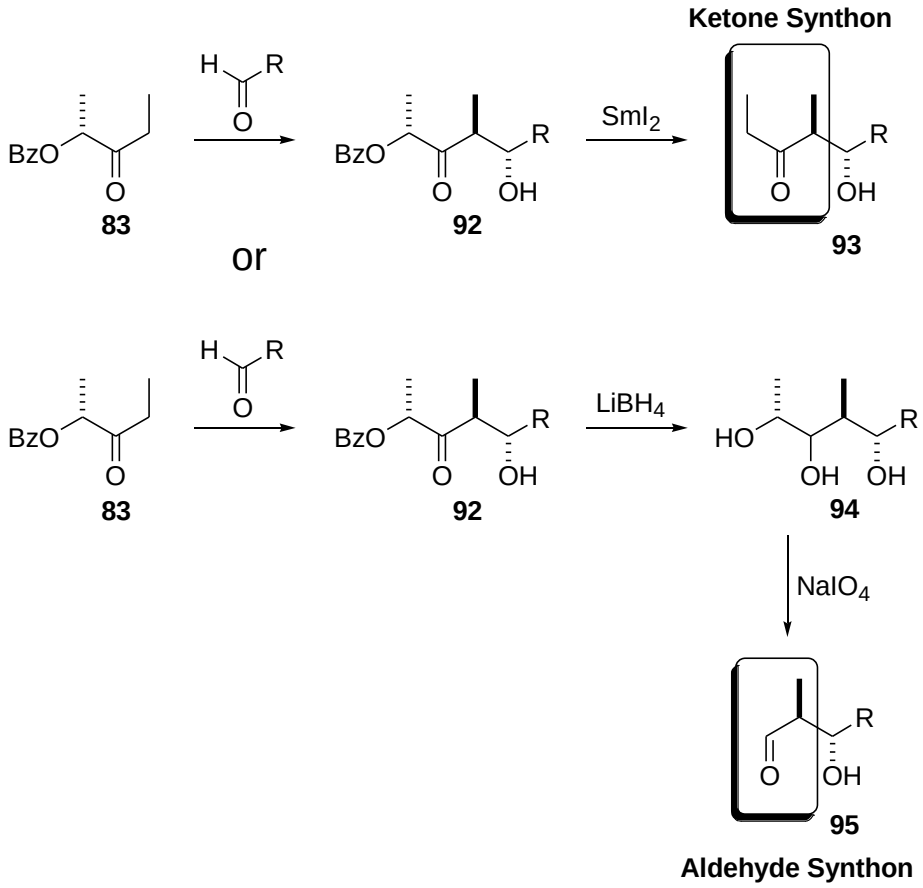



**Figure 1.25:** *Versatility of Paterson's lactate derived ketone* **83** *auxiliary*

## 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*.[23] 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 $[\alpha^{25}_{D}]$ +21.8° (c 1.0, $CH_2Cl_2$). 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.

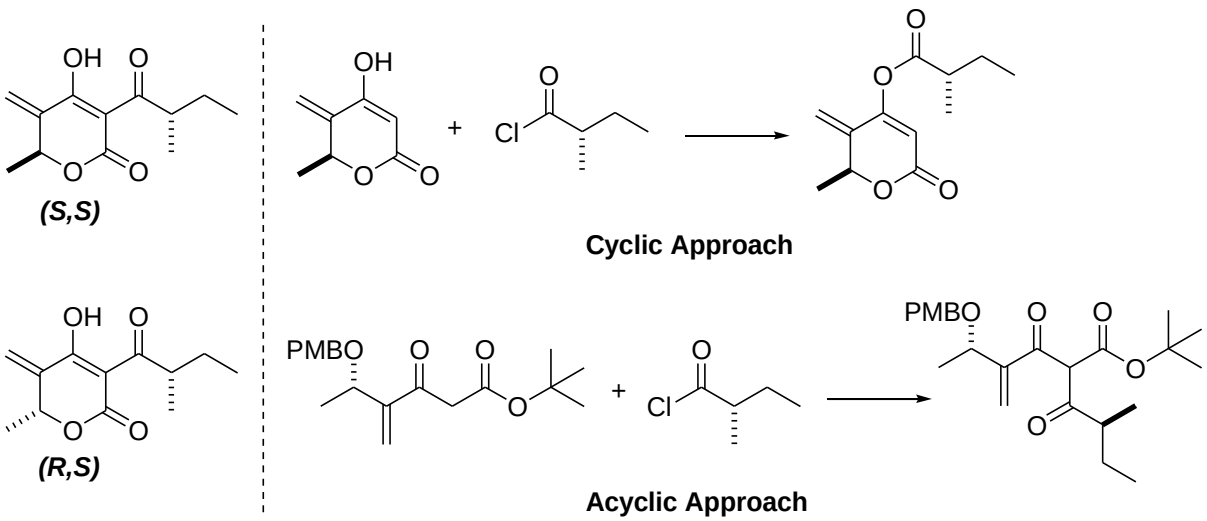



***Figure 1.26:*** *The main synthetic attempts towards total synthesis of CR377* (**9**)

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.[127] 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 dolabriferol (**10**) (Figure 1.27), a marine polypropionate isolated from the *Dolabrifera dolabrifera* species.[24] Dolabriferol (**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 ultilised to afford the natural product (**10**). Substrate control was achieved using Paterson's lactate derived (*R*)-ketone to generate all but the $C_6$ stereogenic centres present in dolabriferol (**10**), whose adjacent methyl and oxygen substituents possess two symmetrical *anti*-structural moieties.

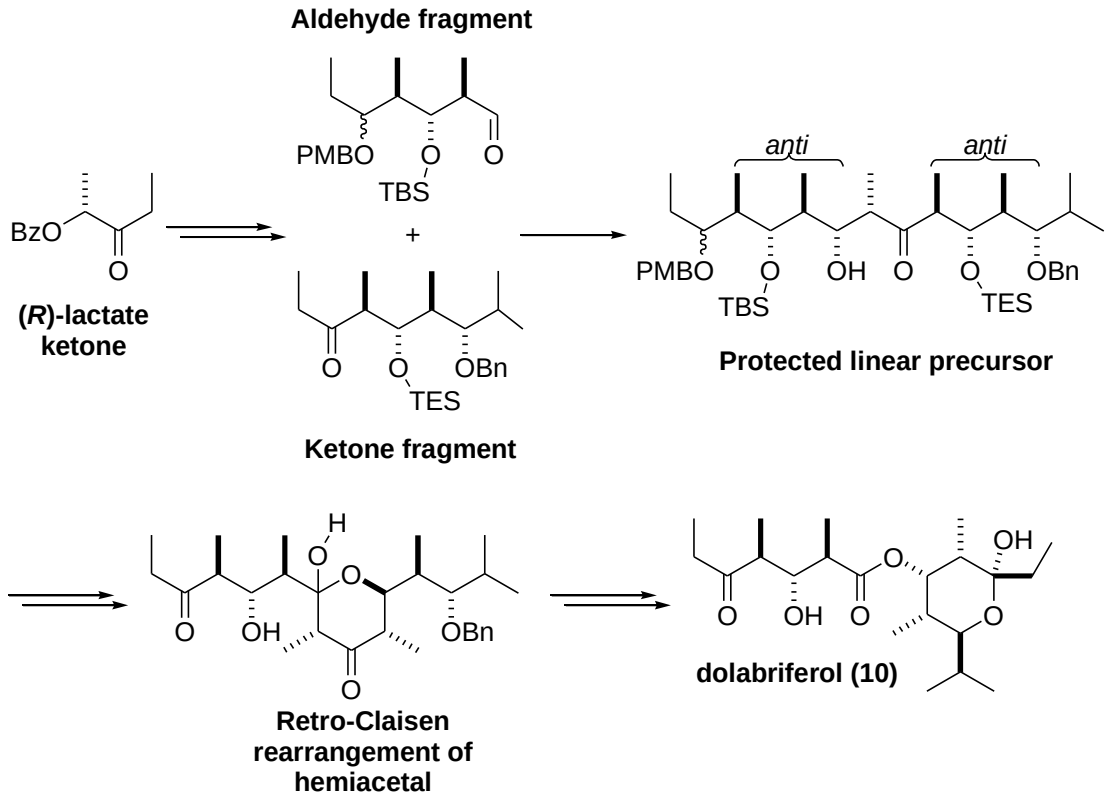



***Figure 1.27:*** *Total synthesis of dolabriferol (**10**) following a pseudo biomimetic approach*

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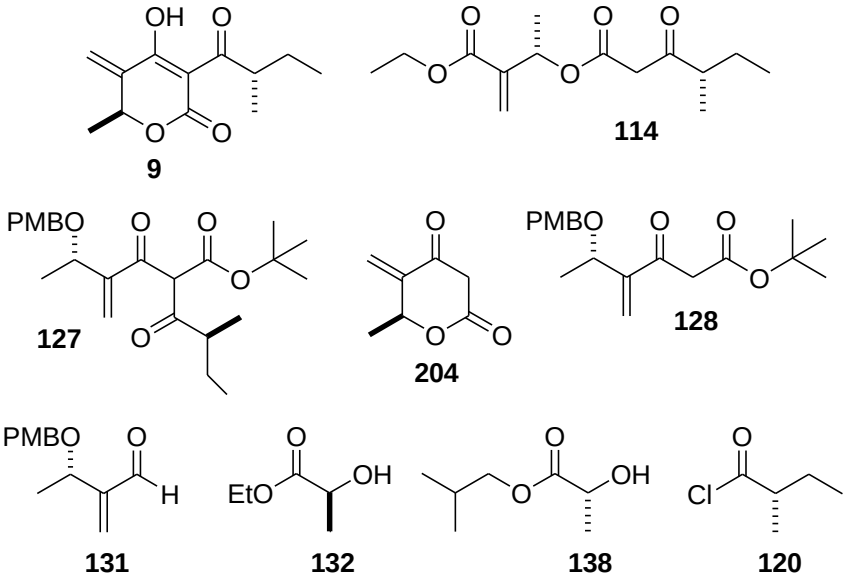
# Chapter Two

# 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*

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 A[2] (**96**), alternaric acid[3-5] (**97**) and dehydroacetic acid[6] (**98**) (Figure 2.2). From $^{1}$H-$^{1}$H and $^{1}$H-$^{13}$C 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 $^{13}$C 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.

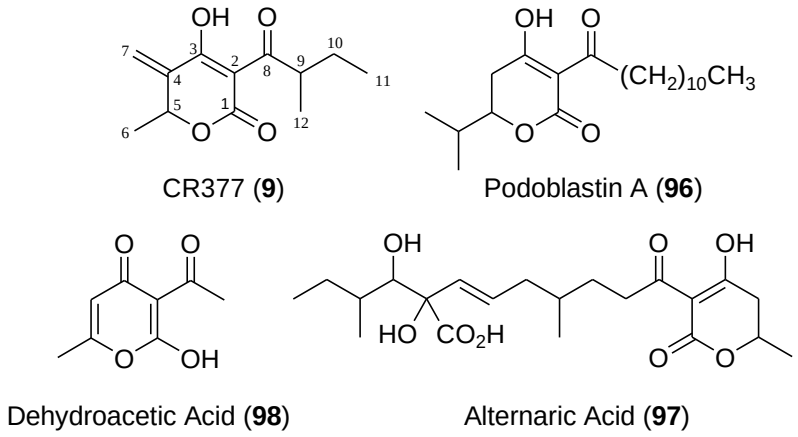



***Figure 2.2:*** *The proposed structure of CR377* (**9**) *and known tricarbonyl natural products podoblastin A* (**96**)*, dehydroacetic acid* (**98**) *and alternaric acid* (**97**) *used for structural determination*

Analysis of the $^{1}H$-$^{1}H$ 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 $C_4$-$C_7$ 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 δ 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 $C_1$ ester and the $H_5$ methine proton but not the $H_6$ methyl suggests that partial structure 2 is completed through linking the $C_1$ ester to the $C_5$ through the ester oxygen.

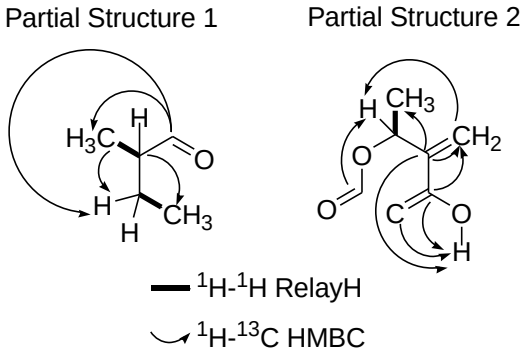
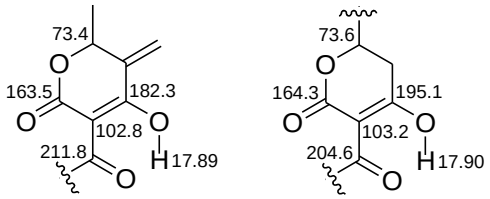



***Figure 2.3:*** *Partial CR377* (**9**) *structures based on extensive 2D-NMR analysis*

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-pyrone. 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).




CR377 (**9**) Podoblastin A (**96**)

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

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.

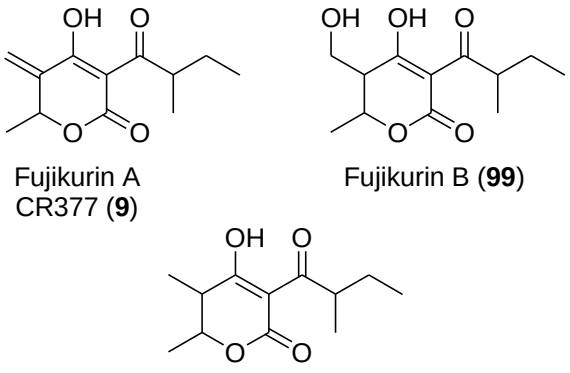



***Figure 2.5:*** *Recently identified and reported Fujikurins A-D (***9***,* **99**-**101***) isolated from Fusarium fujikuroi*

### 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

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,[1] the relative and absolute stereochemistry of the natural product was not established at the $C_5$ and $C_9$ 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.

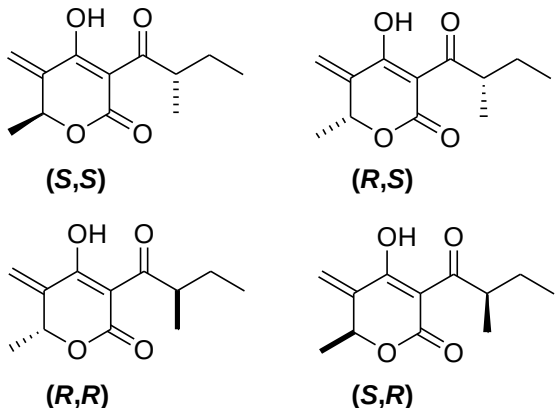



***Figure 2.6:*** *The four possible stereoisomers of CR377* (**9**)

It has been reported that carolic acid[16,17] (**102**) and agglomerin A[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-pyrones 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.

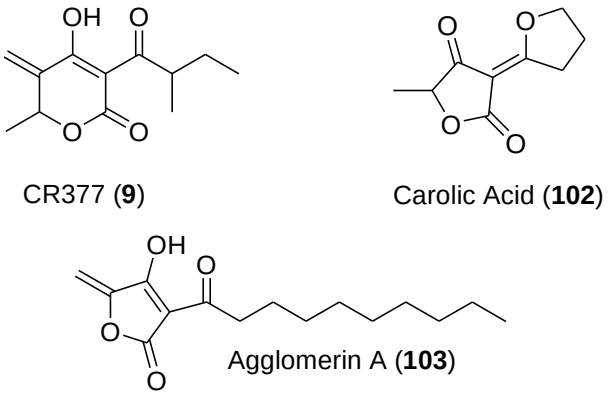



***Figure 2.7:*** *CR377* (**9**) *and similar five-membered α-furanone systems carolic acid* (**102**) *and agglomerin A* (**103**)

### 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 δ 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-methyl-butyryl 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-methyl-butyryl 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.

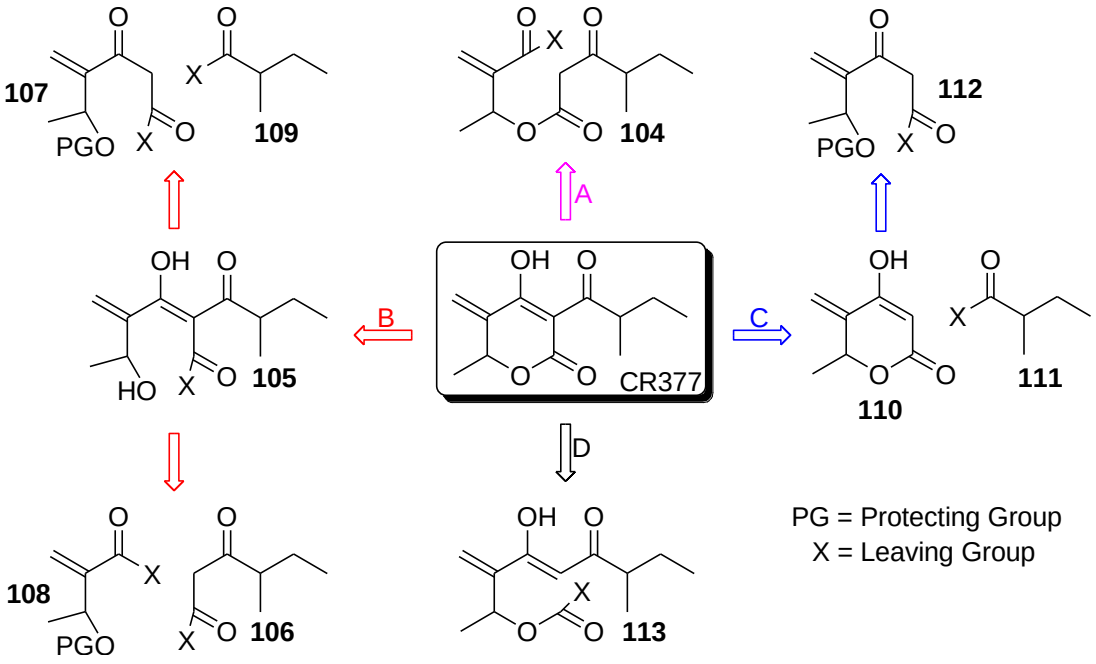



***Figure 2.8:*** *The possible retrosynthetic disconnections towards CR377* (**9**)

## 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.

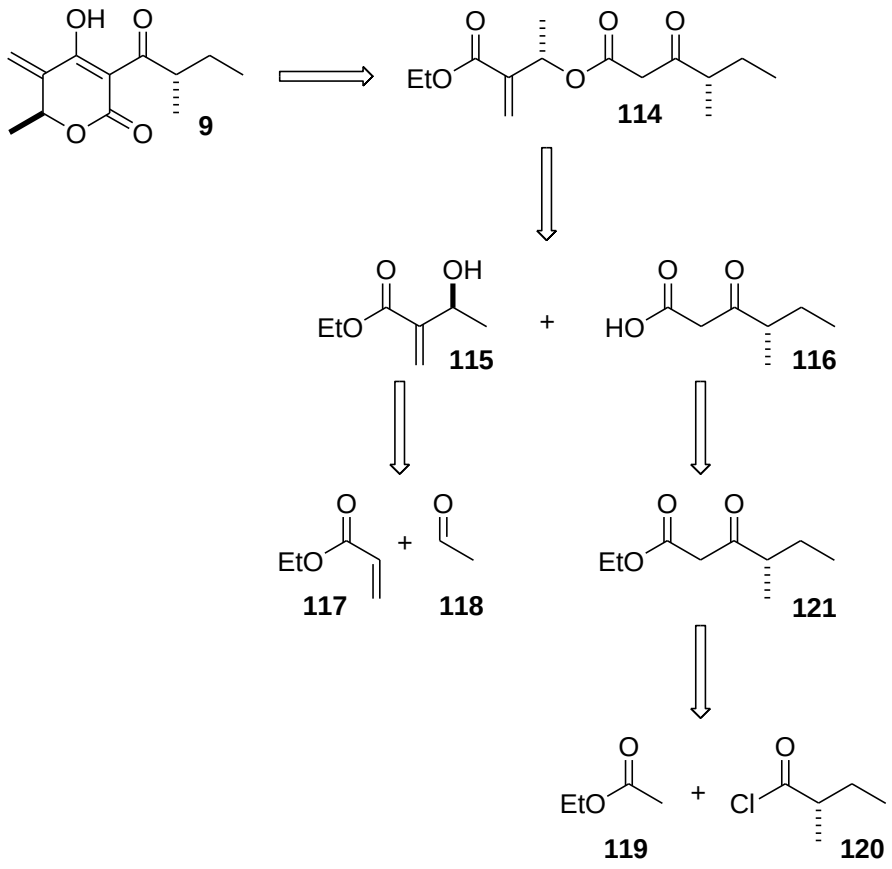



***Figure 2.9:*** *Retrosynthesis of CR377* (**9**) *using an intramolecular cyclisation approach*

### 2.2.2 Intramolecular Cyclisation Model Studies

Dieckmann reactions have been reported for the synthesis of unsaturated five-membered ring systems,[19] 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.

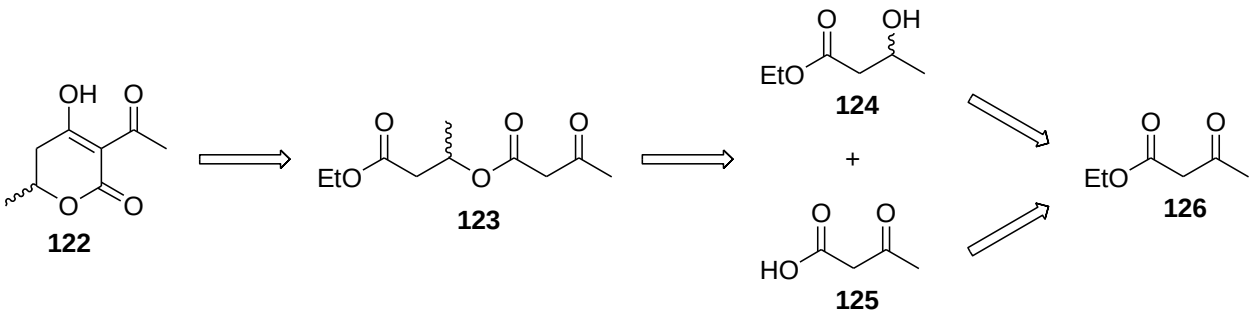


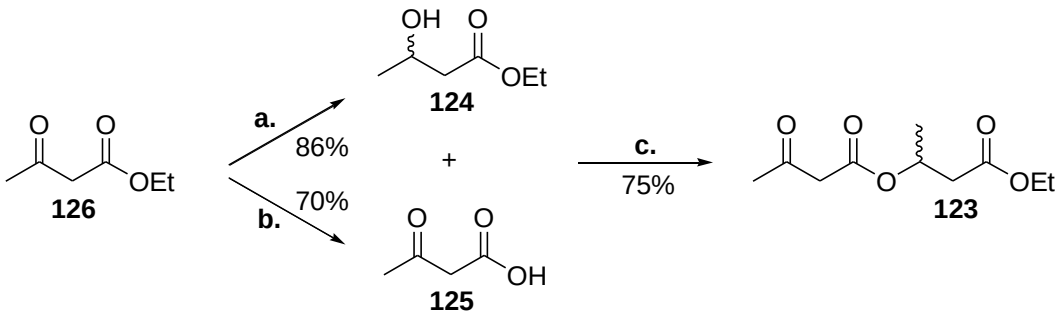

***Figure 2.10:*** *Retrosynthesis of acyl-dihydropyrone* **122** *model system*

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*.[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,[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 $H_2O$, 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*[22] (Scheme 2.1). β-keto acid **125** and DMAP were combined and added to a stirring solution of β-hydroxy ester **124** in $CH_2Cl_2$ 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

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.[22]




**Reagents and Conditions: a.** $NaBH_4$ (1.5eq), EtOH, -10°C, 30 minutes. **b.** NaOH (1.6eq), THF/$H_2O$, RT, 4 hours. **c.** DCC (2.4eq), DMAP (1.5eq), $CH_2Cl_2$, 0°C for 15 minutes, then 15 hours RT.

***Scheme 2.1:*** *Synthesis of the β-hydroxy ester* **124***, β-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 α-protons of the β-keto ester **123** to invoke cyclisation. The reaction was conducted in deuterated chloroform to allow for continual $^1$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 $^1$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.

| Base | Solvent | Equivalents | Time (hrs) | Product |
|---|---|---|---|---|
| **DBU** | $CDCl_3$ | 1 | 6 | NR |
| **NaH** | THF | 1 | 6 | NR |
| **NaOEt** | EtOH | 1 | 6 | NR |
| **$^{i}$PrMgCl** | THF | 1 | 6 | NR |

***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.

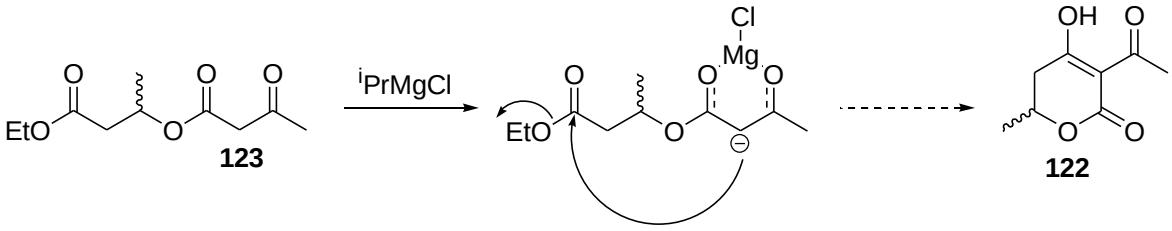



***Figure 2.11:*** *Proposed cyclisation using $^{i}$PrMgCl deprotonation/chelation approach*

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.

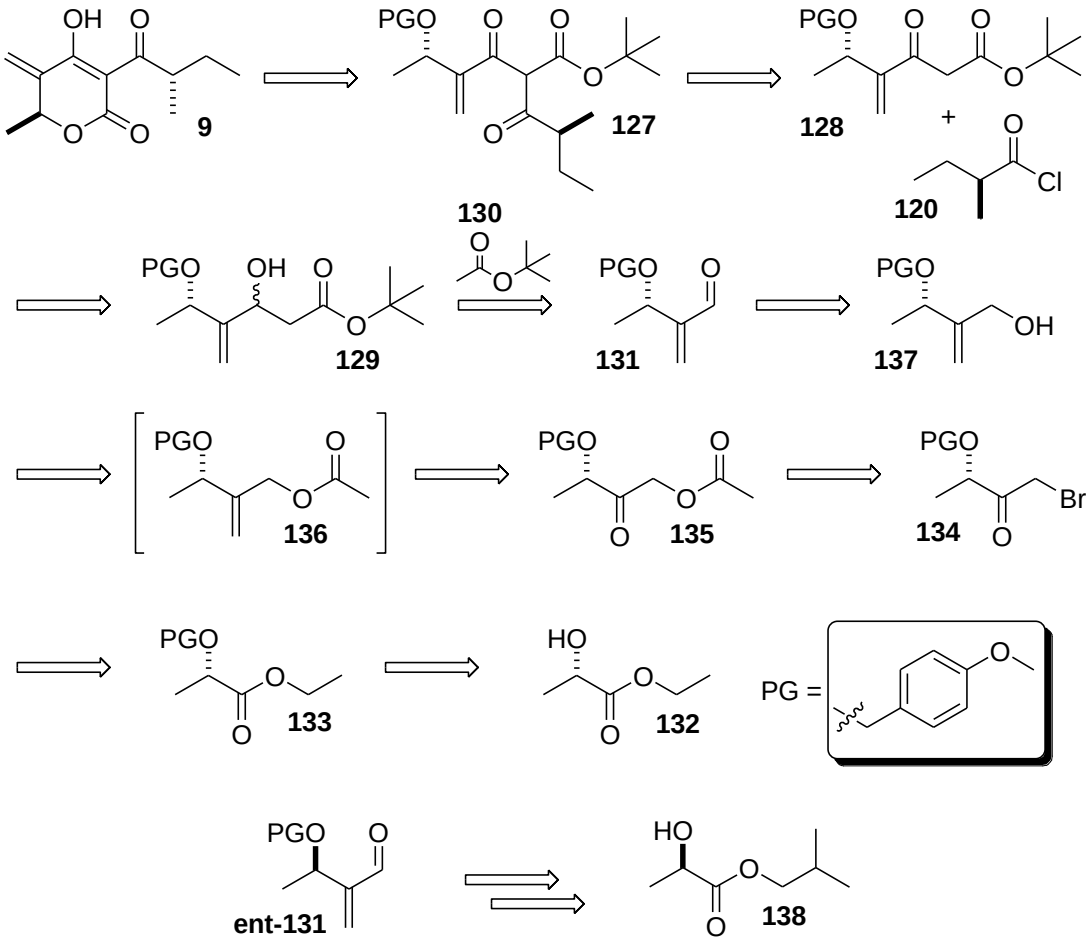



***Figure 2.12:*** *Retrosynthesis for the acyclic lactonisation approach towards CR377* (**9**)

### 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**.

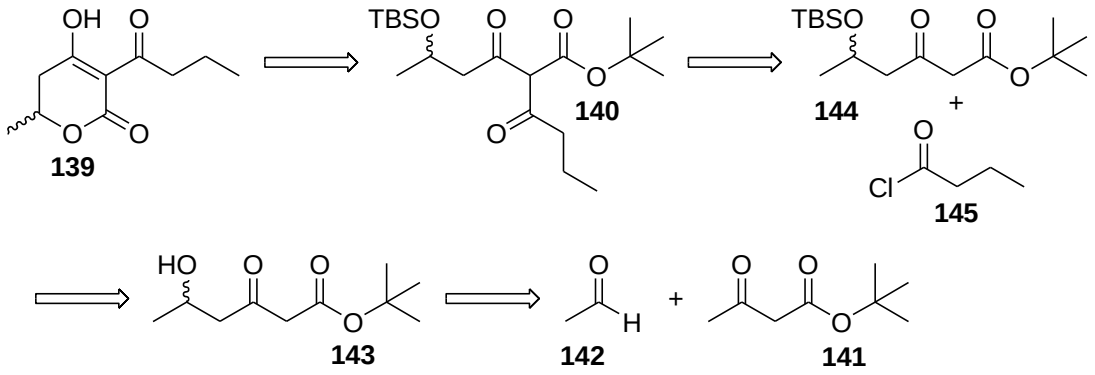
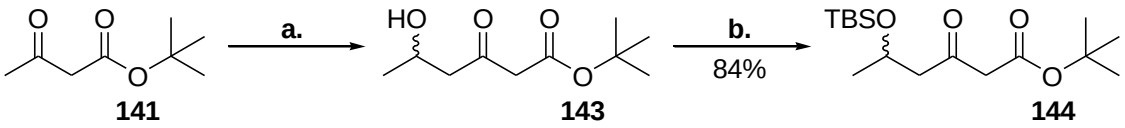



***Figure 2.13:*** *Synthesis of model system* **139** *to test the acyclic lactonisation approach*

Following a modified procedure from Yamaguchi *et al*,[23] 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.[24] 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 $^{1}$H 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.[25] 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[26] the protection of the crude alcohol **143** as the TBS-ether was achieved in $CH_2Cl_2$ 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).

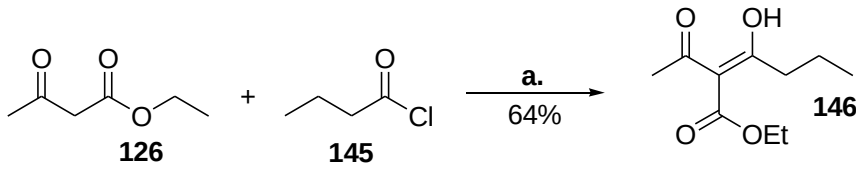



**141** **143** **144**

**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), $CH_2Cl_2$, 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 $CH_2Cl_2$ 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.

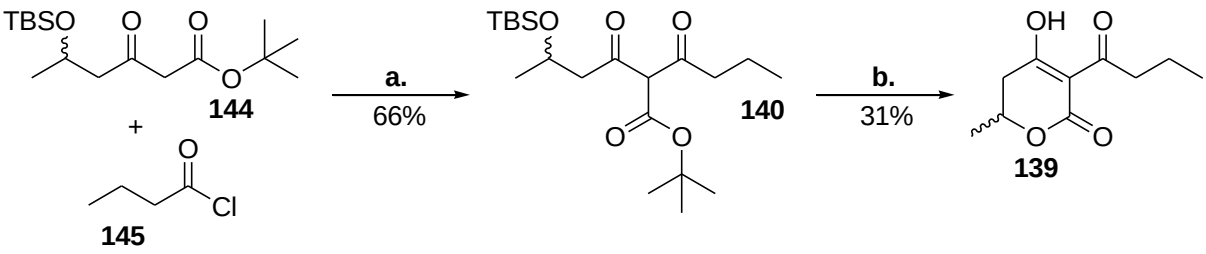



**126** **145**

**Reagents and Conditions: a.** $MgCl_2$ (1.7eq), pyridine (2.0eq), $CH_2Cl_2$, 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 $CuSO_4$ solution. The aqueous $CuSO_4$ 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.** $MgCl_2$ (1.7eq), pyridine (2.0eq), $CH_2Cl_2$, 0°C, then 1 hour at RT. **b.** HF/Pyr/Pyr (1.0eq), THF, RT, 24 hours, then TFA (0.1eq), $CH_2Cl_2$, RT, 24 hours.

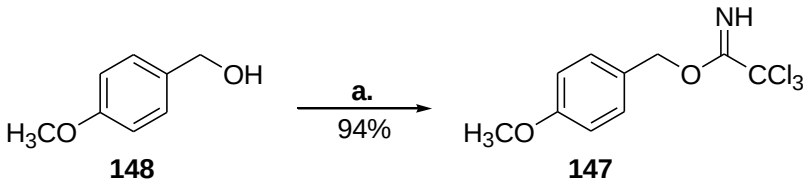
***Scheme 2.4:*** *Acylation and lactonisation to give the acyl-dihydropyrone* **139** *model system.*

### 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 ultilised 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.




**148** **147**

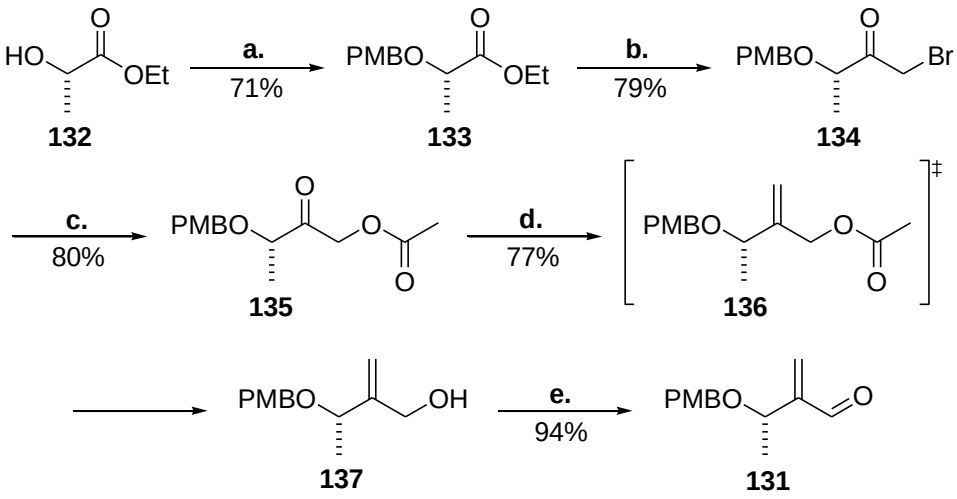
**Reagents and Conditions: a.** 50% KOH, $CH_2Cl_2$, $(n\text{-}Bu)_4NH_4.HSO_4$ (cat.), 0°C, $Cl_3CC{\equiv}N$ (1.2eq), 2 hours at RT.

***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 $CH_2Cl_2$ 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 $R_F$, 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*.[33] 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 dibromomethyllithium 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] $S_N2$ 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

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 $CH_2Cl_2$ at room temperature for one hour.[36] 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**).




**Reagents and Conditions: a.** PMB-imidate **147** (1.3eq), $CH_2Cl_2$, CSA (0.1eq), RT for 4 days. **b.** $CH_2Br_2$ (2.0eq), THF, -78°C, $CH_3Li$ (2.0eq), 2 hours, warmed to 0°C then AcOH (4.0eq). **c.** NaOAc (6.0eq), DMF, RT for 4 hours. **d.** $Ph_3PCH_2I$ **149** (1.0eq), THF, -78°C, n-BuLi (1.0eq), warmed to RT for 30 minutes. **e.** $K_2CO_3$ (0.1eq), MeOH, RT for 3 hours. **f.** DMP (1.3eq), $CH_2Cl_2$, RT for 1 hour.

***Scheme 2.6:*** *Synthesis of aldehyde* (**131**) *from ethyl-(S)-lactate* (**132**)

Looking at the $^1$H NMR spectrum (Figure 2.14) the aldehyde proton resonance at δ 9.60 is easily distinguishable from other proton environments due to its characteristic downfield chemical shift. The two terminal alkenyl $sp^2$ proton resonances appear as singlets downfield at δ 6.56 and δ 6.11, respectively. The oxymethine proton resonates at δ 4.44 and appears as a quartet due to the direct coupling of the methyl doublet at δ 1.30. The remaining resonances at δ 7.24, δ 6.86, δ 4.42, δ 4.34 and δ 3.77 are consistent with those attributed to a *p*-methoxy benzyl ether protecting group. The minor

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.

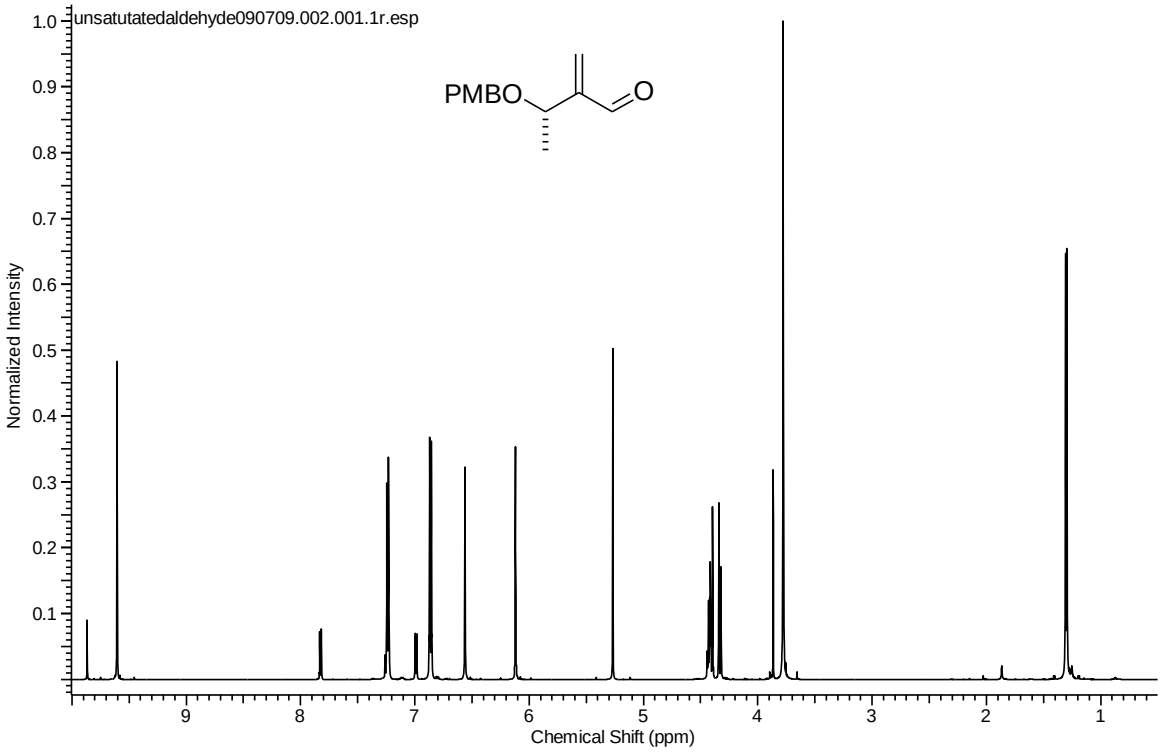



***Figure 2.14:*** *The $^1H$ NMR spectrum of aldehyde* **131** *in $CDCl_3$*

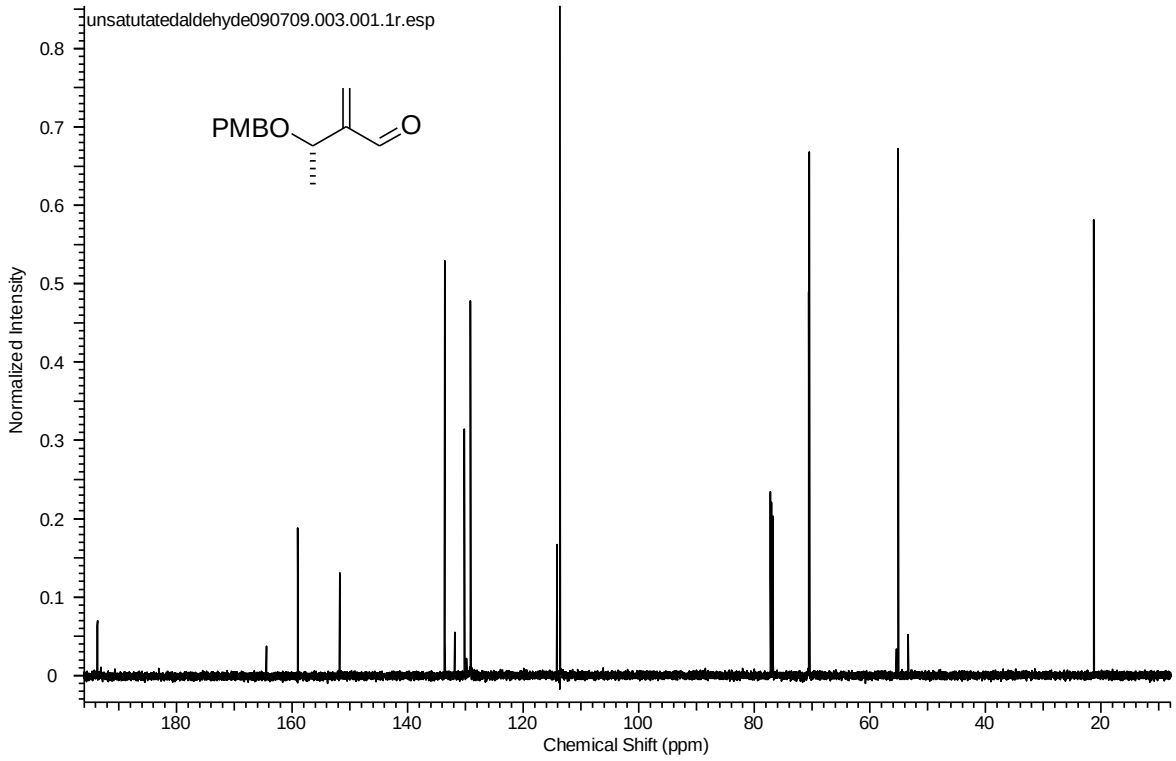
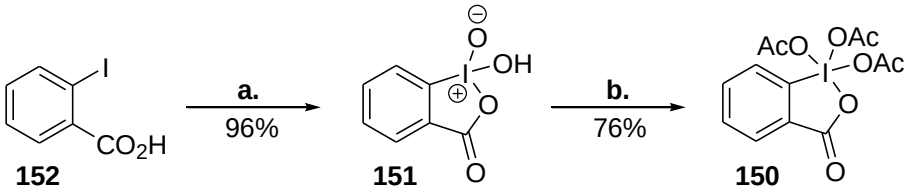



***Figure 2.15:*** *the* $^{13}C$ *NMR spectrum of aldehyde* **131** *in* $CDCl_3$

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.[37,38] Acetylation of the iodoxybenzoic acid (**151**) with a catalytic amount of *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 *et al*[39] was designed to reduce the irregular behavior seen in other reported Dess-Martin acetylations.[40,41]

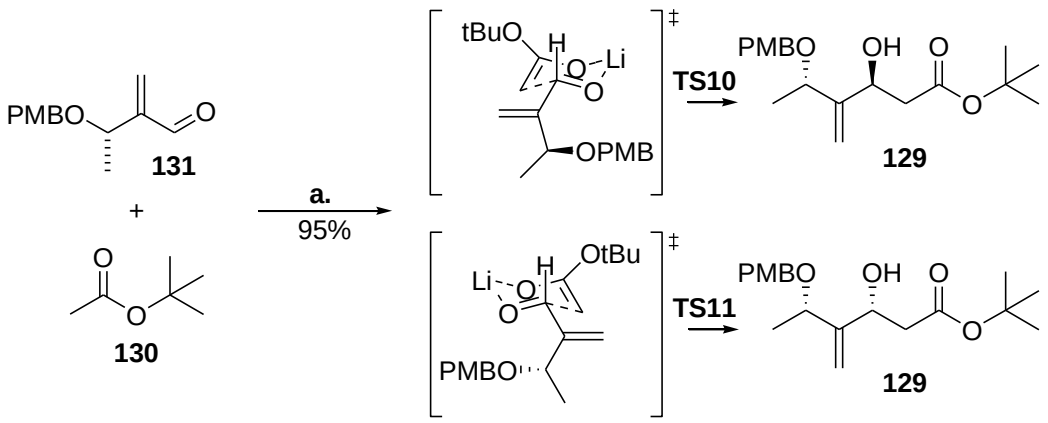



**Reagents and Conditions: a.** $KBrO_3$ (1.3eq), $H_2SO_4$ (0.7M, 1.6eq), 70°C for 4 hours; **b.** *p*-TsOH (cat.), $Ac_2O$, 80°C for 2 hours.

***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 mixure 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 **TS11**, 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.

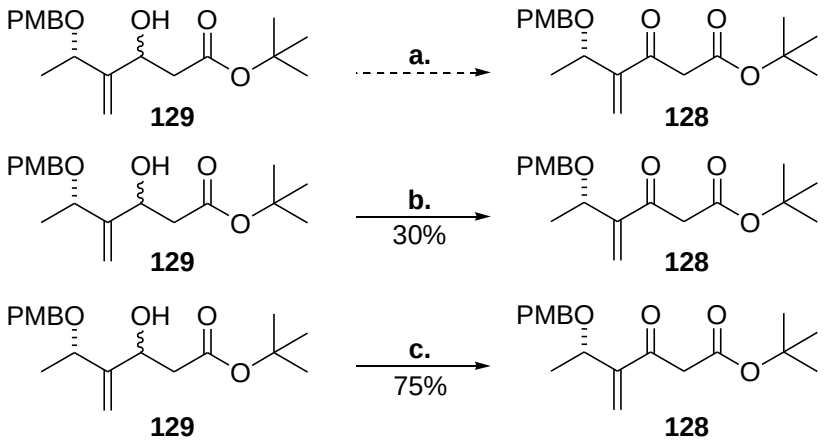



**Reagents and Conditions: a.** LiHMDS (1.7eq), THF, *t*-butyl acetate (**130**) (1.7eq), -78°C, 30 minutes, warmed to 0°C for 2 hours.

***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[42] due to their substrate similiarity. 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.[37,43,44] The secondary alcohol **129** was dissolved in $CH_2Cl_2$ and $H_2O$, 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 (**153**) (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,[45] where a solution of pyridine hydrochloride was added to $CrO_3$ at ambient temperature for 30 minutes. With the newly synthesised PCC (**153**) in hand, following a method detailed by Kamimura *et al*,[46] β-hydroxy ester **129** was dissolved in $CH_2Cl_2$, and at room temperature equal amounts of PCC (**153**) and

celite solid support[47] were added. The dark reaction mixture was stirred for 4 hours and following filtration and purification produced the desired β-keto ester **128** in an acceptable 75% yield.

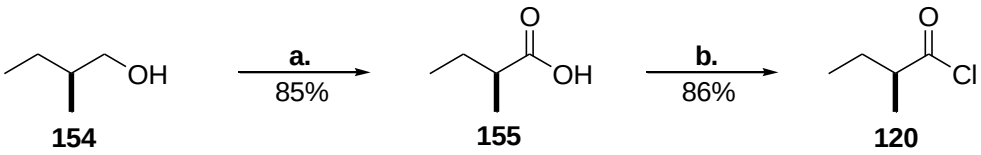



**Reagents and Conditions: a.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hours. **b.** DMP (**150**) (1.3eq), $CH_2Cl_2$, $H_2O$, RT for 3 hours. **c.** PCC (**153**) (2.0eq), $CH_2Cl_2$, celite, RT for 4 hours.

***Scheme 2.9:*** *Swern, DMP and PCC oxidation attempts of β-hydroxy ester* **129**

### 2.3.5 Studies towards the Acyclic Tricarbonyl Precursor 127

To attempt the acylation of β-keto ester **128** to form the acyclic tricarbonyl precursor **127** first required the synthesis of (*S*)-2-methylbutyryl chloride (**120**) acylating agent from the commercially available (*S*)-2-methylbutanol (**154**) (Scheme 2.10). Conversion of this enantiomerically pure alcohol **154** to the analogous carboxylic acid **155** was achieved using Jones oxidation[48] without causing epimerisation of the α-methyl substituent.[49] The alcohol **154** was dissolved in acetone and at 0°C was added to a premixed solution of $CrO_3/H_2SO_4/H_2O$ 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 **155** in 85% yield. Conversion of the acid **155** to the acyl halide **120** was achieved in 86% excellent yield by dissolving the acid **155** in thionyl chloride.[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 **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 (**120**) product (bp. 115°C).[51]

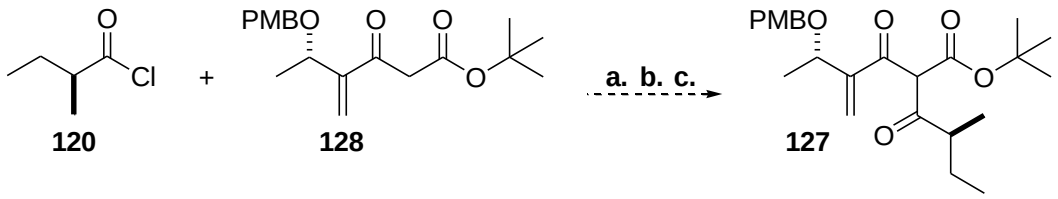



**Reagents and Conditions: a.** $CrO_3$ (0.1M), $H_2SO_4$, acetone, $H_2O$, 0°C for 30 minutes, then EtOH. **b.** $SOCl_2$ (3.0eq), 50°C, 2 hours.

***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 ultilising $^i$PrMgCl 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: a.** $MgCl_2$ (1.7eq), pyridine (2.0eq), $CH_2Cl_2$, 0°C, then 1 hour at RT. **b.** $^{i}$PrMgCl (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[52] 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.

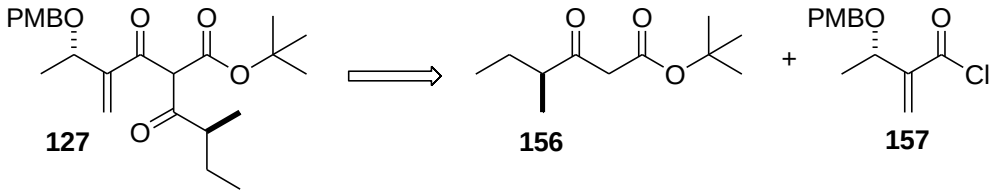
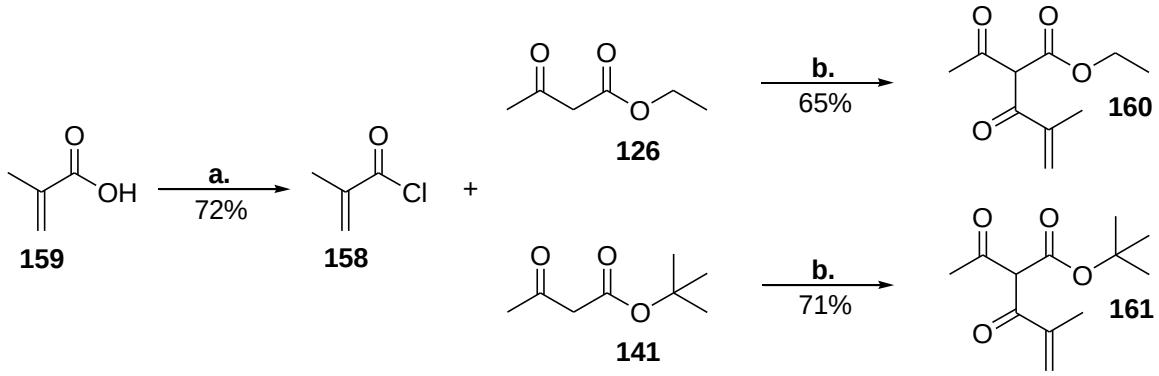



***Figure 2.16:*** *Revised retrosynthesis towards the acyclic tricarbonyl precursor* **127**

To test this new approach firstly, methacryloyl chloride (**158**) was synthesised directly from methacraylic acid (**159**) in 72% yield using oxalyl chloride and a catalytic amount of DMF (Scheme 2.12).[53] From the conditions used above,[52] 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 $^{i}$PrMgCl 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.

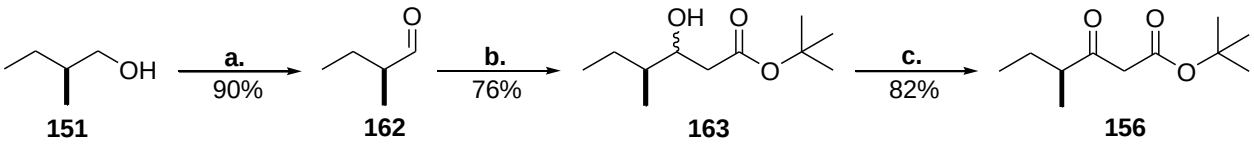



**Reagents and Conditions: a.** $(COCl)_2$ (1.1eq), $CH_2Cl_2$, DMF, 0°C then 40°C for 3 hours. **b.** $^{i}$PrMgCl (1.2eq), THF, methacryloyl chloride (**158**) (1.0eq), -78°C, 2 hours.

***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.[54] 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

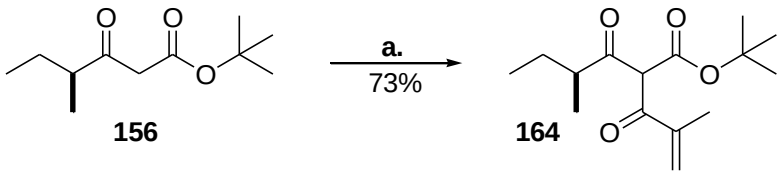
76% yield. The aldol adduct **163** was dissolved in $CH_2Cl_2$ and oxidised to the planned β-keto ester **156** in 82% using PCC (**153**) and celite, at room temperature for 4 hours.




**Reagents and Conditions: a.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (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), $CH_2Cl_2$, celite, 4 hours RT.

***Scheme 2.13:*** *The three step synthesis of β-keto ester* **156** *from (S)-2-methylbutanol (*__154__*)*

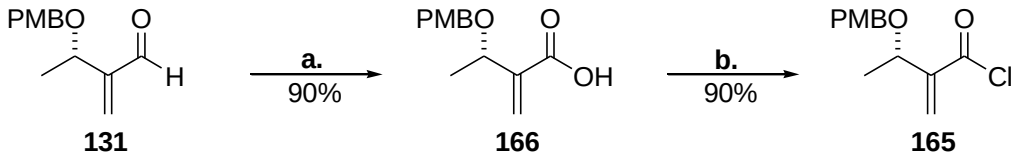
With the β-keto ester **156** in hand, and an excess amount of methacryloyl chloride (**158**) it became apparent in addition to the model systems **160** and **161** synthesised above (Scheme 2.12) to look into the acylation of β-keto ester **156** with methacryloyl chloride (**158**) (Scheme 2.14). 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 $^{i}$PrMgCl 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**).




**Reagents and Conditions: a.** $^{i}$PrMgCl (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*-butyl 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 al*[55] 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 $H_2O$ at room temperature, 2-methylbut-2-ene, followed by $NaClO_2$ and $NaH_2PO_4$ were added together and the reaction was stirred for 2 hours. The mixture was then diluted with $CH_2Cl_2/H_20$ (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 chloride[50] and oxalyl chloride[53] methods as previously used above, however both cases failed to produce the desired transformation. During this time it was discovered that Ghosez *et al*[56] had developed a α-chloroenamine for the formation of acyl halides under mild conditions. It was also noted that Jimenez and coworkers[57] 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 $CH_2Cl_2$ at ambient temperature followed by the dropwise addition of the α-chloroenamine reagent.

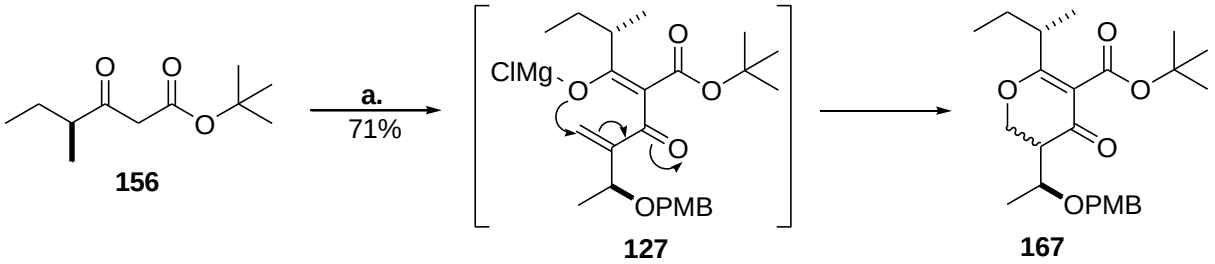



**131** **166** **165**

**Reagents and Conditions: a.** $NaClO_2$ (5.0eq), $NaH_2PO_4$ (4.0eq), t-BuOH, 2-methylbut-2-ene, $H_20$, RT for 2 hours, acidified with TFA. **b.** 1-Chloro-N,N-2-trimethyl-1-propenylamine (1.0eq), $CH_2Cl_2$, 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 $^{i}$PrMgCl (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 $^{1}$H 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 addition[58,59] 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.

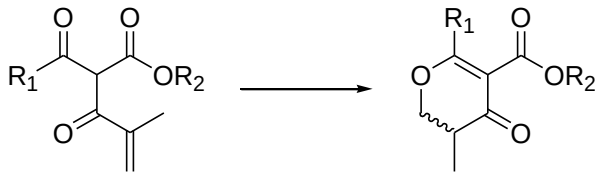



**156** **127** **167**

**Reagents and Conditions: a.** $^{i}$PrMgCl (1.2eq), THF, acid chloride **165** (1.0eq) -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**).



$R_1 = CH_3$, $R_2 = CH_2CH_3$
$R_1 = CH_3$, $R_2 = C(CH_3)_3$
$R_1 = CH(CH_3)CH_2CH_3$, $R_2 = C(CH_3)_3$

***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).

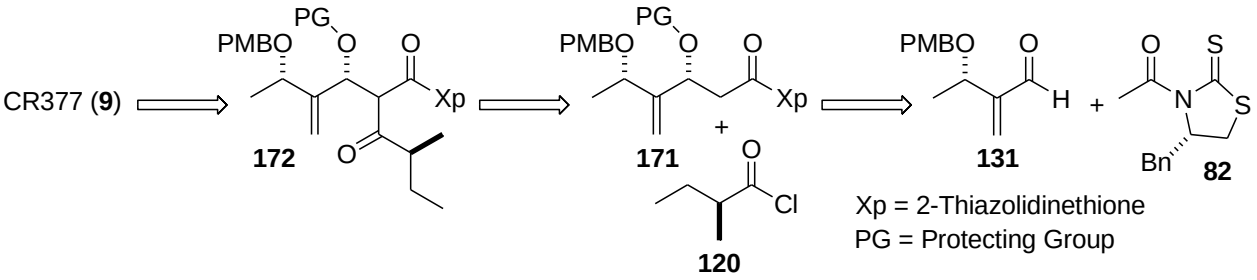
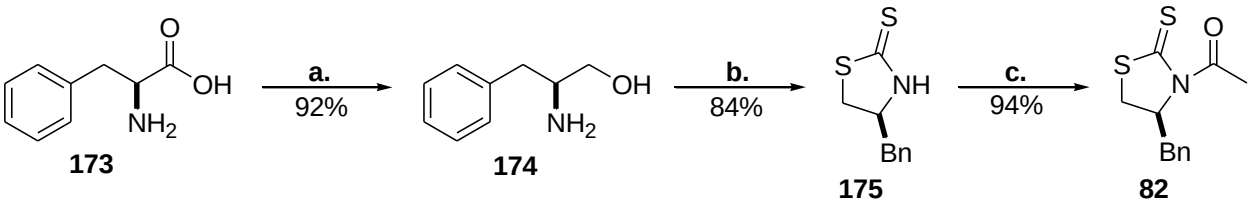



***Figure 2.16:*** *Revised Acylation approach towards synthesis of a protected acyclic precursor* **172**

Excellent stereoselectivities have been observed for acetate aldol condensations using 1,3-oxazolidine-2-thiones and 1,3-thiozolidine-2-thiones.[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,[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,[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.

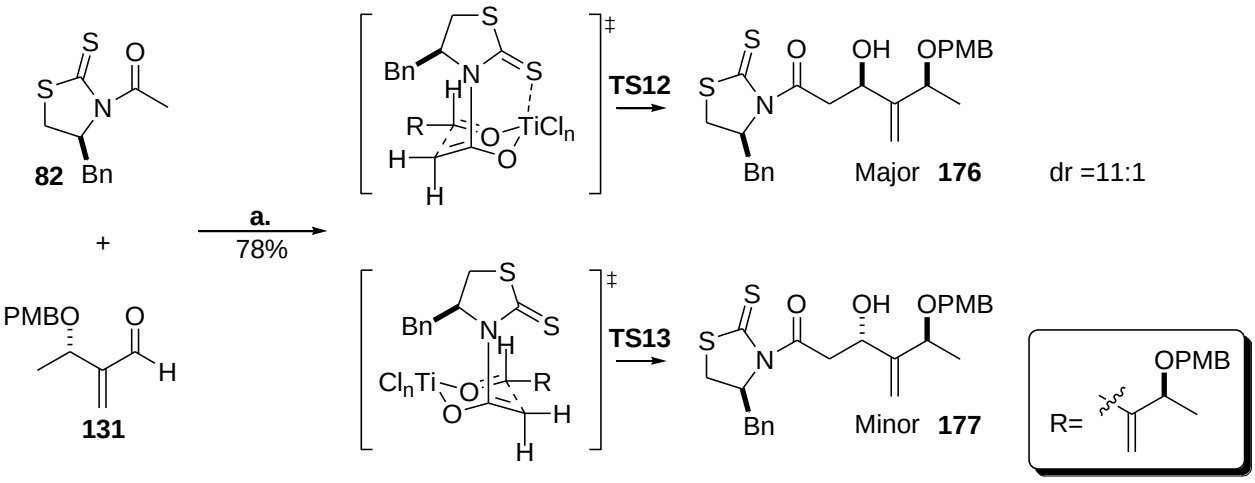
The borane reduction of (*S*)-phenylalanine (**173**) to (*S*)-phenylalanol (**174**) was achieved in 92% following a procedure detailed by Evans *et al*.[67] Nagao's auxiliary **175** was then obtained in 84% yield as white needles using a procedure from Delaunay *et al*,[68] in which (*S*)-phenylalanol (**174**) was refluxed with KOH and $CS_2$ for 16 hours. Nagao's auxiliary **175** was acylated using a modified method from Yadav *et al*,[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.




**Reagents and Conditions: a.** $BF_3.OEt_2$ (1.0eq), $BH_3.SMe_2$ (1.1eq), THF, reflux for 8 hours, then NaOH/THF/$H_2O$, reflux for a further 15 hours. **b.** KOH (1M), $CS_2$ (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**)

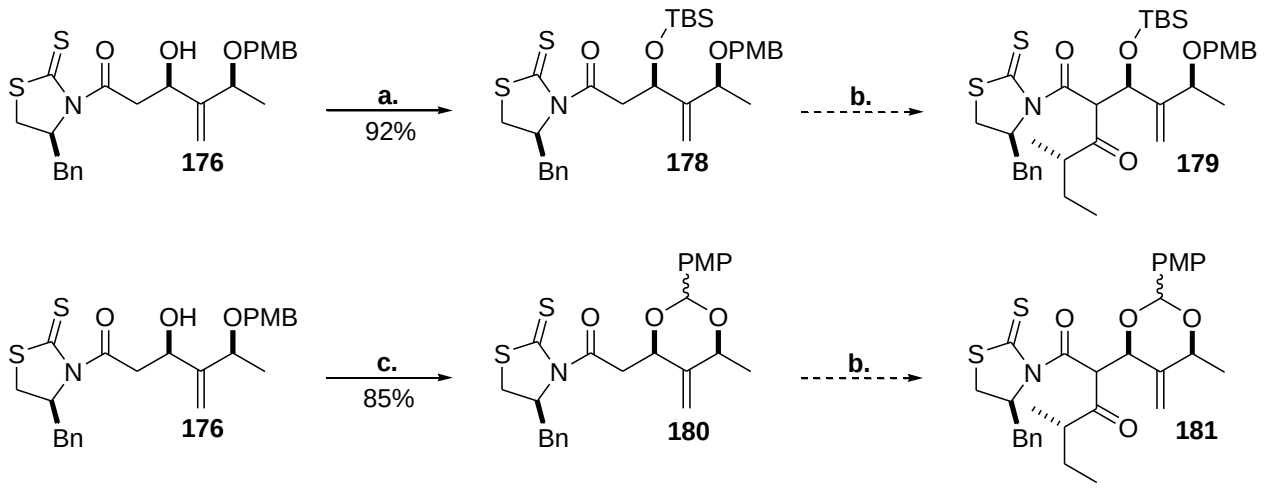
The determination of the stereochemical outcome for these Evans' based acetate auxiliary aldols has been rationalised by consideration of the competing chair transition states (Scheme 2.19).[62,64] Transition state **TS12** illustrates the additional sulfur coordination with the titanium enolate, and 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.[66] 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*[70] was ultilised for the formation of the sole *syn-syn* aldol adduct **176** (Scheme 2.19), where the acetate auxiliary **82** was complexed with $TiCl_4$ for 30 minutes at -40°C. A slight excess of $^{i}Pr_2NEt$ 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 $CH_2Cl_2$ 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.** $TiCl_4$ (1.5eq), $^{i}Pr_2NEt$ (1.90eq), $CH_2Cl_2$, -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**,[70] which was achieved in 92% overall yield by the addition of TBSOTf and 2,6-lutidine in $CH_2Cl_2$ 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**.[71] Adaption of a procedure used by Burgos *et al*,[72] 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**.



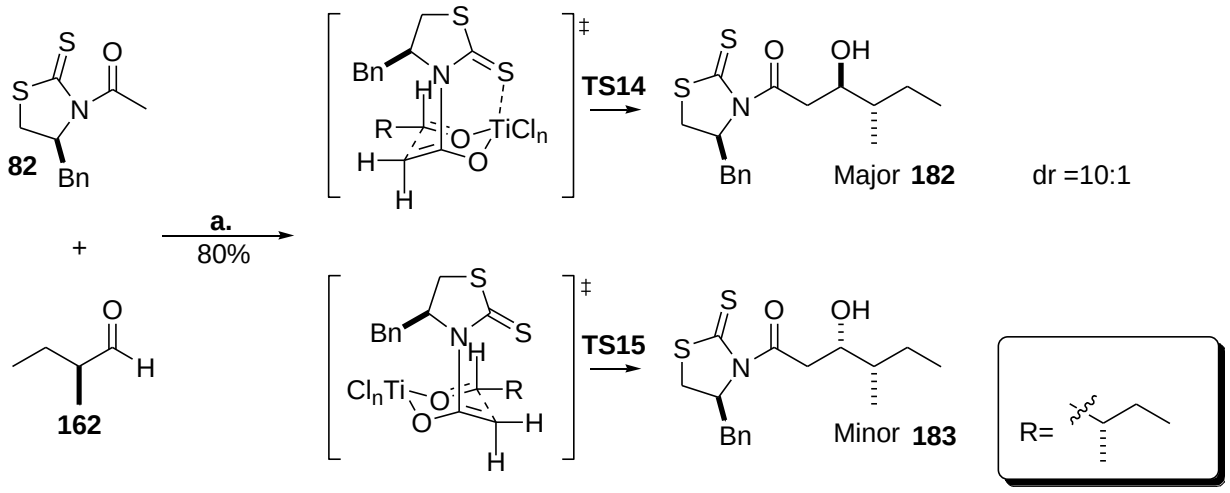

**Reagents and Conditions: a.** TBSOTF (1.5eq), 2,6-lutidine (2.0eq), $CH_2Cl_2$, -78°C for 3 hours. **b.** t-BuLi (1.0eq), THF, (*S*)-2-methyl butyryl chloride (**120**) (1.5eq), -78°C for 2 hours. **c.** DDQ (1.2eq), $CH_2Cl_2$, $H_2O$, RT for 2 hours.

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

Athough 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**.[73] The acetate-aldol **176** adduct was converted to the PMP-acetal **180** in 85% yield under the normal PMB-ether cleavage conditions,[74,75] as following oxidation with DDQ in $CH_2Cl_2$ 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

thione aldol adduct **182** appeared a viable pathway forward. Application of the above successful titanium tetrachloride mediated aldol as reported by Crimmins *et al*[70] 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**.

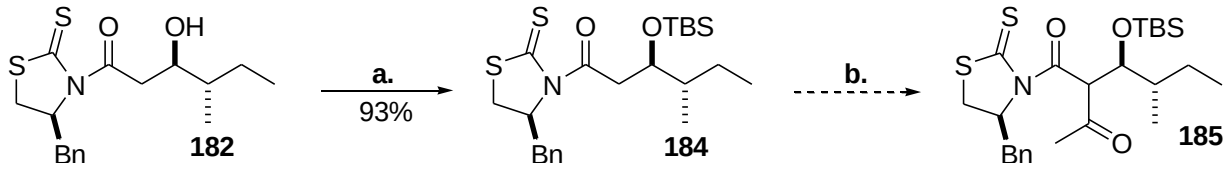



**Reagents and Conditions:** $TiCl_4$ (1.5eq), $^iPr_2NEt$ (1.90eq), $CH_2Cl_2$, -40°C, for 30 minutes, then (*S*)-2-methyl-aldehyde (**162**), -78°C for 2 hours.

***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.

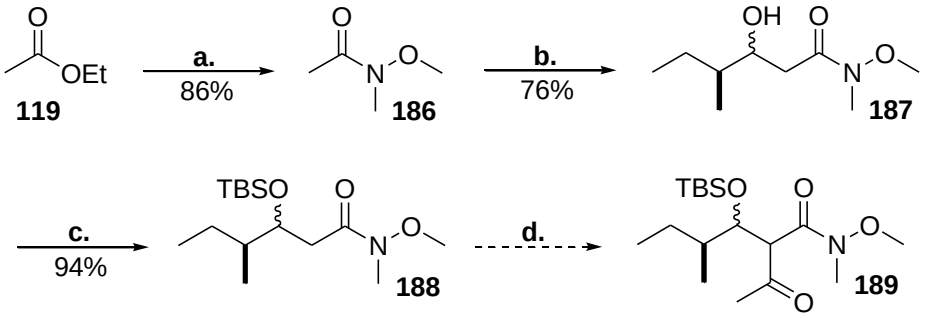



**Reagents and Conditions: a.** TBSOTF (1.5eq), 2,6-lutidine (2.0eq), $CH_2Cl_2$, -78°C for 3 hours. **b.** t-BuLi (1.0eq), THF, acetyl chloride (**22**) (1.5eq), -78°C for 2 hours.

***Scheme 2.22:*** *Synthesis of TBS-protected β-hydroxy amide* (**184**) *and the acylation attempt with acetyl chloride* (**22**)

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*,[76] where ethyl acetate (**119**) was added to a solution of *N*,*O*-dimethylhydroxylamine in THF and $Et_2O$. 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 diastereosiomers 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**.

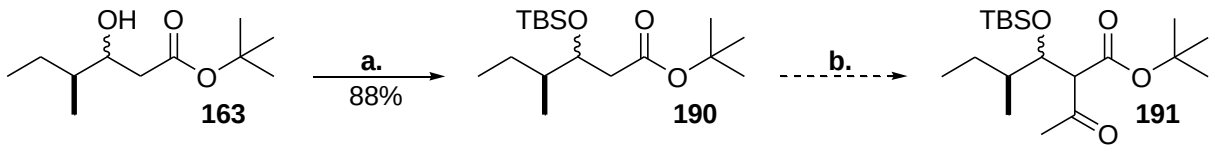



**Reagents and Conditions: a.** MeONH(Me).HCl (2.50eq), $Et_2O$, THF, $^{i}PrMgCl$ (5.0eq), -20°C for 30 minutes, then 0°C for 1 hour. **b.** LiHMDS (1.1eq), THF, aldehyde **162** (1.2eq), -78°C, 30 minutes, warmed to 0°C for 2 hours. **c.** TBS-Cl (1.1eq), imidazole (2.0eq), DMF, RT for 15 hours. **d.** 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 ($pK_a$) 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-aldol 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.[77,78] As above, acetyl chloride (**22**) was chosen to determine whether acylation of this silyl protected adduct **190** to form a protected 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.

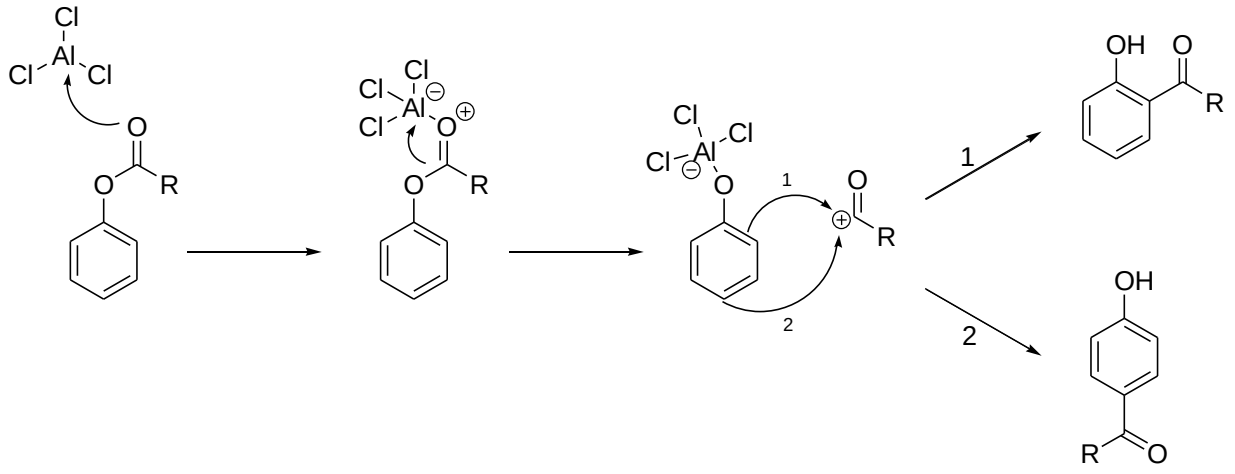
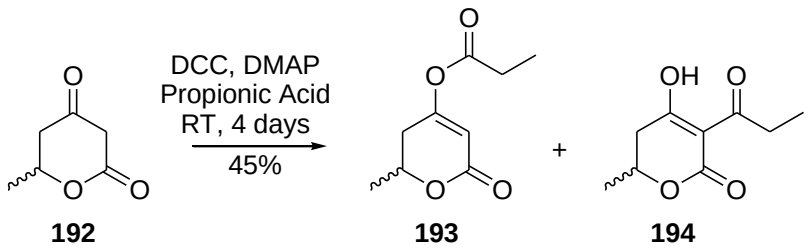



***Figure 2.17:*** *Fries-Rearrangement of aromatic phenolic esters with $AlCl_3$*

The accepted intermolecular mechanism for the Fries-rearrangement[81,82] initially involves coordination of the Lewis acid ($AlCl_3$) 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.[83,84] Tabuchi and coworkers'[85] work initially showed that DCC and DMAP could be used to effectively conduct Fries-type rearrangements on pyrone substrates. In 1994,[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 $^{1}$H NMR spectrum.




**192** **193** **194**

***Figure 2.18:*** *Propionic acid acylation of pyrone* **192** *and rearrangement of diester* **193**

Miyakado and coworkers[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%.

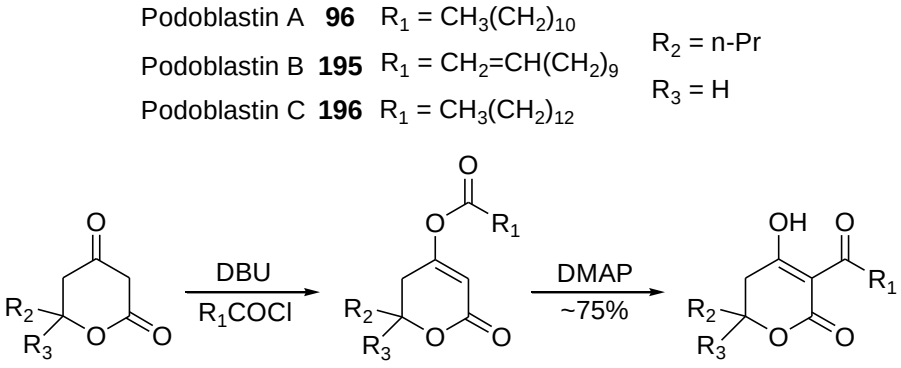
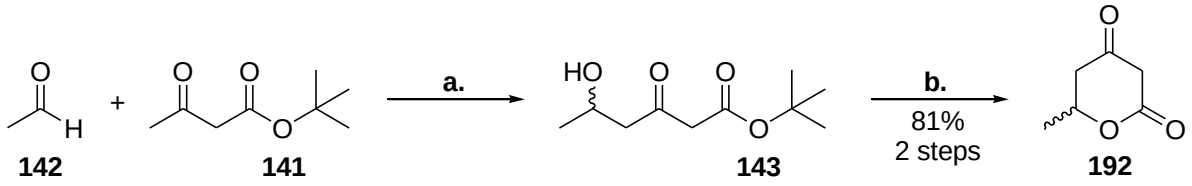



***Figure 2.19:*** *Synthesis of Podoblastin A, B and C* (**96**, **195** and **196**) *using an O- to C-acyl rearrangement approach*

### 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 $CH_2Cl_2$ 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.

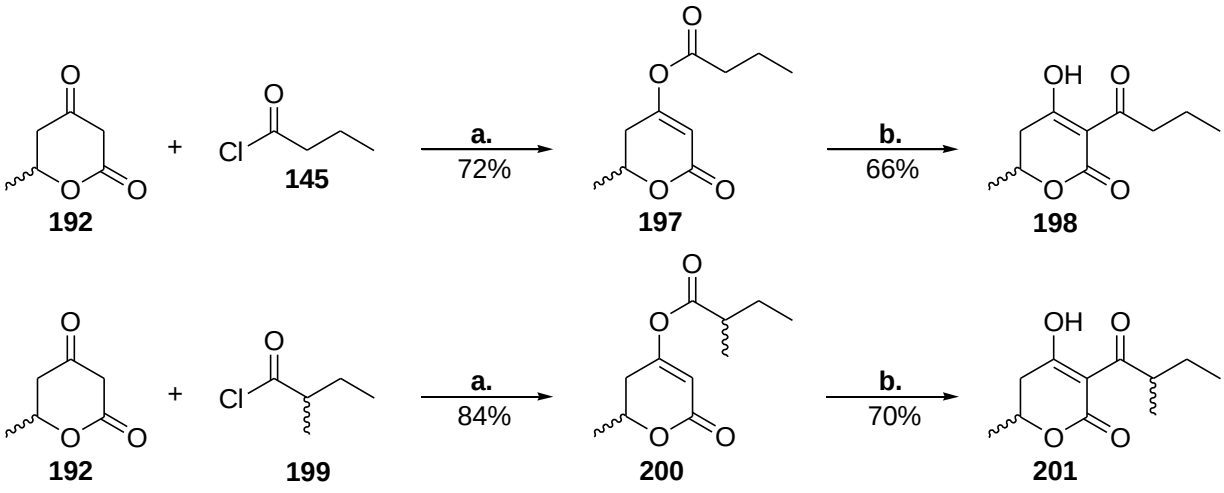



**142** **141** **143** **192**

**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), $CH_2Cl_2$, 0°C, RT for 15 hours.

***Scheme 2.25:*** *Synthesis of model racemic lactone* **192**

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 *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).




**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 δ 17.9. As this product only contains one chiral centre the signal at δ 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 δ 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 δ 204.4, δ 194.9, and δ 164.2 represent the three carbonyl functionalities that form the tricarbonyl system. The signal at δ 102.9 is also indicative of the highly deshielded methine carbon between the three carbonyls.

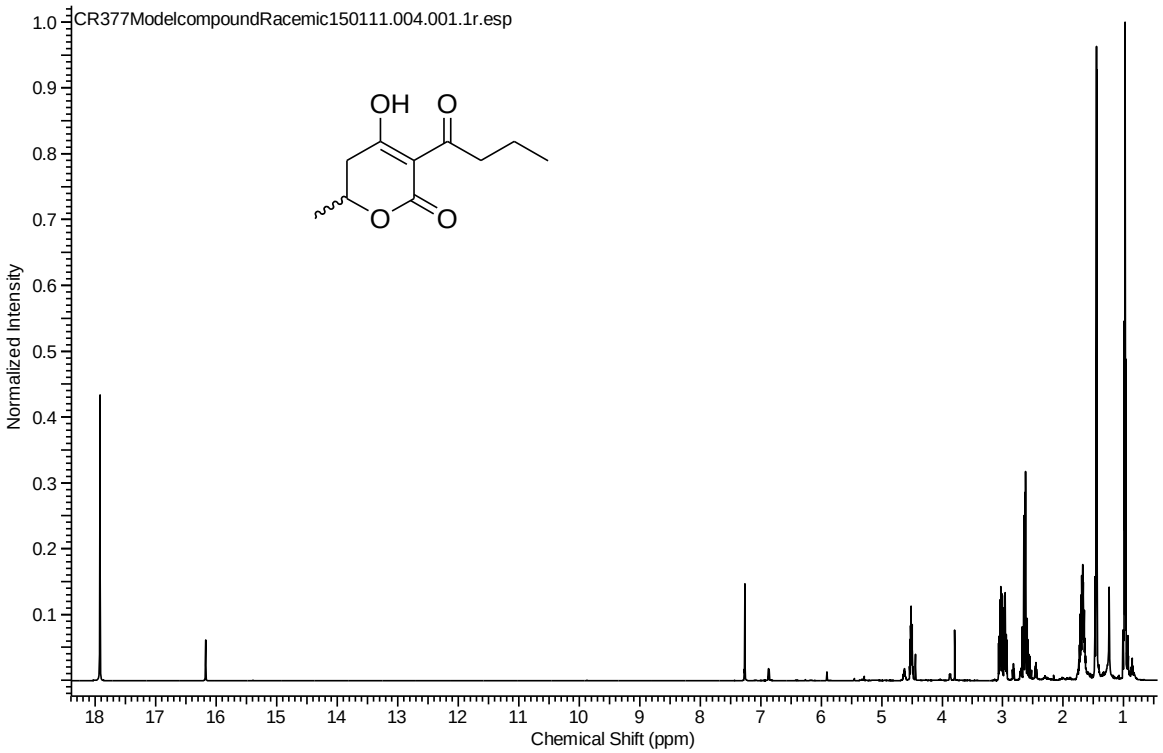



***Figure 2.20:*** *The $^{1}$H NMR spectrum of model tricarbonyl system* **198** *in $CDCl_3$*

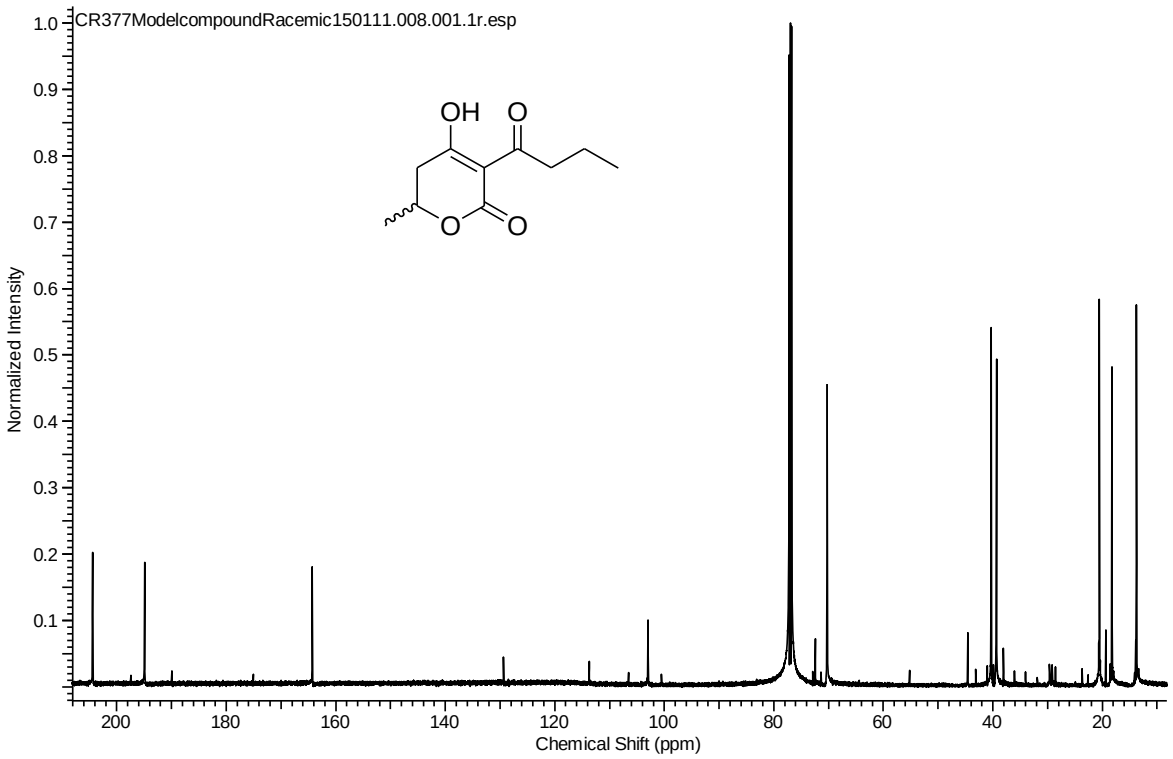



***Figure 2.21:*** *The $^{13}C$ NMR spectrum of model tricarbonyl system* **198** *in $CDCl_3$*

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.

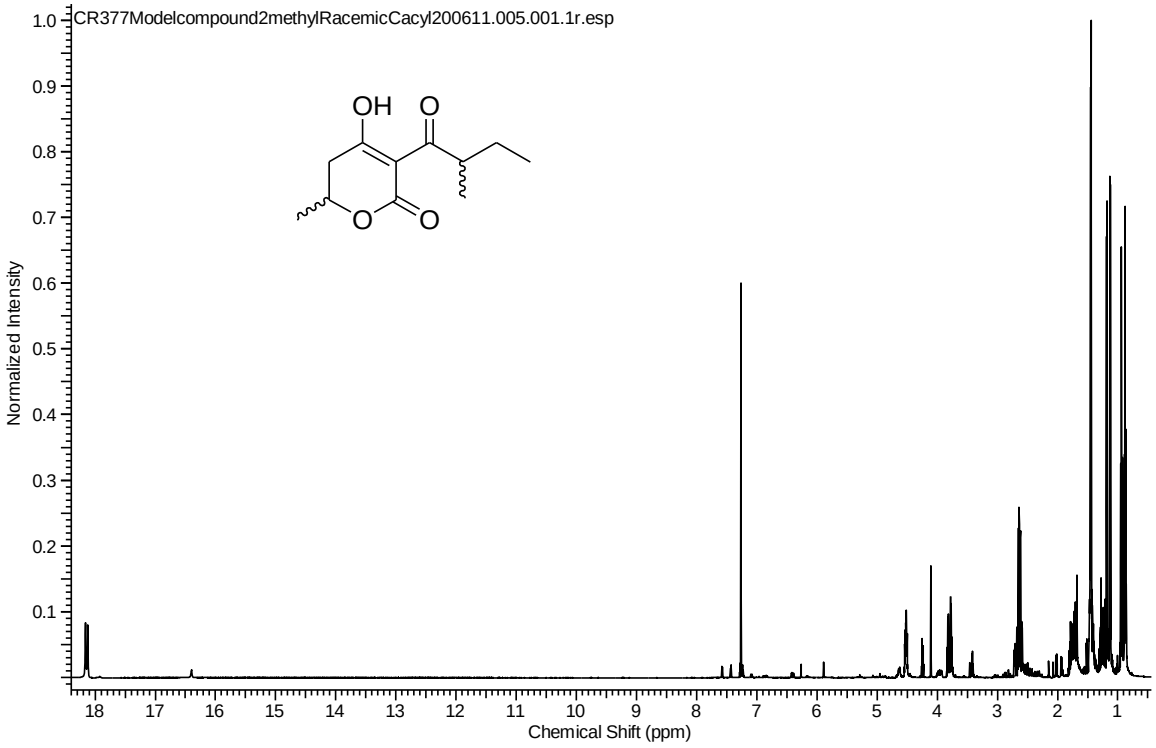



***Figure 2.22:*** *The $^{1}H$ NMR spectrum of model tricarbonyl system* **201** *in $CDCl_3$*

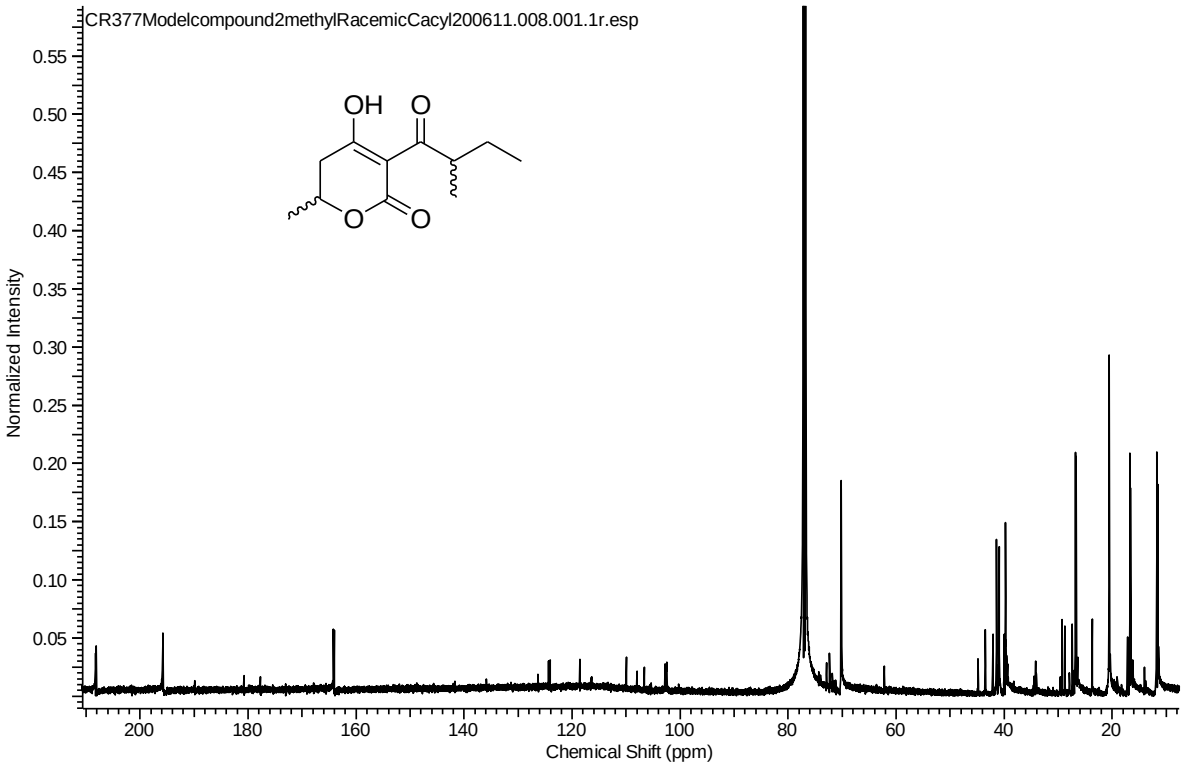
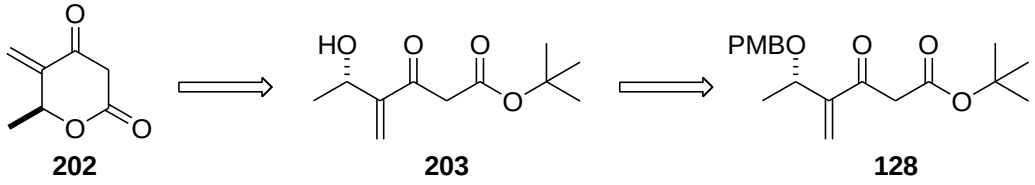



***Figure 2.23:*** *The $^{13}C$ NMR spectrum of model tricarbonyl system* **201** *in $CDCl_3$*

### 2.4.3 Acqusition of Unsaturated Lactone 202

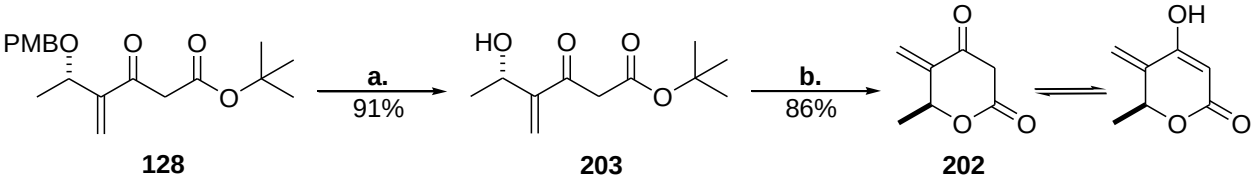
The overall success of the two acyl rearrangements from the diesters **197** and **200** towards their respective tricarbonyl methane model systems **198** and **201** strongly indicated that this synthetic approach presented a promising pathway towards achieving the first total synthesis of CR377 (**9**). 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).




**202** **203** **128**

***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 $CH_2Cl_2$ and $H_2O$ 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**. [74,75] 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 $CH_2Cl_2$ 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).[86]




**Reagents and Conditions: a.** DDQ (1.2eq), $CH_2Cl_2$, $H_2O$, 0°C then RT for 2 hours. **b.** TFA (1.1eq), $CH_2Cl_2$, 0°C, RT for 15 hours.

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

Looking at the $^1H$ 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 a 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.[88]

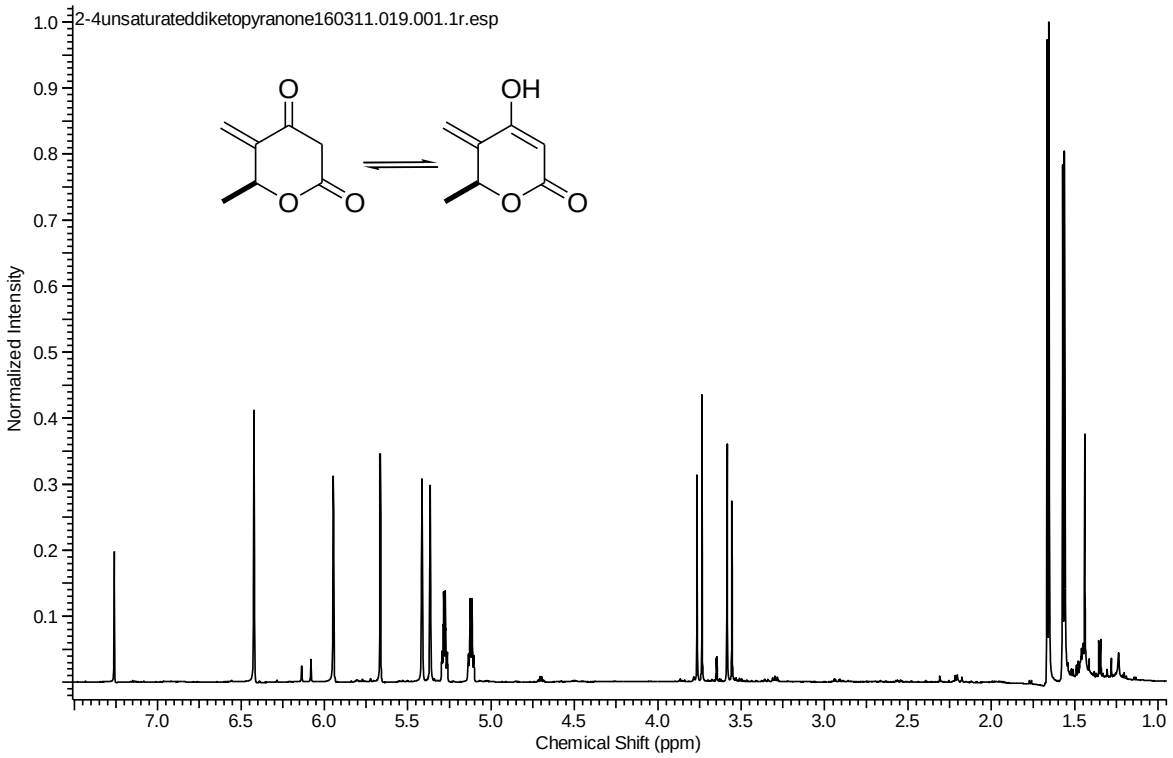



***Figure 2.25:*** *The $^1H$ NMR of unsaturated lactone* (**202**) *in $CDCl_3$*

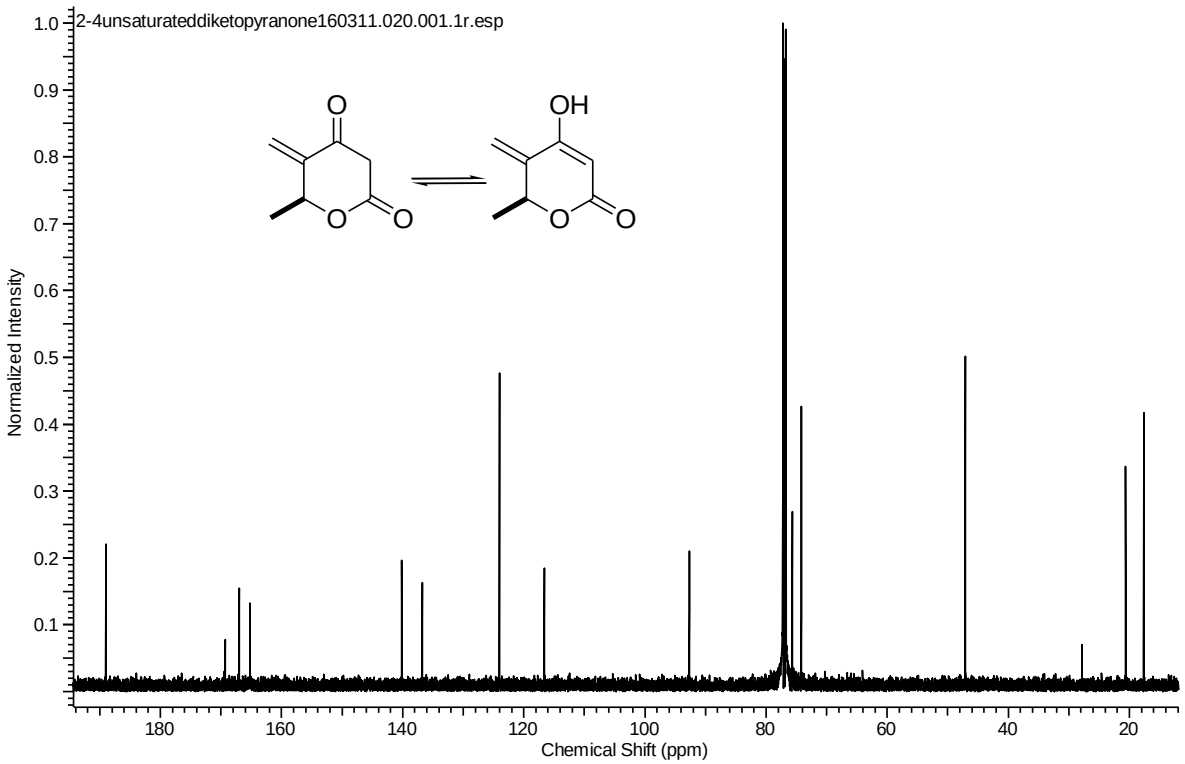
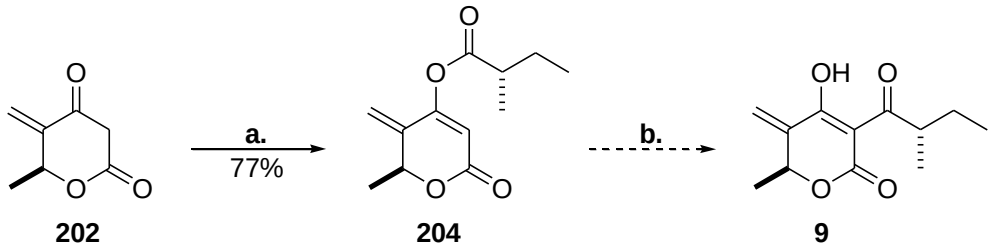



***Figure 2.26:*** *The $^{13}C$ NMR of unsaturated lactone* (**202**) *in $CDCl_3$*

### 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**.




**202** **204** **9**

**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

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**.[89] 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]

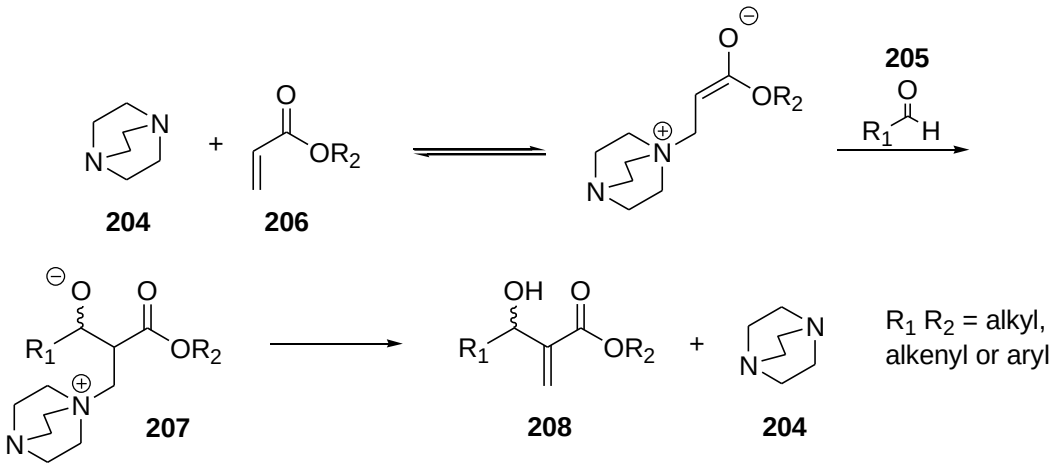
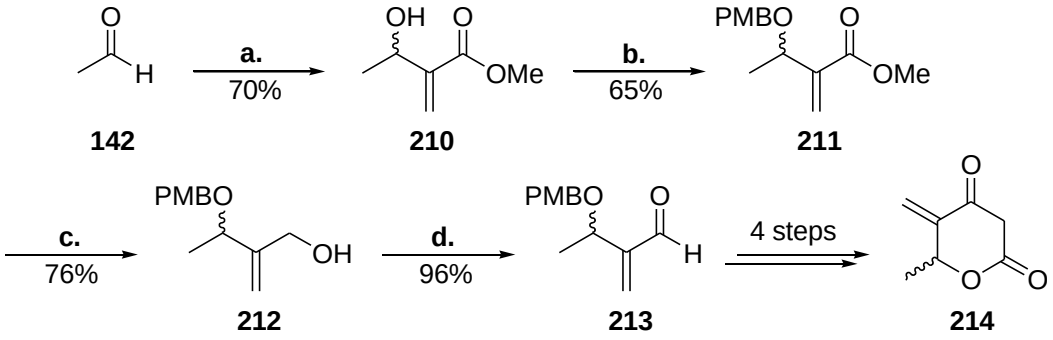



***Figure 2.27:*** *The proposed Bayliss-Hillman reaction mechanism*

In 2001, Yu and coworkers[92] reported the efficient use of the Bayliss-Hillman reaction for the preparation of a 3-hydroxy-2-methylenepropionate substrates using a stoichometric 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/$H_2O$ (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

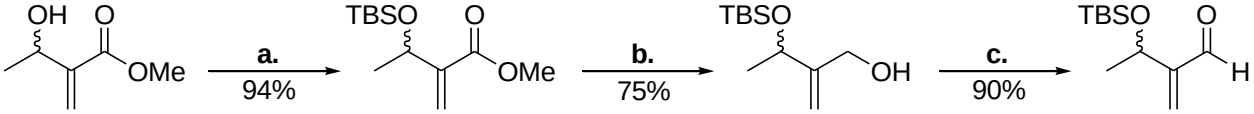
remaining residue was purified by column chromatography to give the racemic 3-hydroxy-2-methylene butyric acid methyl ester (**210**) adduct in 70% yield as clear oil. Use of the identical procedure for the PMB protection of ethyl-(*S*)-lactate (**132**) (Scheme 2.6) was directly applied to the newly synthesised β-hydroxy methyl ester **210**,[31,32] such that PMB-imidate **147** and CSA was added at room temperature to a solution of alcohol **210** in $CH_2Cl_2$. 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.[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).




**Reagents and Conditions: a.** Methyl acrylate (**209**) (3.0eq), DABCO (1.0eq), dioxane, $H_2O$, RT for 48 hours. **b.** PMB-imidate **147** (1.0eq), $CH_2Cl_2$, CSA (0.1eq), RT for 4 days. **c.** DIBALH (3.0eq), $CH_2Cl_2$, -78°C for 3 hours then 0°C for 1 hour. **d.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hours.

***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 **217**[93] and oxidised to the aldehyde **218** under Swern conditions.[95]



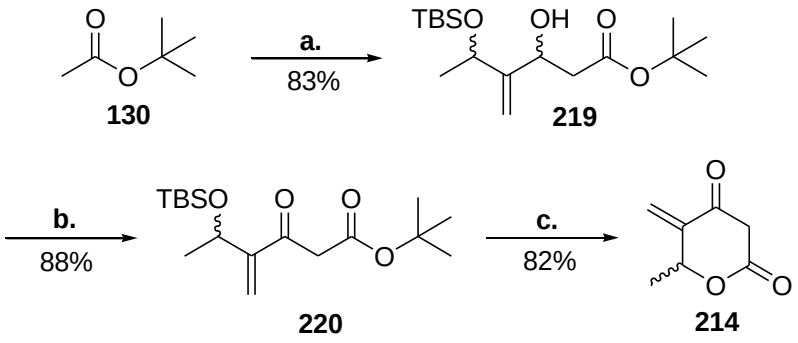

**210** **216** **217** **218**

**Reagents and Conditions: a.** TBS-Cl (1.1eq), imidazole (2.0eq), DMF, RT for 15 hours. **b.** DIBALH (3.0eq), $CH_2Cl_2$, -78°C for 3 hours then 0°C for 1 hour. **c.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hours.

***Scheme 2.30:*** *Synthesis of TBS-protect aldehyde* (**218**)

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 $CH_2Cl_2$, PCC and celite were

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*,[96] β-keto ester **220** was then dissolved in $CH_3CN$ and $CH_2Cl_2$, 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.



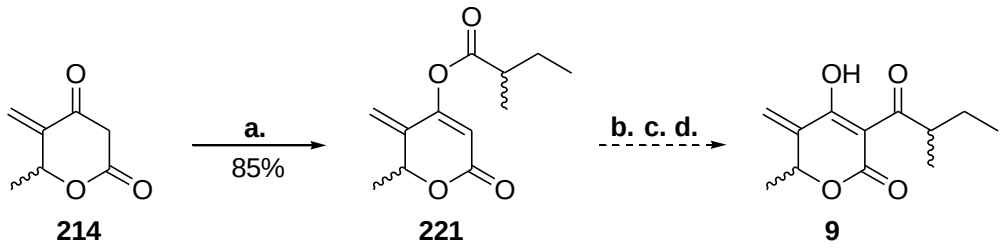

**Reagents and Conditions: a.** LiHMDS (1.1eq), THF, t-butyl acetate (**130**) (1.1eq), aldehyde **218** (0.90eq) -78°C, 30 minutes, warmed to 0°C for 2 hours. **b.** PCC (2.0eq), $CH_2Cl_2$, celite, RT, 4 hours. **c.** 40% $HF_{aq}$, $CH_2Cl_2$, $CH_3CN$, 0°C for 2 hours.

***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 $CH_2Cl_2$ 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.



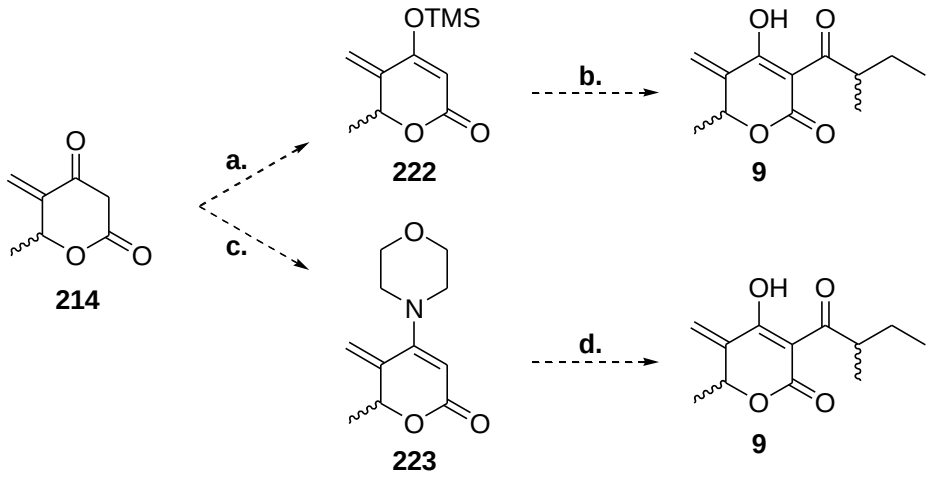

**214** **221** **9**

**Reagents and Conditions: a.** DBU (1.1eq), toluene, 2-methyl butyryl chloride (**199**) (1.1eq), 0°C for 2 hours. **b.** PPY (0.05eq), toluene, 85°C for 6 hours. **c.** $BF_3.OEt_2$ (5.0eq), 85°C for 6 hours. **d.** $AlCl_3$ (2.2eq), $CH_2Cl_2$, RT to 40°C for 6 hours.

***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 chemisty[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 $CH_2Cl_2$ at 0°C for two hours. Following this, the

mixture was cooled to -78°C and $TiCl_4$ 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.[105] 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), $CH_2Cl_2$, 0°C, 2 hours. **b.** $TiCl_4$ (1.0eq), 2-methylbutyryl chloride (**199**) (1.2eq), $CH_2Cl_2$, -78°C for 2 hours, RT for 2 hours. **c.** Morpholine (1.30eq), toluene, *p*-TSOH (0.05eq), 115°C for 6 hours. **d.** $NEt_3$ (1.0eq), 2-methylbutyryl chloride (**199**) (1.2eq), $CHCl_3$, 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.[106] 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

CR377 (**9**) outweighed the lack of literature precedent. Adaption of a procedure by Schobert *et al*,[107] β-keto lactone **214** was dissolved in toluene and morpholine, and a catalytic amount of *p*-TsOH was added. The reaction mixture was heated to reflux for six hours, in which time the elimination of $H_2O$ 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 *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 ultilising an acylation/rearrangement process similar to that employed towards the synthesis of Podoblastin A (**96**). The formation of cyclic pyranone **192** from *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[108,109] will facilitate the acylation and rearrangement pathway. Oxidation of the thiophenol to the sulfoxide[110] should then allow elimination to reform the alkene by thermolysis[111] and afford the natural product CR377 (**9**) (Figure 2.29).

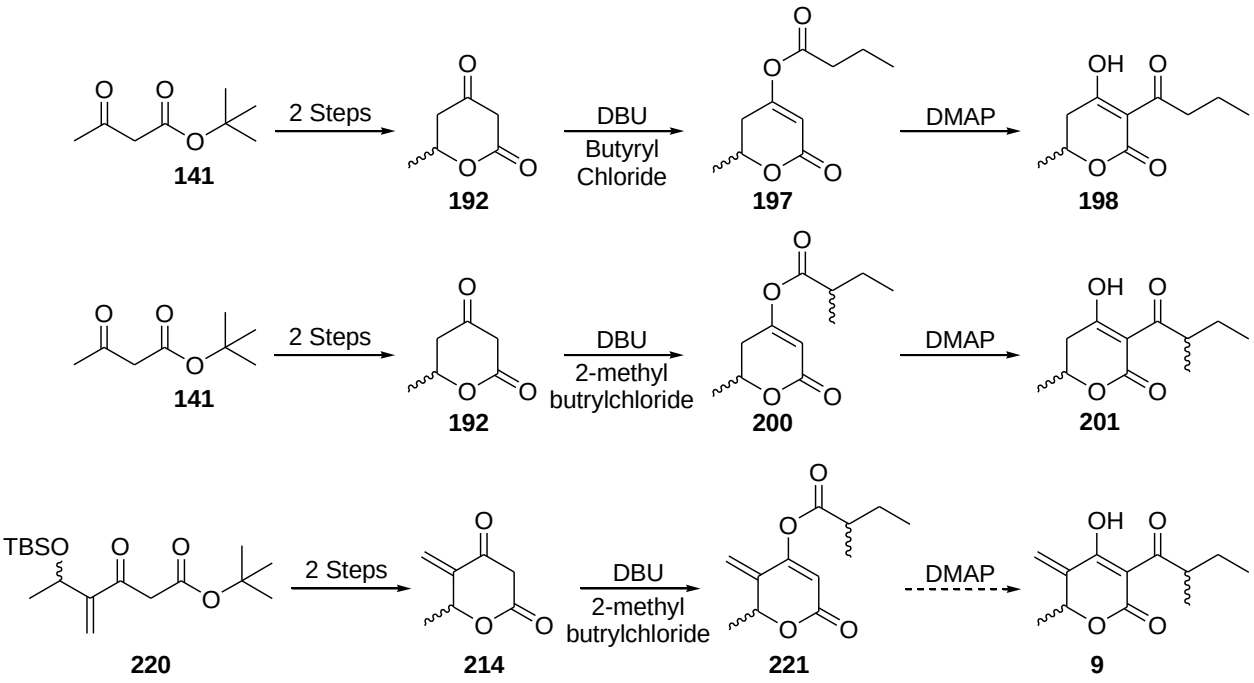
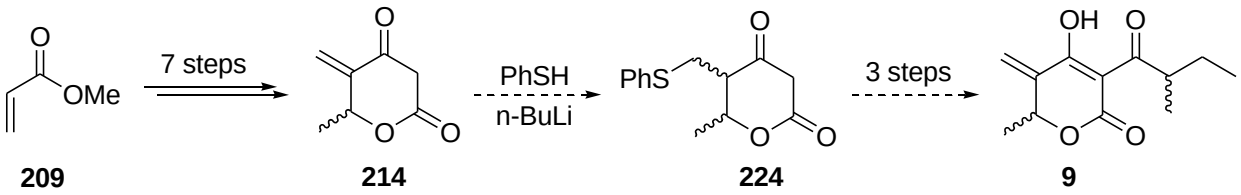



***Figure 2.28:*** *Synthesis of model systems* (**198**) *and* (**201**) *and attempted synthesis of CR377* (**9**) *using an acylation and rearrangement approach.*

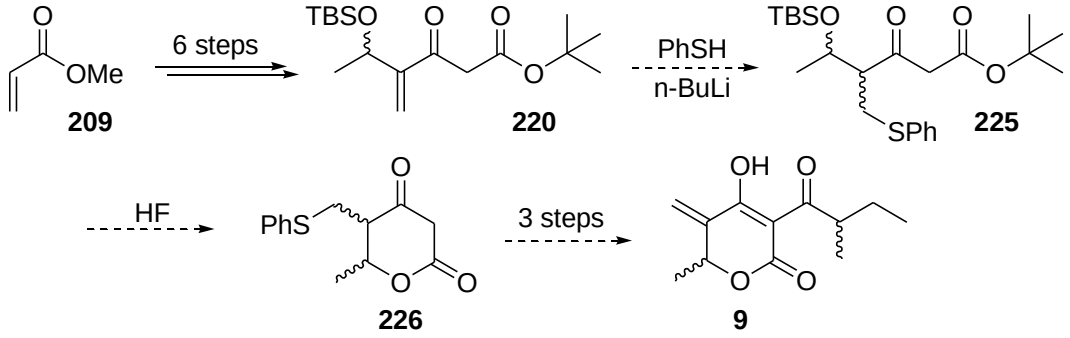
As shown in Schemes 2.30 and 2.31 the racemic unsaturated lactone **214** can be formed in seven linear steps from methyl acrylate (**209**). Michael addition of thiophenol to the pyrone **214** would serve to protect the alkene functionality and hence remove the perceived conjugation problems as seen 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**).




**209** **214** **224** **9**

***Figure 2.29:*** *Synthesis of CR377* (**9**) *following acylation and rearrangement of a protected lactone* (**224**) *system.*

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**).




**209** **220** **225** **226** **9**

***Figure 2.30:*** *Linear alkene protection for the acylation and rearrangement approach towards 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**)[7] 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**).[112] 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[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 $NaHCO_3$ 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.

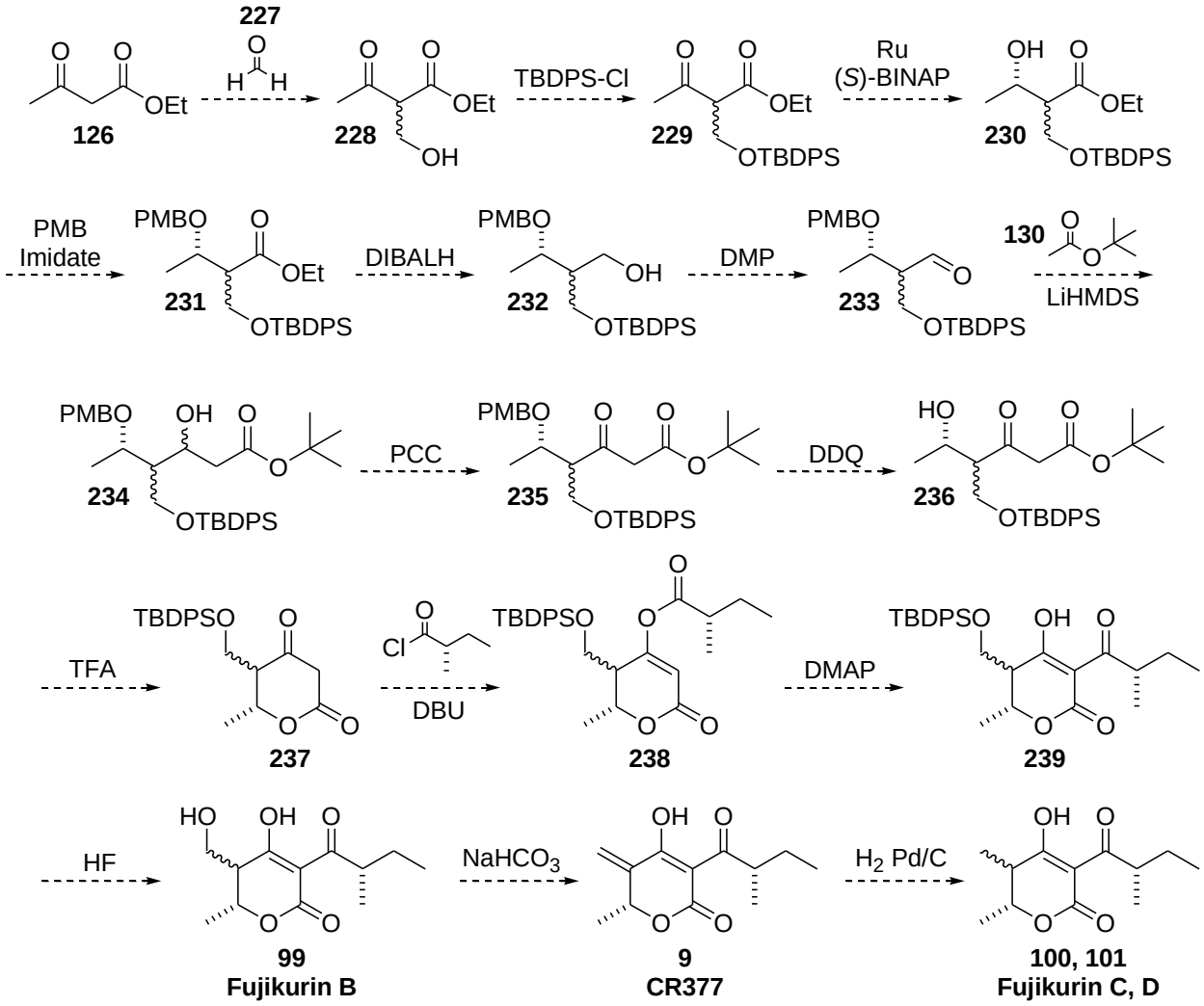



***Figure 2.31:*** *Revised synthetic approach towards CR377* (**9**) *and related fujikurin natural products*

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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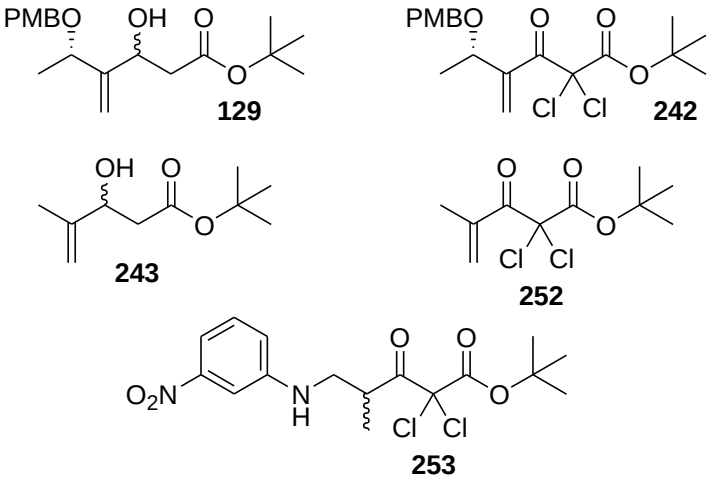
# Chapter Three

# 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*-methoxybenzylidine 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 $CH_2Cl_2$ 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 α-epimerisation[17] or β-elimination[18] side-products and intermediate decompositions.[15]

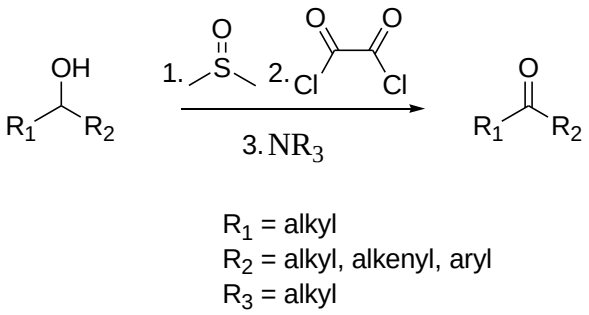



***Figure 3.1:*** *Outline for the generic Swern oxidation*

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 dimethylchlorosulfonium ion. Addition of the alcohol then results in reaction with the dimethylchlorosulfonium 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]

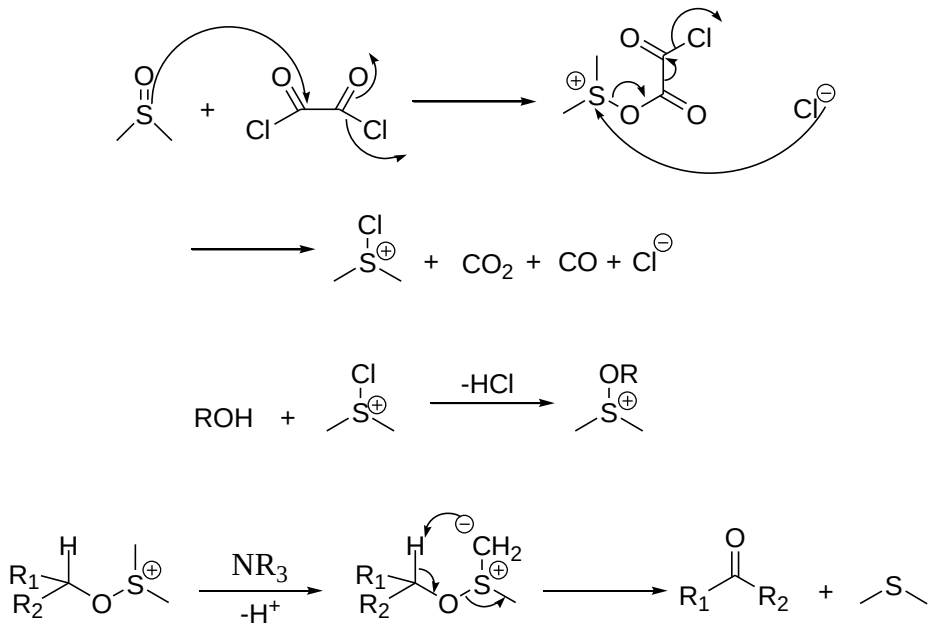
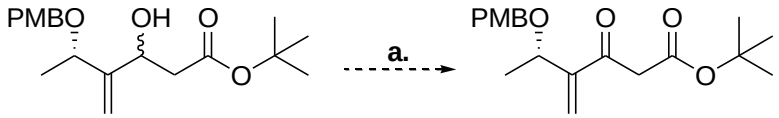



***Figure 3.2:*** *Swern oxidation mechanism*

### 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[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.




**129** **128**

**Reagents and Conditions: a.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (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**).[20] 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.

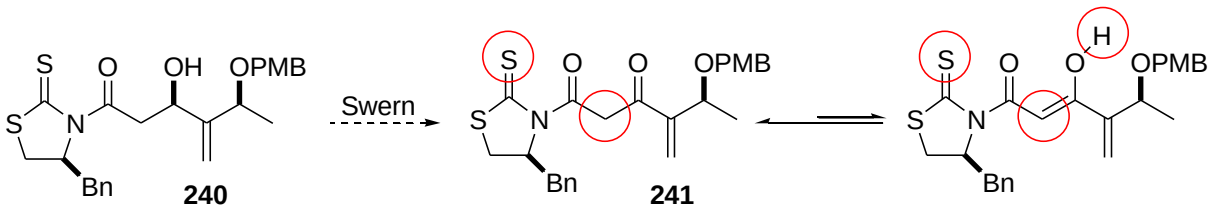
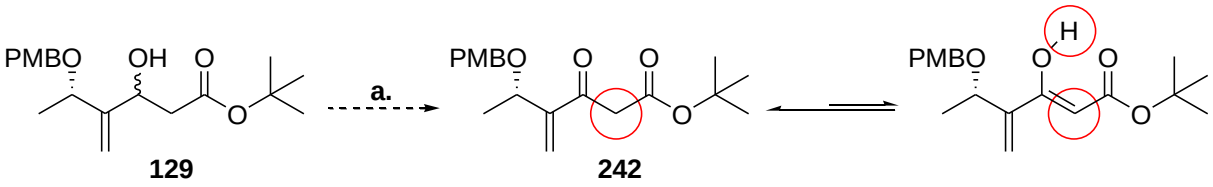



***Figure 3.3:*** *Swern Oxidation of β-hydroxy amide* **240** *indicating the NMR inconsistencies observed for the predicted β-keto amide* **241** *product*

In the initial study,[20] 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 thiazoldine 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).




**129** **242**

**Reagents and Conditions: a.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (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 spectras 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 C*H*OH 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 C*H*OH 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.

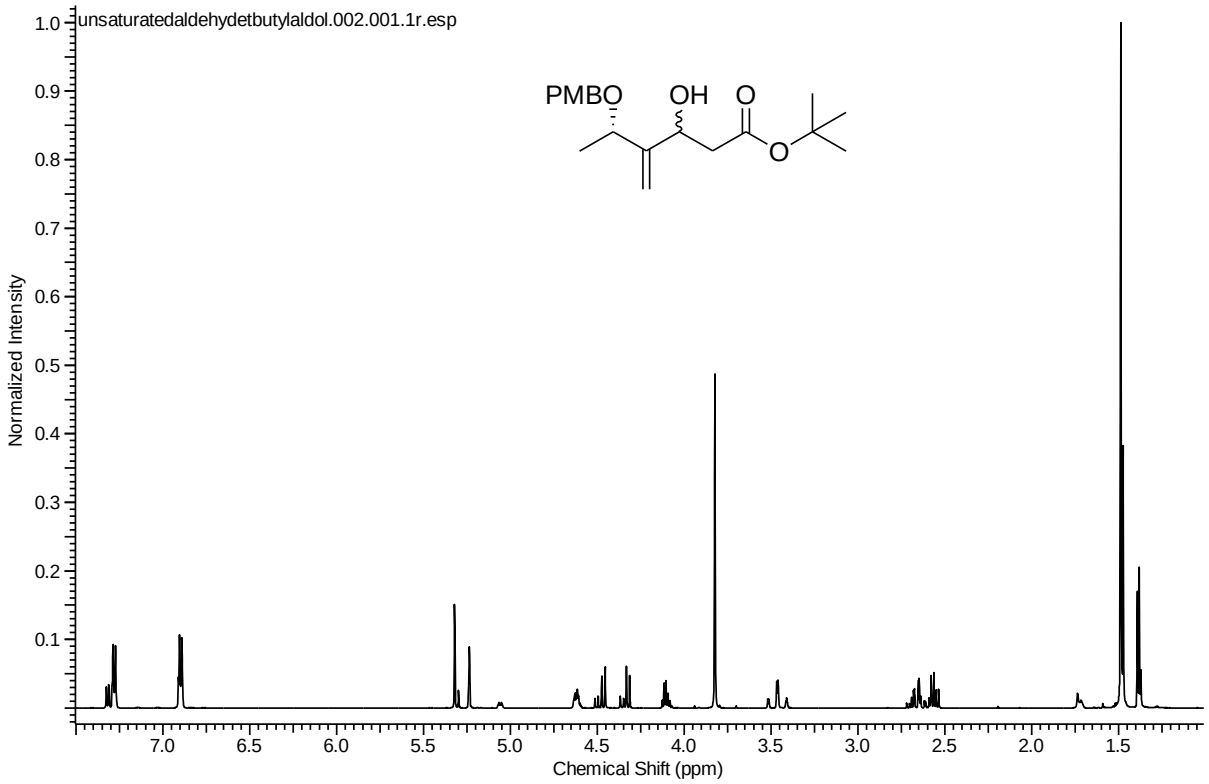



***Figure 3.4:*** *The $^{1}H$ NMR spectrum for β-hydroxy ester* **129** *in $CDCl_3$*

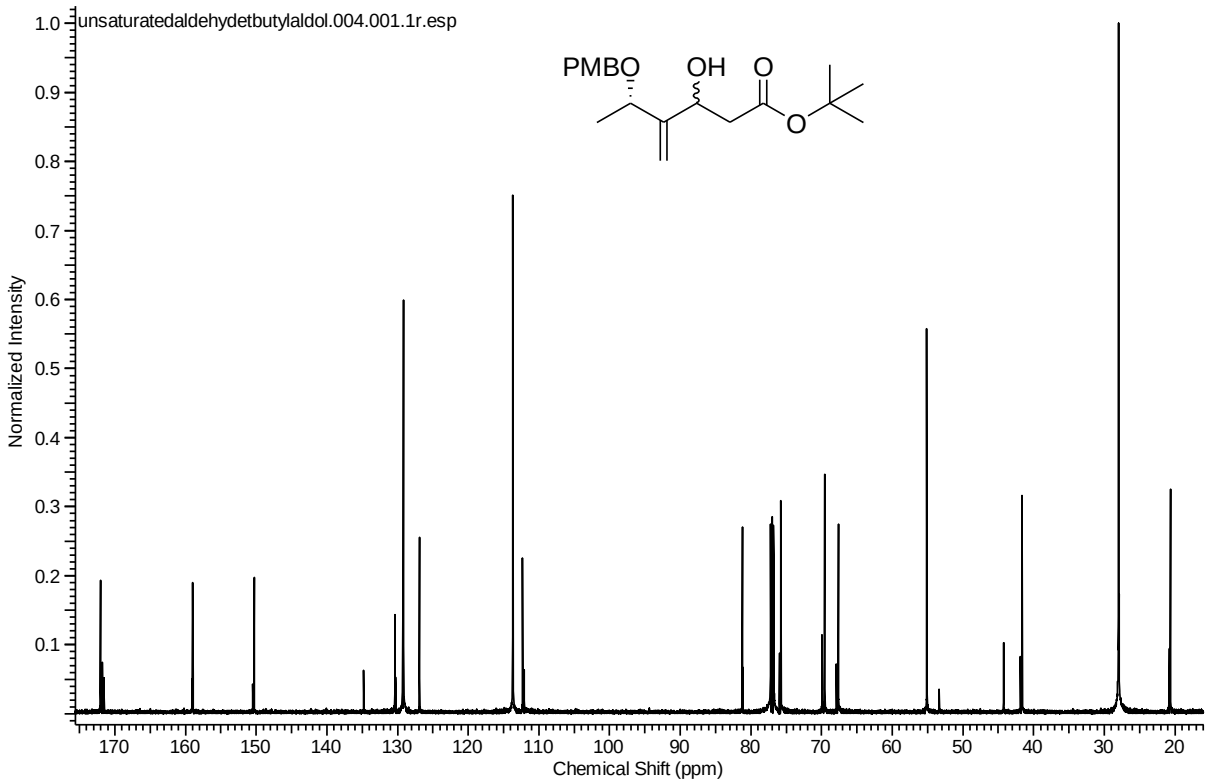
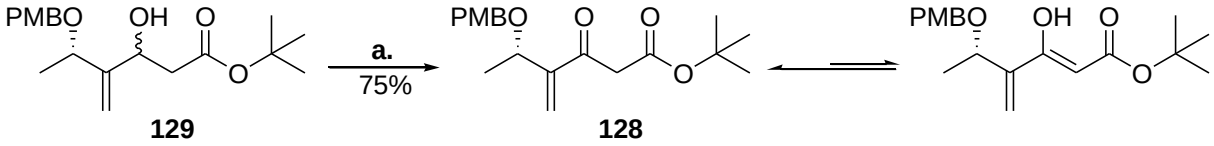



***Figure 3.5:*** *The $^{13}C$ NMR spectrum for β-hydroxy ester* **129** *in $CDCl_3$*

This required oxidative conversion to β-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 β-hydroxy ester **129** (Scheme 3.3).[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.




**129** **128**

**Reagents and Conditions: a.** PCC (2.0eq), $CH_2Cl_2$, celite, RT for 4 hours.

***Scheme 3.3:*** *Successful oxidation of β-hydroxy ester* **129** *using PCC*

The NMR spectra of the oxidised β-keto ester **128** product shown in Figures 3.6 and 3.7, the absence of the C*H*OH hydrogen signal is immediately apparent. The diastereotopic methylene ($CH_2$) protons have been shifted downfield to δ 3.65 as a result of the oxidised hydroxyl moiety and now appear as doublet of doublets. Their integration shows the predominance of the β-keto tautomer of **128**. The vinylic protons have also been shifted downfield to δ 6.15 and δ 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 δ 12.35 and δ 6.00 are indicative of enol and vinylic protons. The singlet at δ 5.28 is due to methylene chloride residual solvent. The main difference between the two carbon spectrums is the resonance at δ 193 indicative of the newly oxidised ketone carbon, followed by the apparent loss of a *C*-OH signal in the δ 60-80 region.

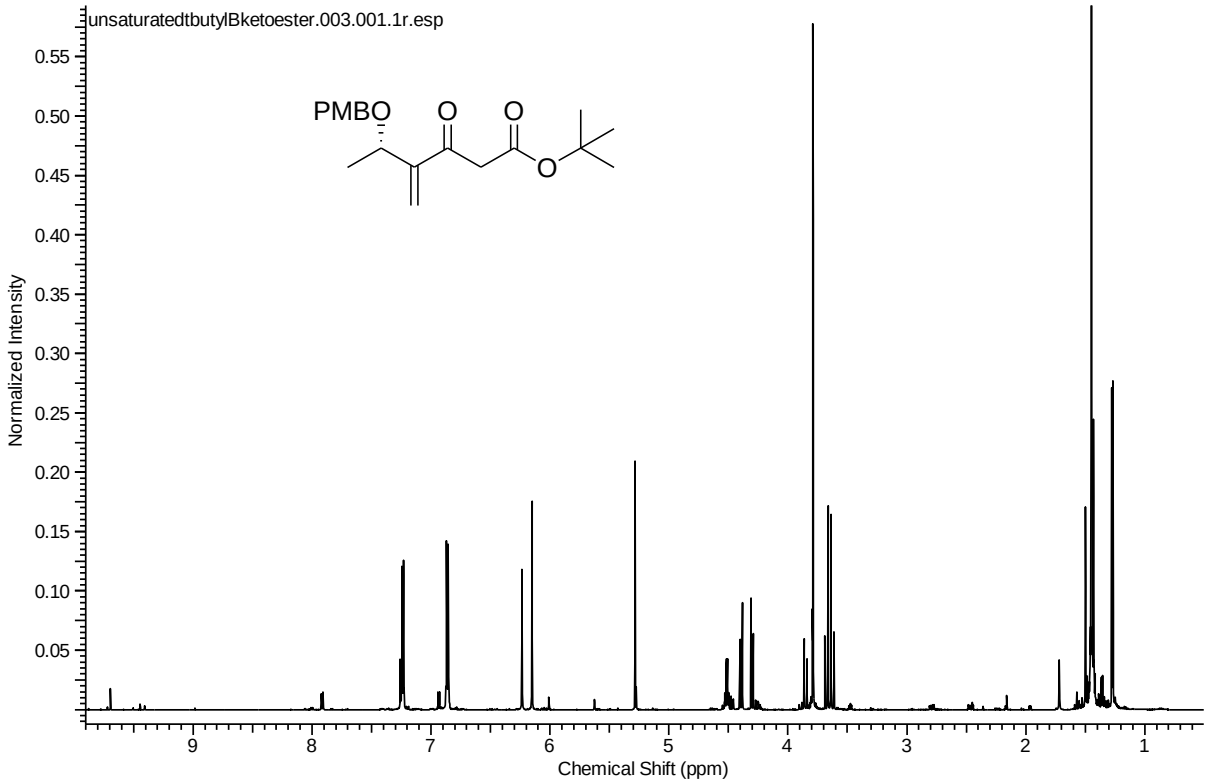



***Figure 3.6:*** *The $^{1}H$ NMR spectrum of β-keto ester* **128** *in $CDCl_3$*

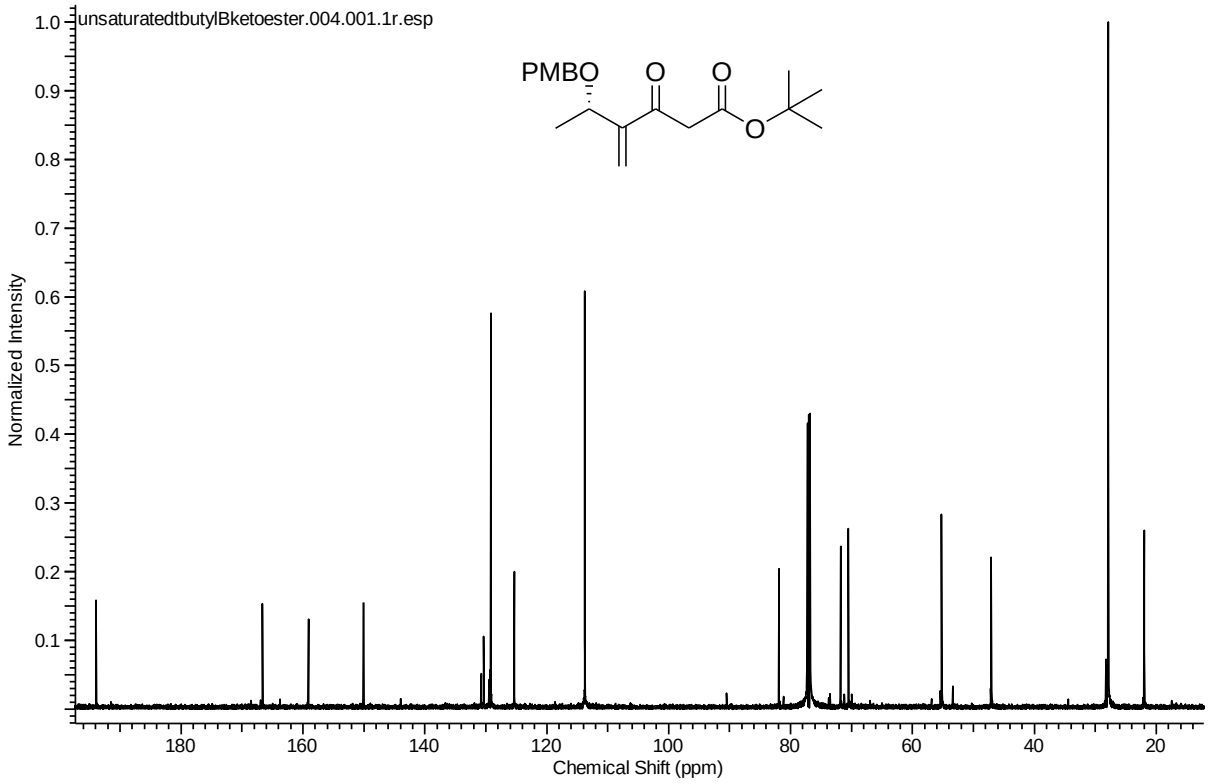
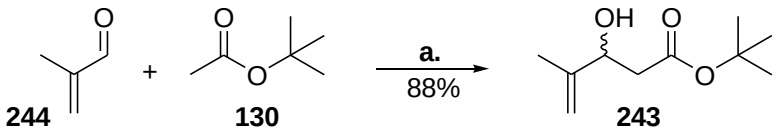



***Figure 3.7:*** *The $^{13}C$ NMR spectrum of β-keto ester* **128** *in $CDCl_3$*

## 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 endeavour 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[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.

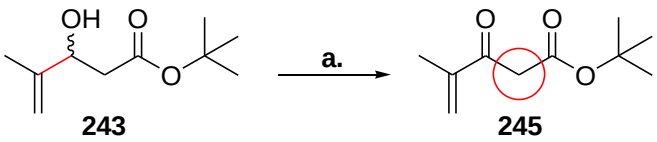



**Reagents and Conditions: a.** LiHMDS (1.2eq), THF, -78°C, 2 hours, then warmed to RT.

***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 $CH_2Cl_2$ at -78°C. The mixture was stirred for 30 minutes to ensure complete formation of the alkoxysulfonium 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.




**243** **245**

**Reagents and Conditions: a.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (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 $^{13}C$ 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.

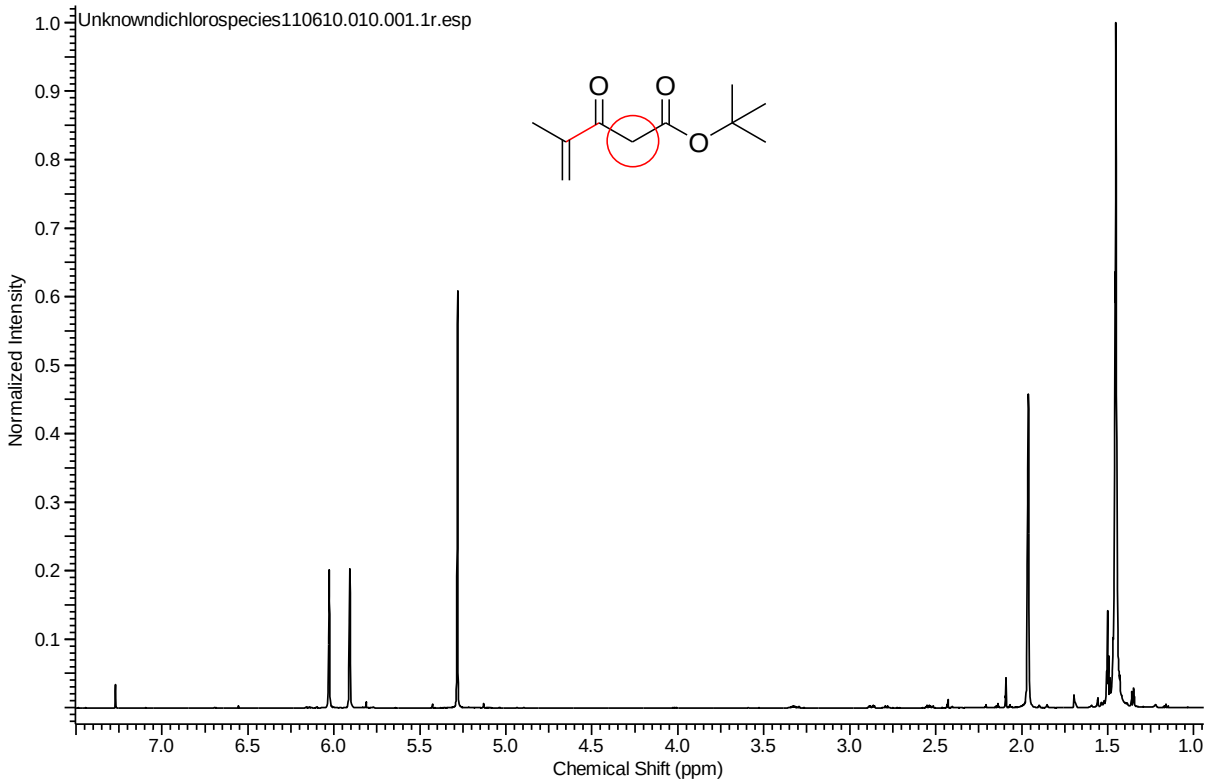



***Figure 3.8:*** *The $^{1}H$ NMR spectrum of unknown model oxidised product* **245** *in $CDCl_3$*

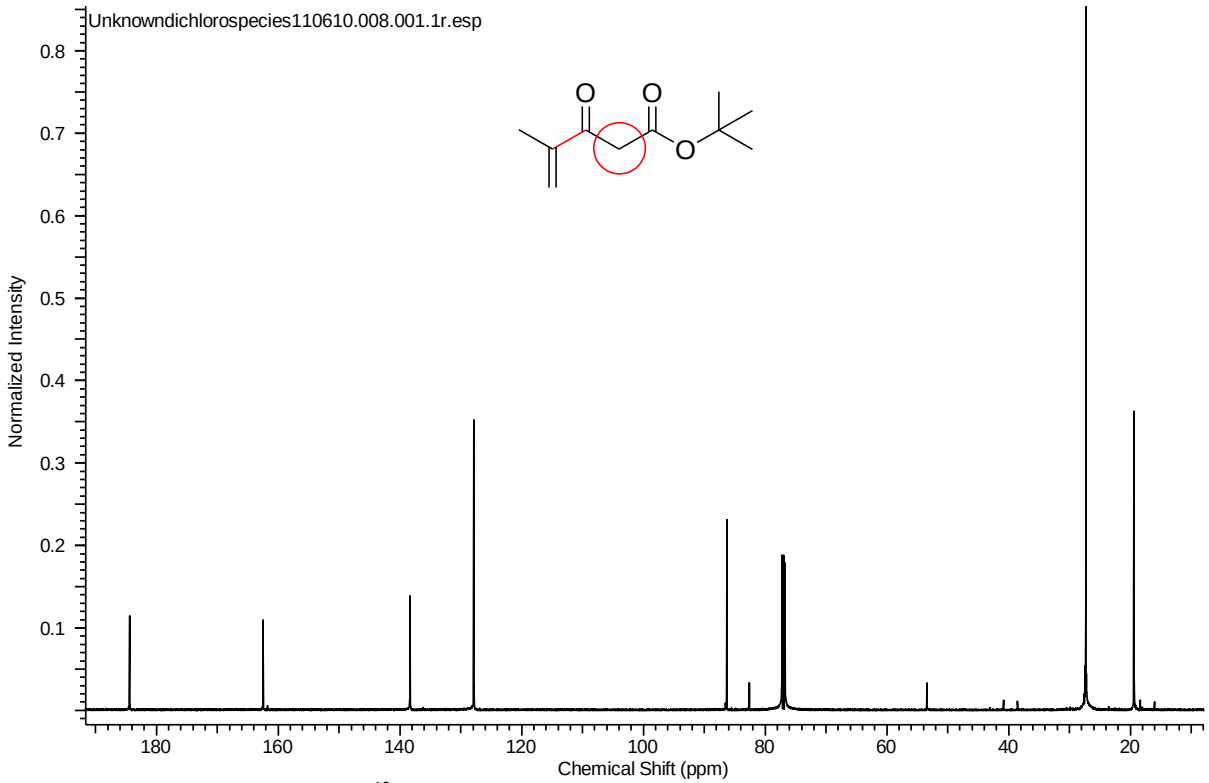
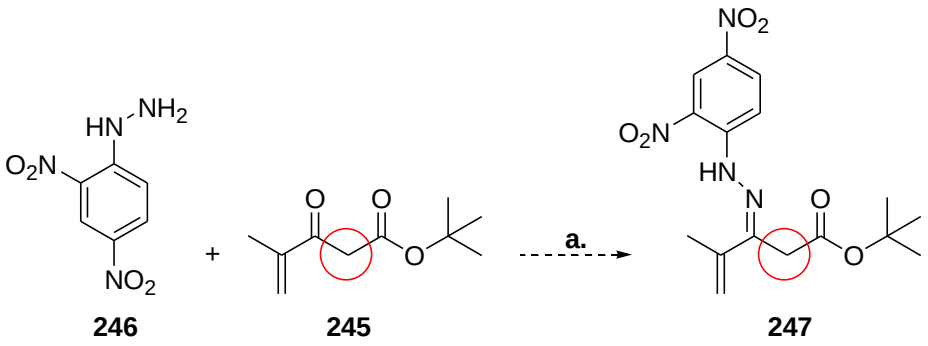



***Figure 3.9:*** *The $^{13}C$ NMR spectrum of unknown model oxidised product* **245** *in $CDCl_3$*

### 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).[23] 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*[24] the unknown oxidation product **245** was dissolved in ethanol and was added to a premade solution of 2,4-dinitrophenylhydrazine (**246**), ethanol and $H_2SO_4$ 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.




**Reagents and conditions: a.** Dinitrophenylhydrazine (**246**) (1.3eq), EtOH, $H_2SO_4$ (3 drops), reflux for 1 hour.

***Scheme 3.6:*** *Attempted synthesis of the predicted dinitrophenylhydrazone* **247** *derivative*

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.

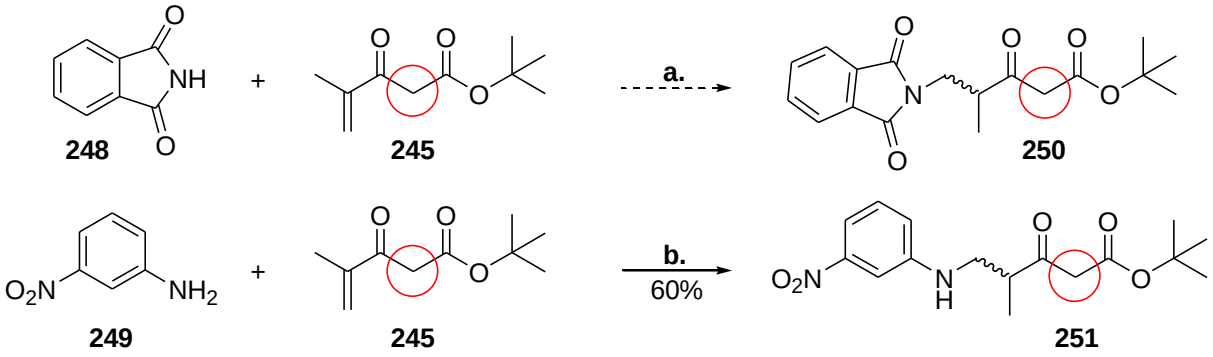
From spectroscopic analysis, it was believed that the unknown oxidation product **245** possessed an α,β-unsaturated carbonyl functionality, which through resonance stabilisation could promote 1,4-conjugate addition over 1,2-direct addition. Although there are numerous potential nucleophiles that will 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.[25] Prior to this most of the documented literature for aza-michael addition was dedicated to the development of β-amino acids.[26] Lithium amides, universally known as strong bases have been recently recognised as suitable nucleophiles for aza-michael additions.[27,28]

Following the procedure outlined by Hawkins' *et al*,[27] 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 ultilised 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 δ 6.87-7.52, the amine signal at δ 4.45, the methyl doublet at δ 1.37 and the new coupled protons at δ 3.32 and δ 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 δ 197 and δ 161, and only the six $sp^2$ carbons obtained from the aniline addition also confirm the loss of the unsaturated methylene functionality.




**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**

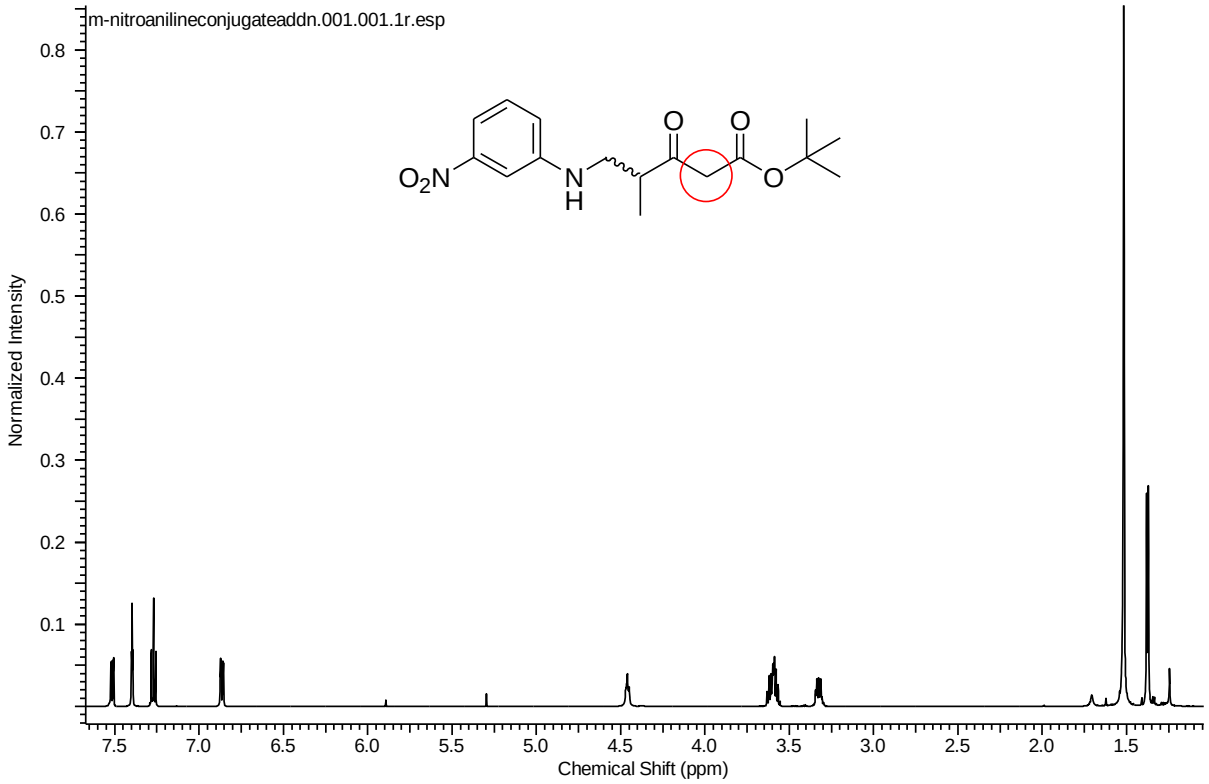



***Figure 3.10:*** *The $^{1}H$ NMR spectrum of m-nitroaniline conjugate addition product* **251** *in $CDCl_3$*

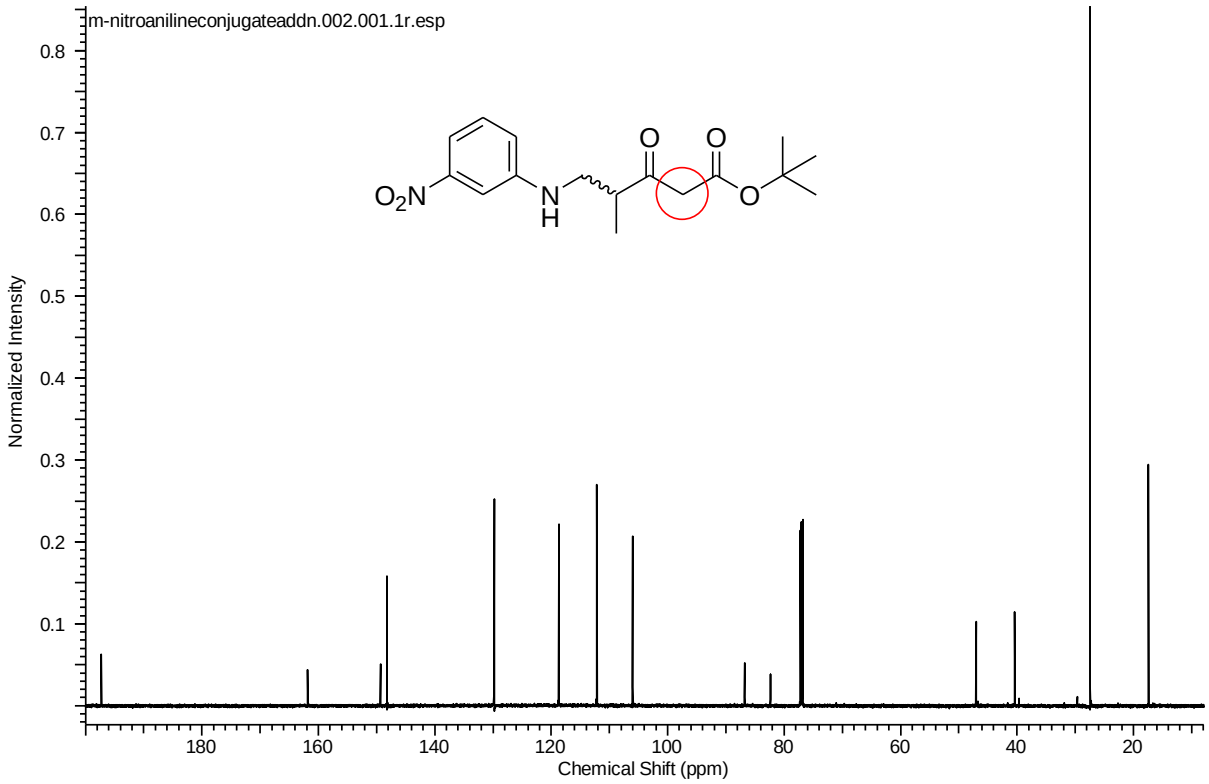
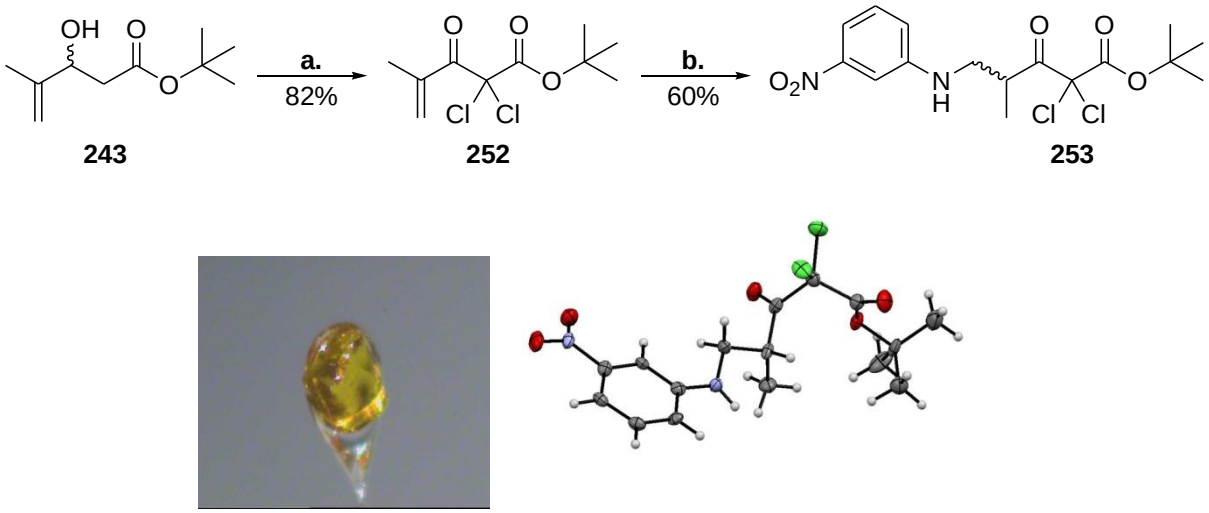



***Figure 3.11:*** *The $^{13}C$ NMR spectrum of m-nitroaniline conjugate addition product* **251** *in $CDCl_3$*

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 $C_{16}H_{20}Cl_2N_2O_5$ 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), $CH_2Cl_2$, $NEt_3$ (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 Leenay[29] 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

proportion of enol form is present. Both Yang *et al*[30] and Feldman *et al*[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.

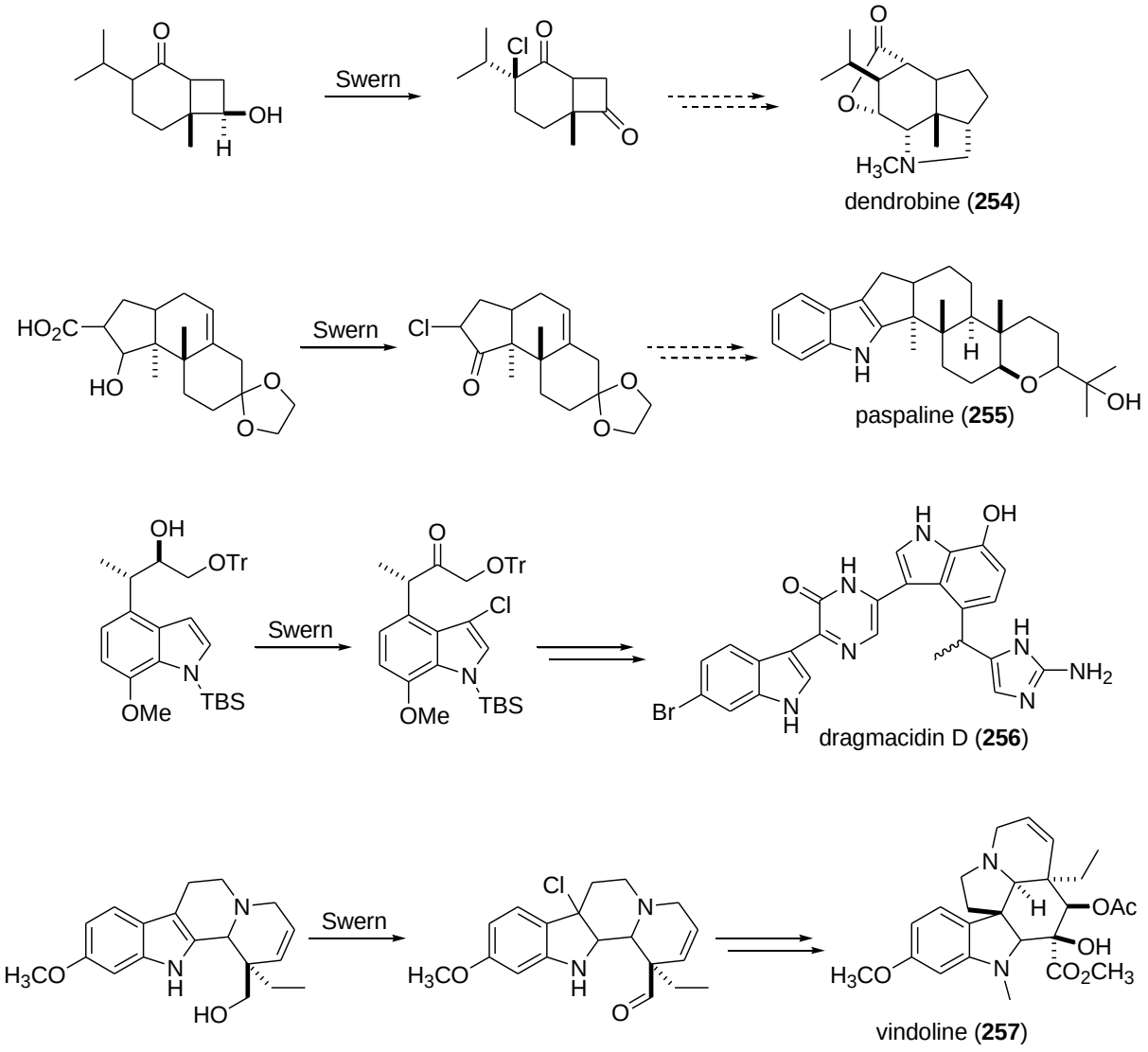



***Figure 3.12:*** *Reported electrophilic chlorinations during Swern oxidations approaches towards natural products dendrobine* (**254**)*, pasapaline* (**255**)*, dragmacidin D* (**256**) *and vindoline* (**257**)

## 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[32,33] and or electrophilic[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 α-position of ketones,[29,34,35] electrophilic aromatic substitution of phenols[36] and other electron-rich aromatics, such as phenyl ethers,[37] anilines and indoles[30,31] (Figure 3.13).

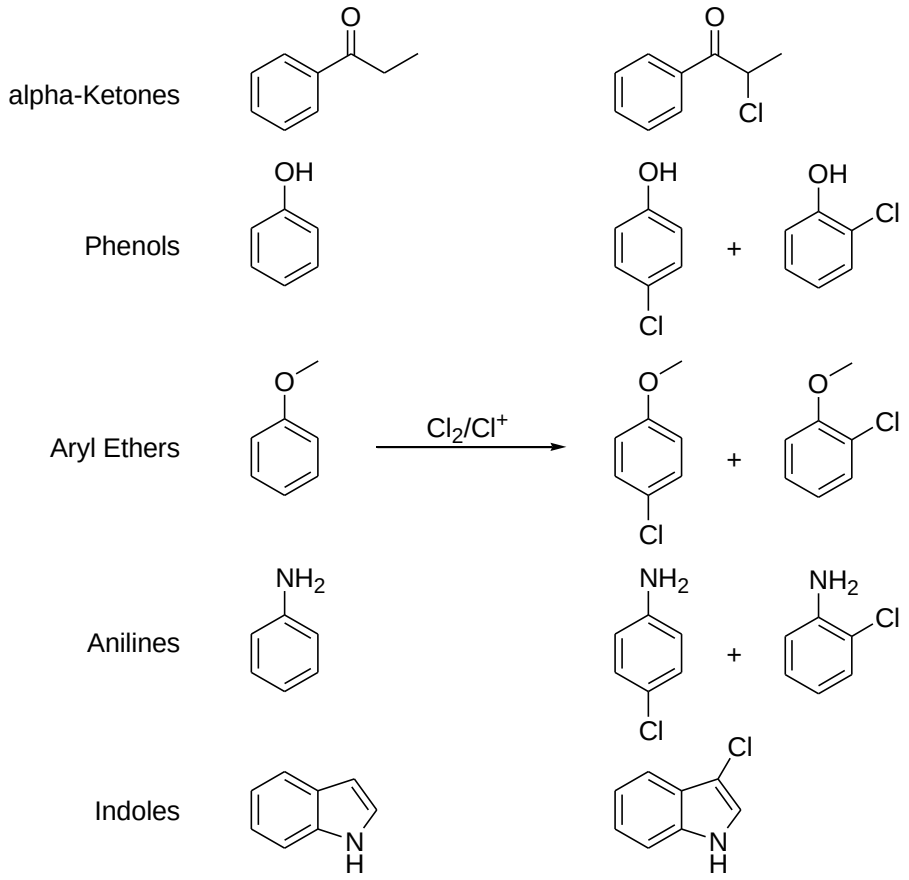



***Figure 3.13:*** *Known electrophilic chlorine addition reactions*

### 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]

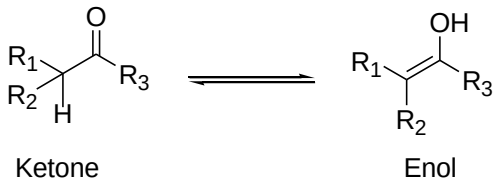



***Figure 3.14:*** *The tautomerism between ketone and enol tautomers*

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.

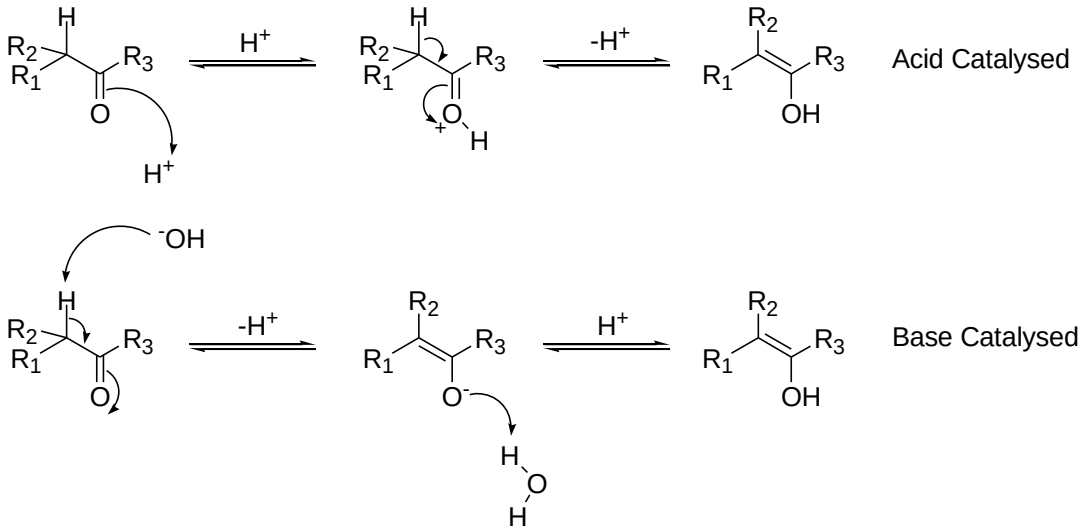



***Figure 3.15:*** *Interconversion between ketone and enol tautomers in acidic and basic conditions*

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.[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.

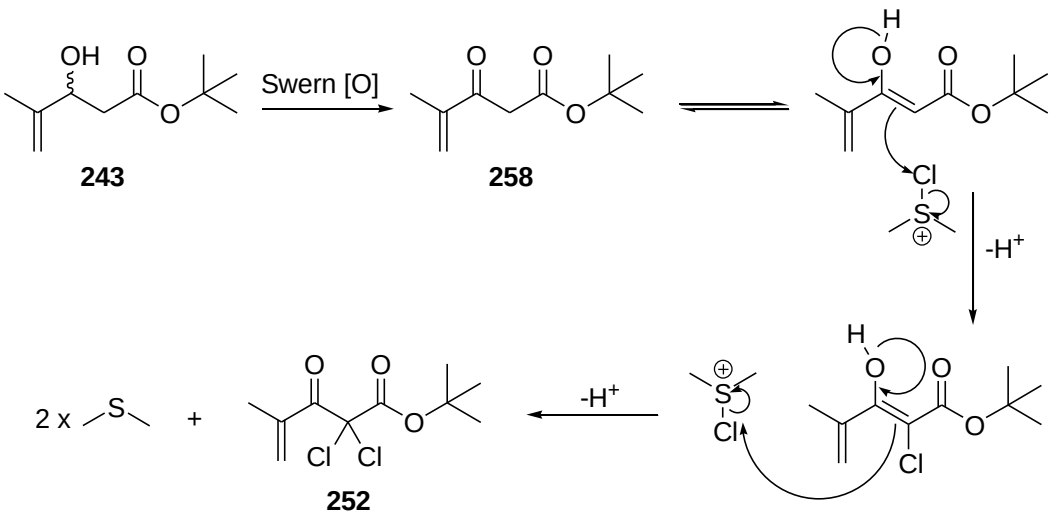



***Figure 3.16:*** *Proposed mechanism for the formation of the oxidised dichlorinated product* **252**

Intriguingly, this proposed formation of the α,α-dichlorinated product **252** requires at least three equivalents of the dimethylsulfonium 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 above[41] (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.

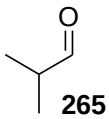
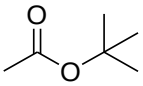
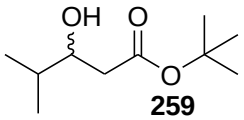
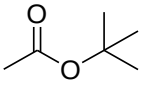
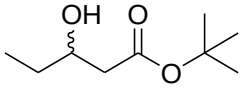
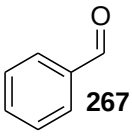
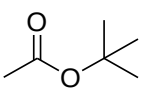
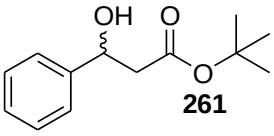
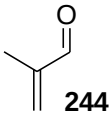
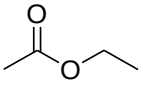
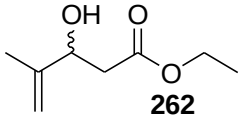
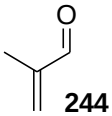
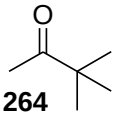
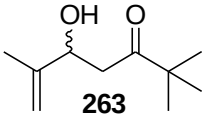
| Aldehyde | Carbonyl Derivative | Reagents | Product | Yield % |
|---|---|---|---|---|
|  **265** |  **130** | LiHMDS (1.2eq)/THF -78°C – 45mins, warm to RT. |  **259** | 93 |
|  **266** |  **130** | LiHMDS (1.2eq)/THF -78°C – 45mins, warm to RT. |  **260** | 95 |
|  **267** |  **130** | LiHMDS (1.2eq)/THF -78°C – 45mins, warm to RT. |  **261** | 90 |
|  **244** |  **119** | LiHMDS (1.2eq)/THF -78°C – 45mins, warm to RT. |  **262** | 80 |
|  **244** |  **264** | LiHMDS (1.2eq)/THF -78°C – 45mins, warm to RT. |  **263** | 81 |

***Table 3.1:*** *Synthesis of a range of β-hydroxy carbonyl products* **259**-**263**

### 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 $CH_2Cl_2$) 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 alkoxysulfonium 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).

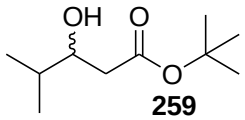
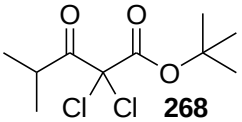
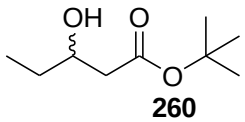
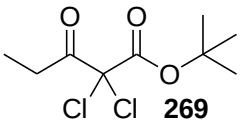
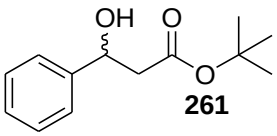
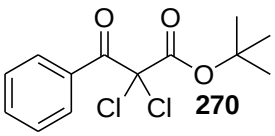
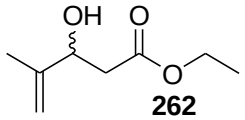
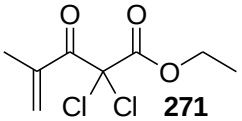
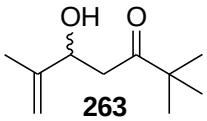
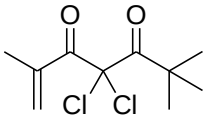
| Aldol Product | Reagents | Product | Yield % |
|---|---|---|---|
|  **259** | DMSO (3eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6eq), -78°C to RT, 12hrs |  **268** | 70 |
|  **260** | DMSO (3eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6eq), -78°C to RT, 15hrs |  **269** | 78 |
|  **261** | DMSO (3eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6eq), -78°C to RT, 2hrs |  **270** | 85 |
|  **262** | DMSO (3eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6eq), -78°C to RT, 2hrs |  **271** | 89 |
|  **263** | DMSO (3eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6eq), -78°C to RT, 6hrs |  **272** | 45 |

***Table 3.2:*** *Swern oxidation of aldol 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.

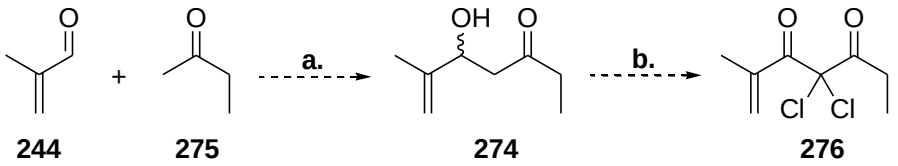
It was also noted that the unsaturated β-hydroxy esters **243**, **261** and **262** gave their respective electrophilic chlorination products **252**, **270** and **271** in excellent yields within the normal Swern oxidation reaction timeframe of one to three hours. The saturated isobutyl and propyl 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.




**244** **275** **274** **276**

**Reagents and Conditions: a.** LiHMDS (1.2eq), THF, -78°C, 2 hours, then warmed to RT. **b.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hours.

***Scheme 3.9:*** *Swern oxidation of β-hydroxy ethyl ketone compound* **274** *to the corresponding dichloroinated dicarbonyl product* **276**

## 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-dichloroinated-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),[3,41] acetic anhydrides,[42,43] sulfur trioxide pyridine complex ($SO_3$.Py)[44] and phosphorus pentoxide.[45] 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.

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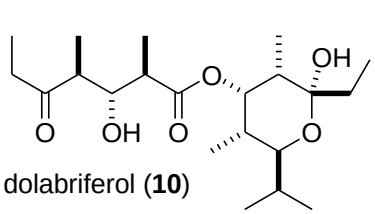
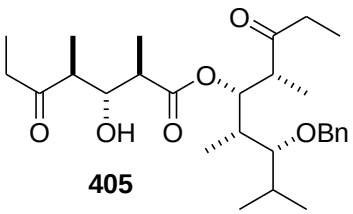
# Chapter Four

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

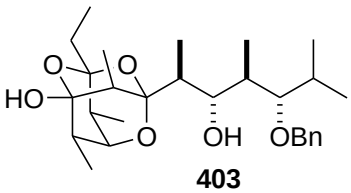
This chapter describes the total synthesis of marine polypropionate dolabiferol (**10**) employing a retro-Claisen rearrangement to construct dolabriferol's (**10**) unique non-contiguous backbone. Key moments of this total synthesis include; the synthesis of linear precursor **398** from the two key 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 $C_4$-$C_6$ and $C_{10}$-$C_{13}$ stereochemical arrays.



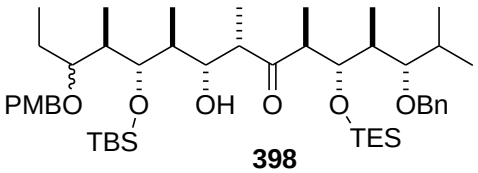
dolabriferol (**10**)



**405**



**403**



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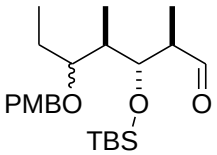
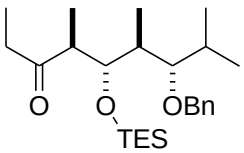
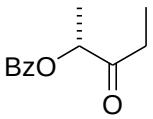


**377**



**363**



**82**

## 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).[2] 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.[1]


***Figure 4.1:*** *Specimens of Dolabrifera dolabrifera*

In 1996, Ciavatta *et al*[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**).[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 coworkders[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: baconipyrones (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).

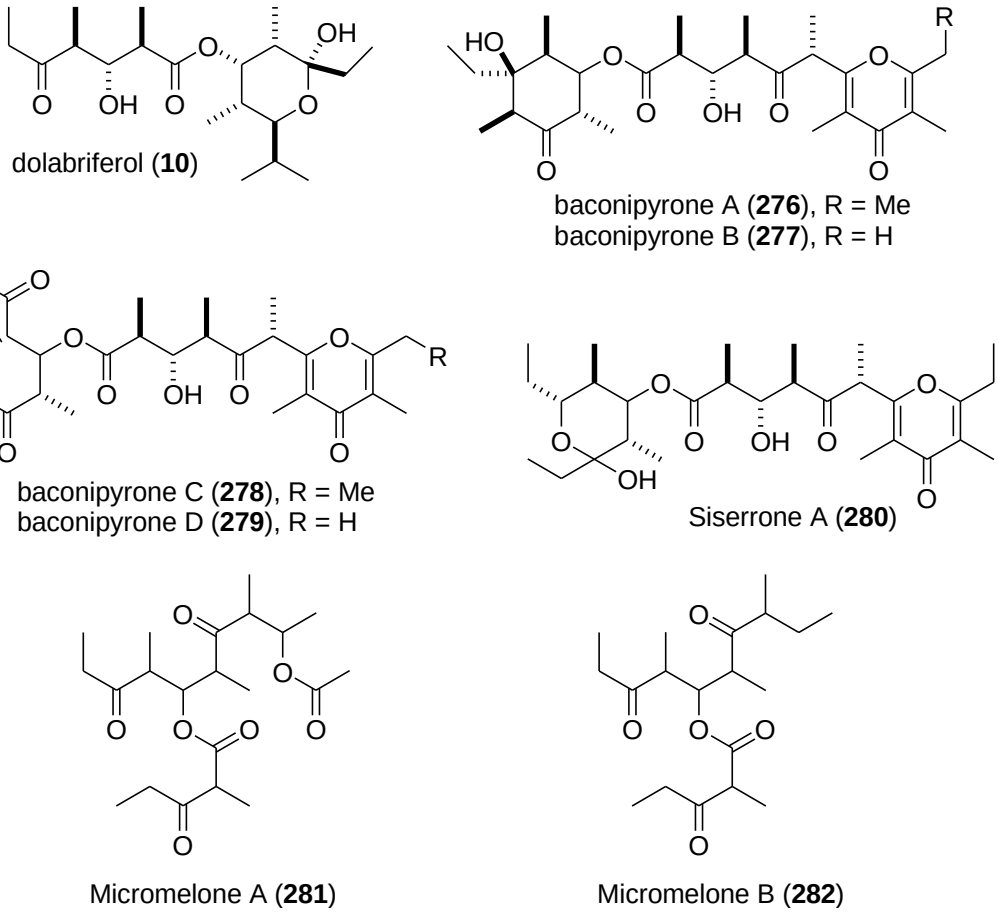



***Figure 4.2:*** *Dolabriferol* (**10**) *and other non-contiguous polypropionate natural products*

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**)[2,6] 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**).

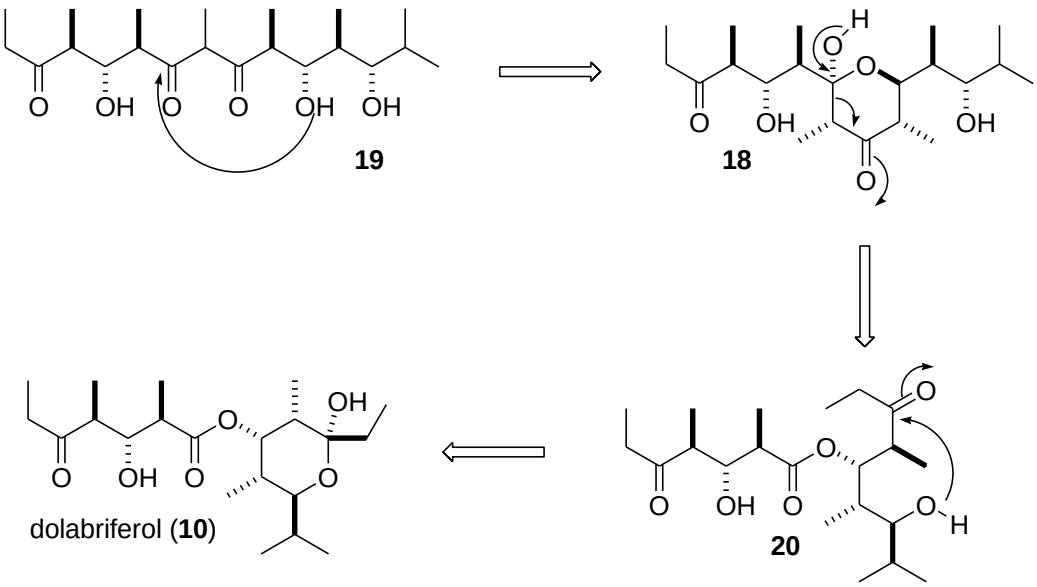



***Figure 4.3:*** *Proposed formation of dolabriferol* (**10**) *from a putative acyclic precursor*

## 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[2] 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*[8] 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.

Aside from Vogel's first total synthesis,[8] and prior to the total synthesis of dolabriferol (**10**) reported by Currie *et al*[9] in 2012 during our own studies, the most novel synthetic approach towards dolabriferol (**10**) was reported by Lister *et al*[10] 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*[11,12] has detailed a computational study of the reaction pathway towards dolabriferol (**10**) beginning with the proposed acyclic precursor compound.

The computational study used ROBIA[12], 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).[11]

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.

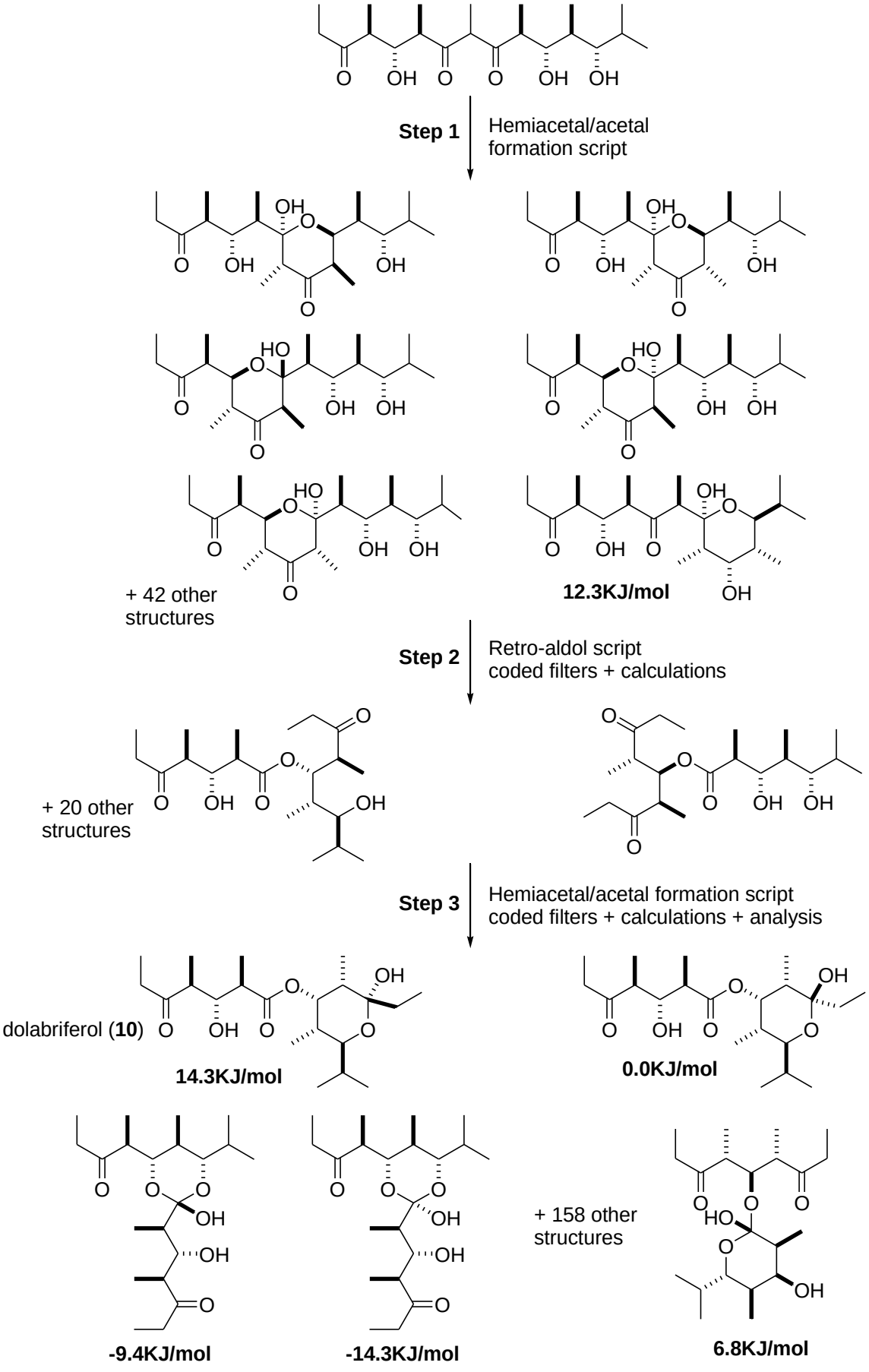



***Figure 4.4:*** *Goodman's three step ROBIA calculation results from putative acyclic precursor*

### 4.2.3 Dias' Studies towards Direct Esterification

In 2003, Dias and co-workers[13] published their attempt towards the synthesis of dolabriferol (**10**). Their strategy was based on a direct esterfication 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**[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).[13] This oxidation based strategy displayed the challenges faced of alternating oxidation states of the oxygen substituents in dolabriferol (**10**) to synthetic chemists.

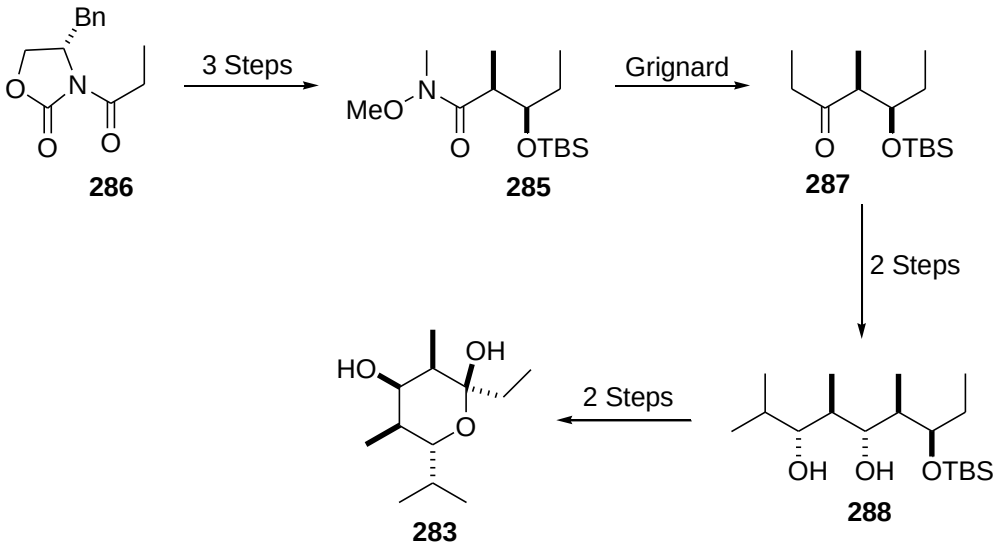



***Figure 4.5:*** *Dias' synthesis of lactol* **283** *fragment*

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**[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[15] revealed that

exhaustive attempts to couple intermediates **283** and **284** in an esterification reaction gave only decomposition products.

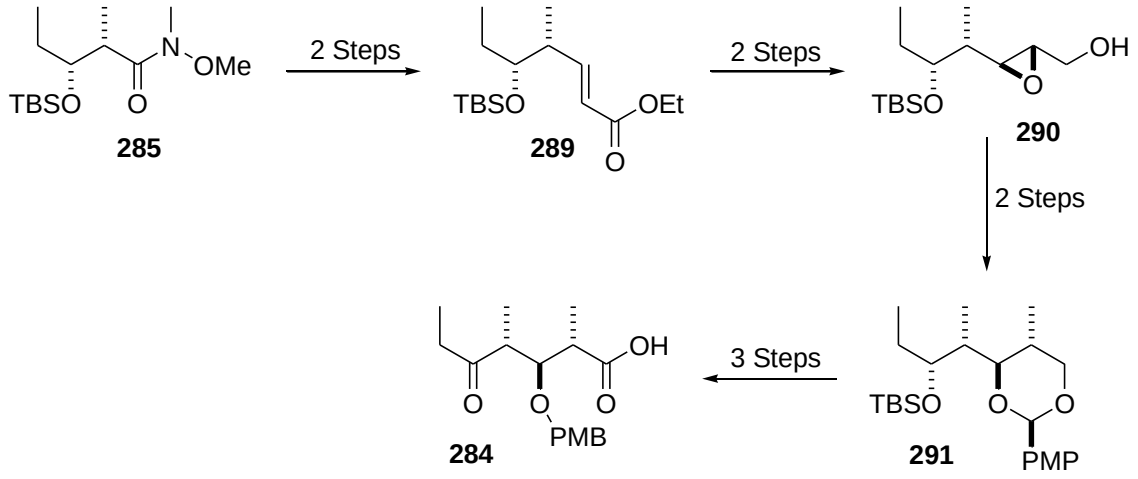



***Figure 4.6:*** *Dias' synthesis of acid* **284** *fragment*

### 4.2.4 Chênevert's Synthesis towards Direct Esterification

In 2003,[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**[17] could be employed to construct both the acid **293** and alcohol **294** fragments required for esterification (Figure 4.7).

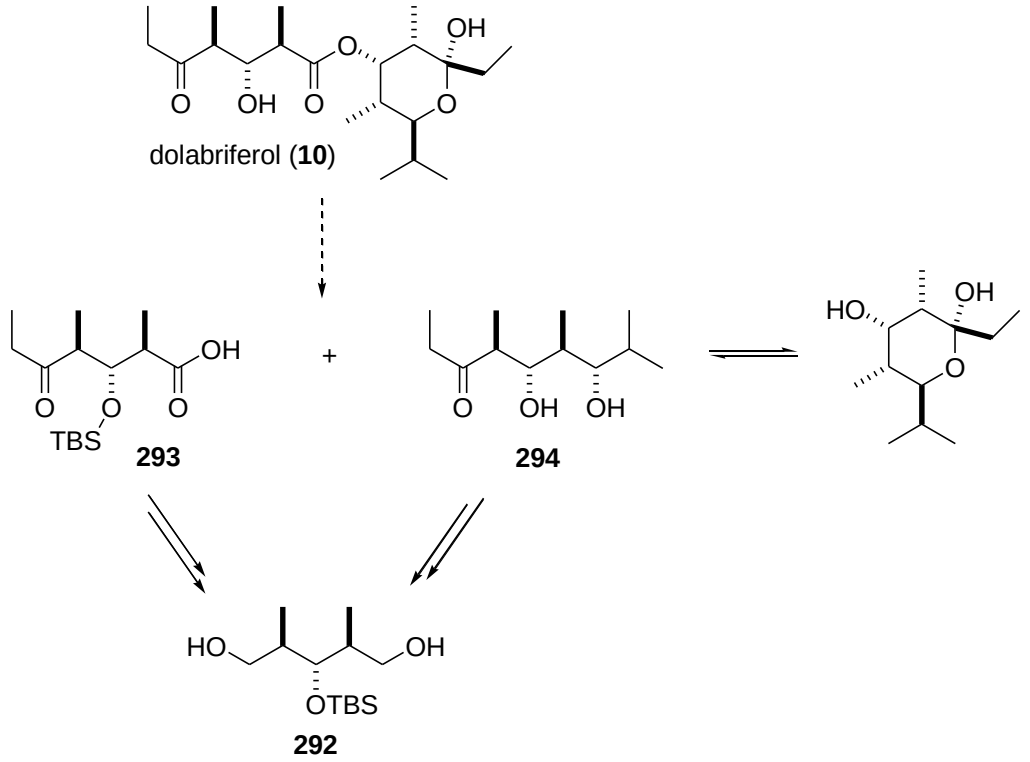



***Figure 4.7:*** *Chênevert's Synthesis Plan towards dolabriferol* (**10**) *from a common precursor* **292**

The synthesis of the keto-acid **293** (Figure 4.8)[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 $RuCl_3$ 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**.

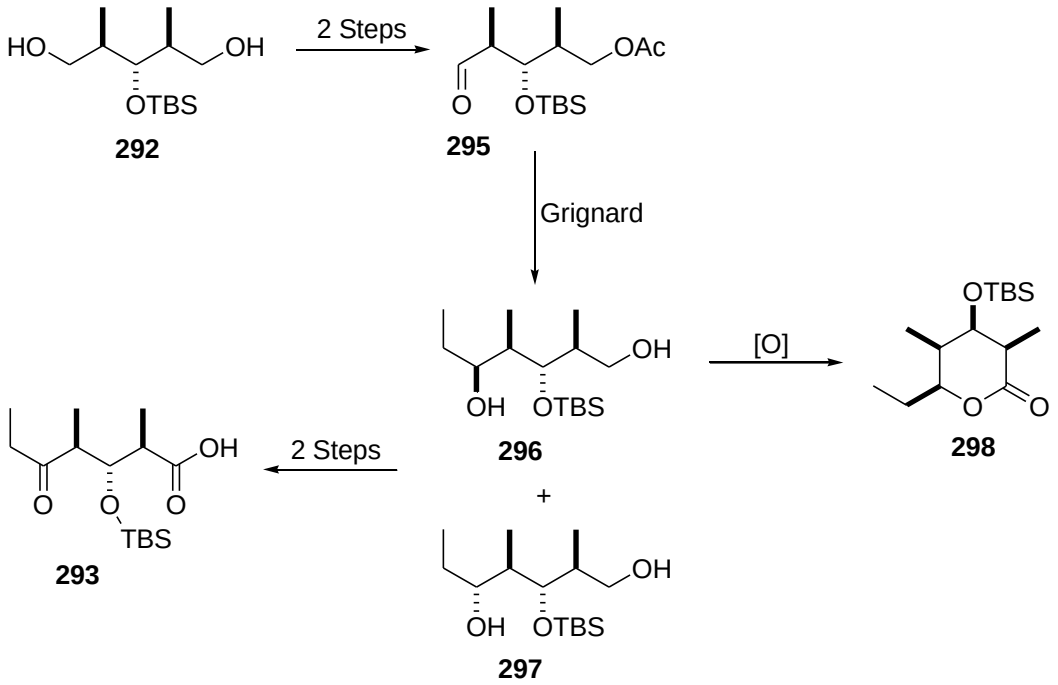



***Figure 4.8:*** *Chênevert's synthesis of the keto-acid fragment* **293**

Recently in 2007, Chênevert and co-workers[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 constucted from the same symmetrical diol **292**.

The synthesis of the lactol **294** moiety of dolabriferol (**10**) (Figure 4.9)[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 hemiactel **294** in 14 linear steps (18% overall yield).

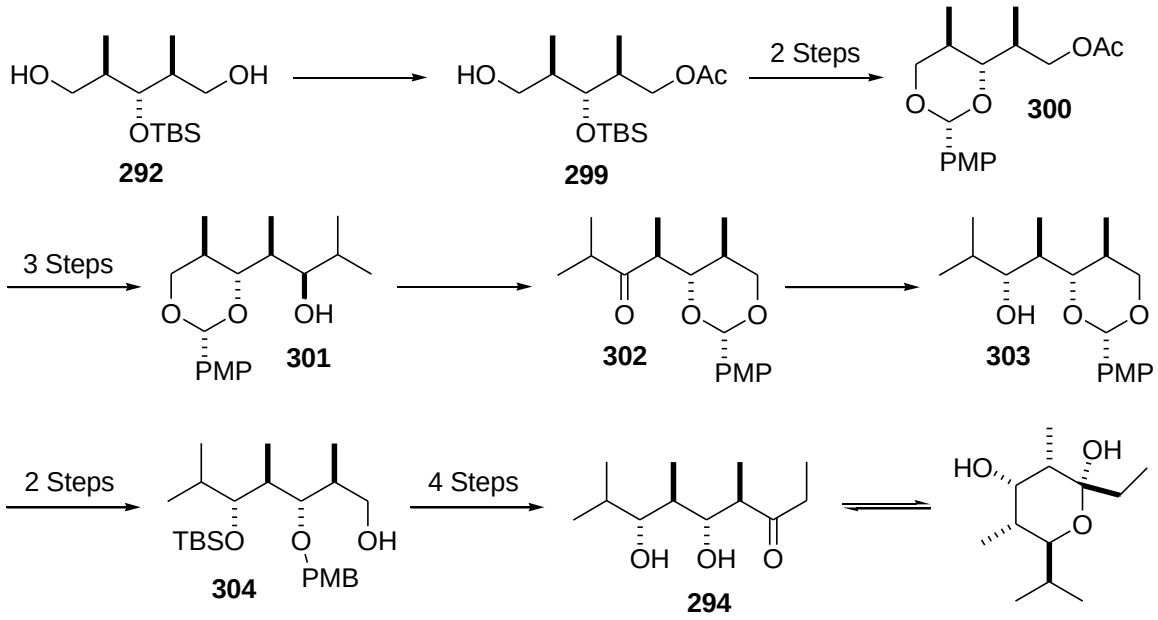



**Figure 4.9:** *Chênevert's synthesis of the lactol fragment* **294**

The two key fragments were to be ultilised in a direct esterfication reaction to complete the total synthesis of dolabriferol (**10**). Since the publication of this lactol fragment **294** in 2007[18] 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*.[13]

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

In 2010, Vogel and co-workers[8] 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*)-enoxysilanes through a $SO_2$ unpolung. As a result, Vogel *et al*[8] have developed a one-pot synthesis for the construction of α,β,γ-*syn-anti* stereotriads. This methodology was then extended to (*E*)-enoxysilanes to produce α,β,γ-*anti-anti* stereotriads (Figure 4.10), which were used to develop efficient syntheses of polypropionate subunits of dolabriferol (**10**).

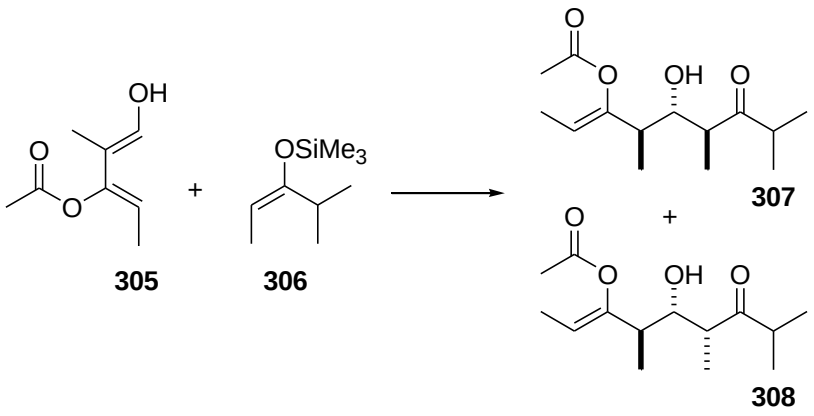



***Figure 4.10:*** *Vogel's one-pot synthesis for the construction of α,β,γ-anti-anti stereotriads* **306** and **307**

The reaction of diene **305** and (*E*)-silyl enol ether **306** with an excess of $SO_2$/toluene in the presence of $(CF_3SO_2)_2NH$, ($Tf_2NH$, 20 mol%) provided a mixture of silyl sulfinates, which were desulfinylated by $^{i}PrOH/MeCN/K_2CO_3$ 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 $Bu_3SnH$ and $Me_3AlCl$ 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.

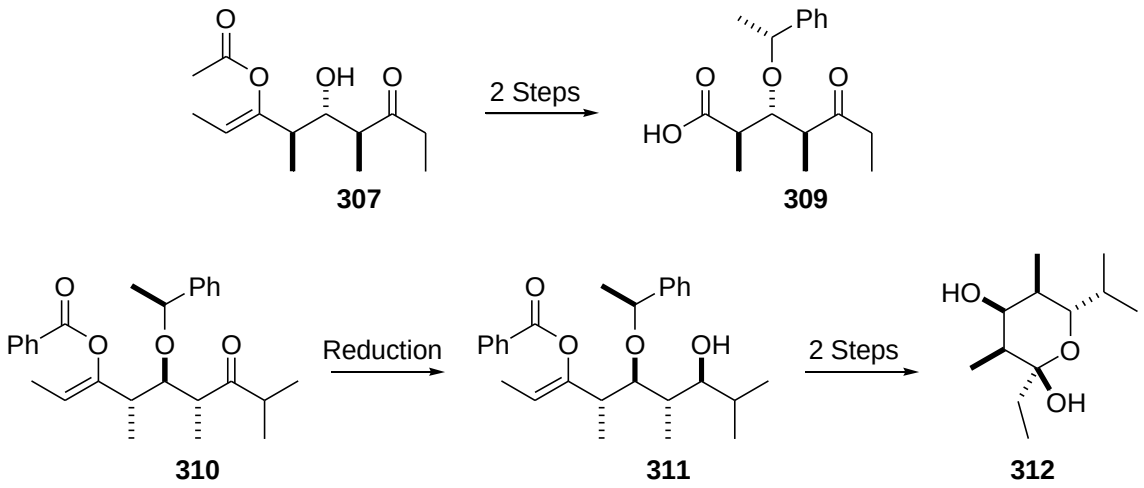



***Figure 4.11:*** *Preparation of the carboxylic* **309** *and hemiacetal* **312** *subunits*

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 $TiCl_4/CH_2Cl_2$ 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 $Bu_3SnOMe$ at 70°C followed by $KF/H_2O$ workup. Subsequent treatment with TFA removed the phenylethyl ether giving ketone **316** in 96% yield. Final deprotection and formation of the cyclic acetal ($Pd(OAc)_2$, $HNEt_2$, TPPTS) gave dolabriferol (**10**) in 99% yield (Figure 4.12), the $^1H$ 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*).

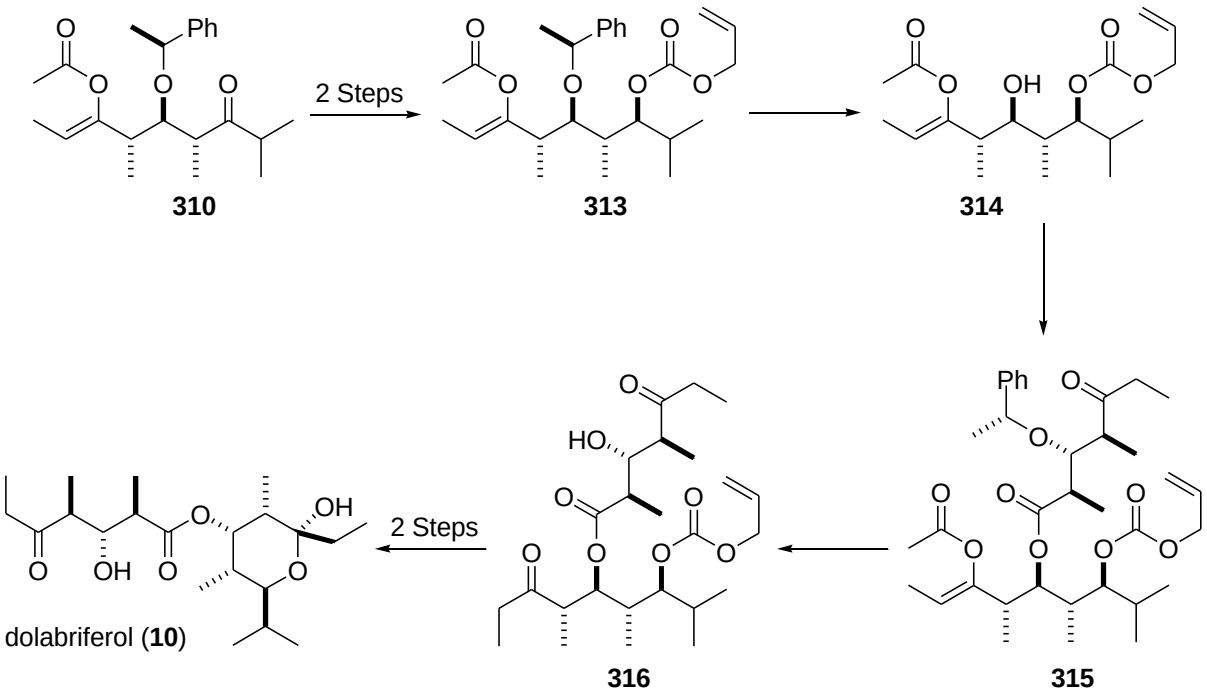



***Figure 4.12:*** *Vogel's total synthesis of dolabriferol* (**10**)

### 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[8] it had been proven difficult to implement, hence in 2006 Lister *et al*[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 $C_6$ 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 $C_3$ 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).

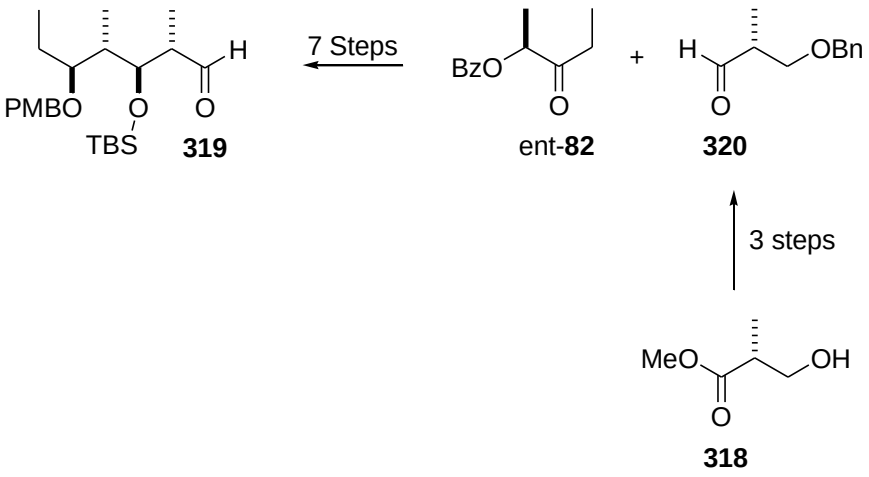



***Figure 4.13:*** *Lister's synthesis of the main aldehyde fragment* **319**

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**.

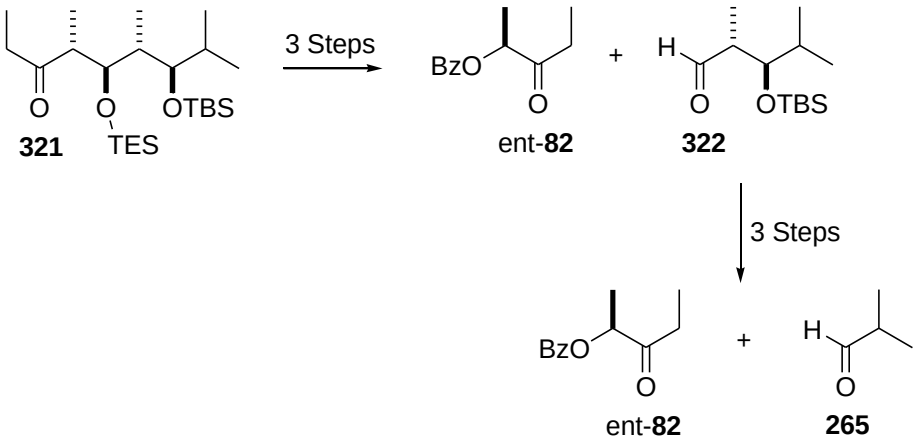



***Figure 4.14:*** *Lister's synthesis of the main ketone fragment* **321**

The two key aldol fragments were combined using a lithium-based aldol (LiHMDS) reaction. The $C_3$ oxidation state was altered to that of the natural product by PMB cleavage, followed by double Swern oxidation to give trione **323**. Both the $C_5$ and $C_{11}$ 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 $CH_3CN/CH_2Cl_2$) it was noted that the TBS-silyl ether could be cleaved, however isolation of spiroacetal **325** led Lister and coworkers[10] 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).

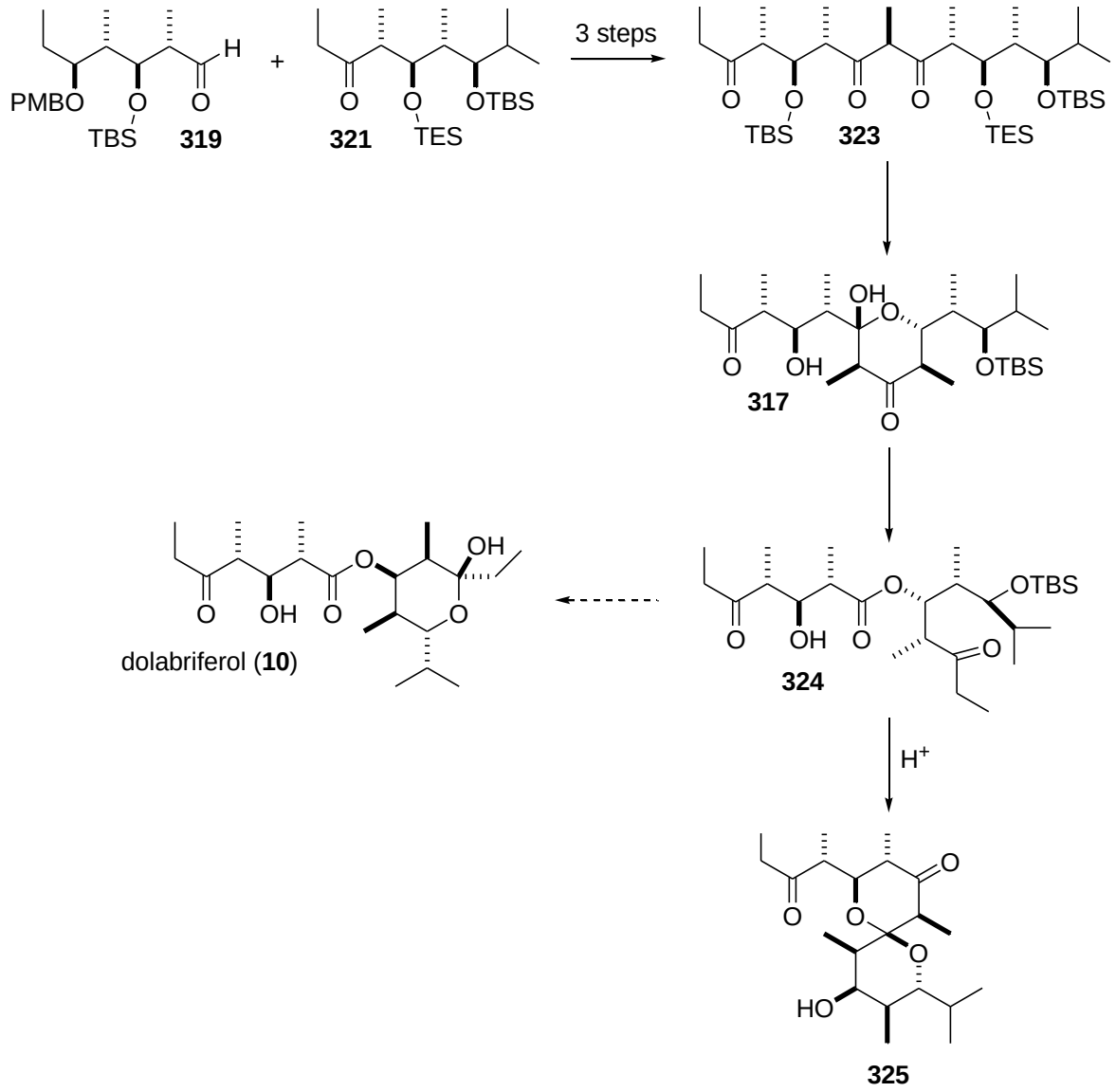



***Figure 4.15:*** *Lister's retro-Claisen approach towards dolabriferol* (**10**)

## 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*,[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 dolabriferol (**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 dolabriferol (**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 $C_5$ alcohol allowing double oxidation of the remaining $C_3$ and $C_7$ 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.

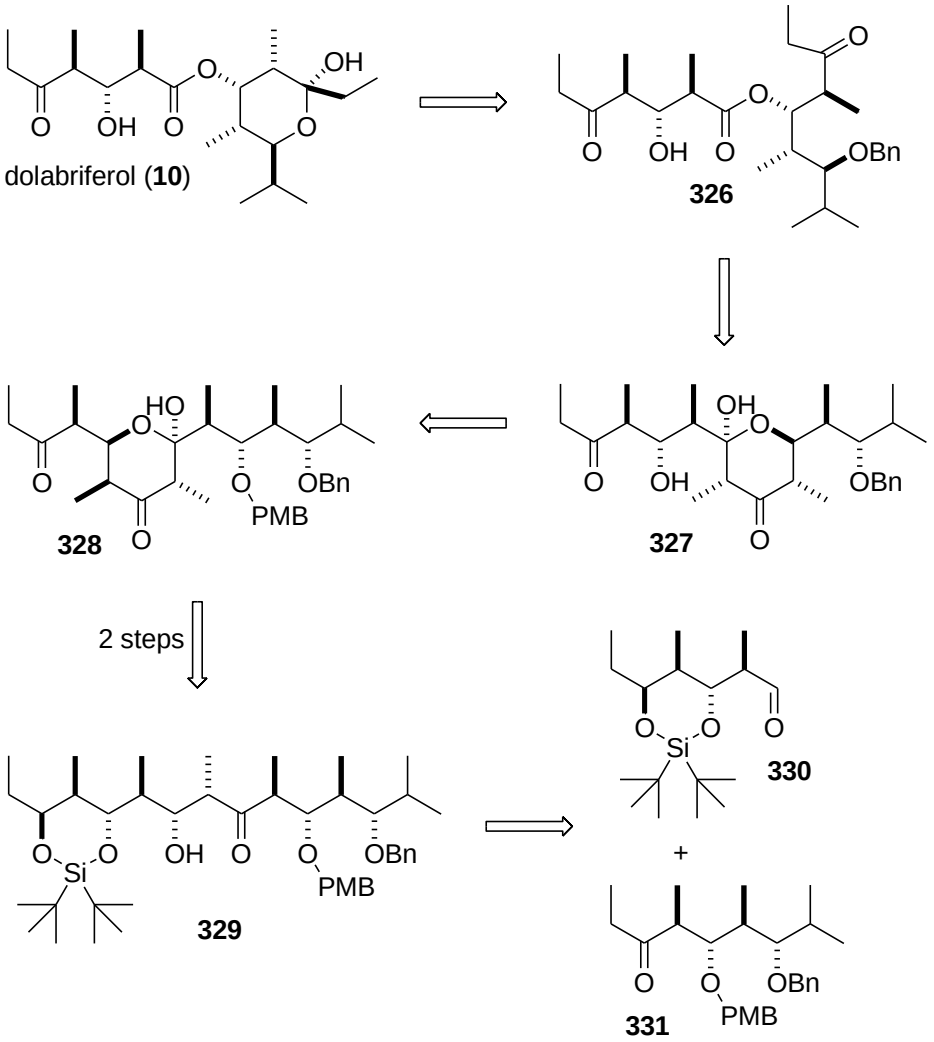



***Figure 4.16:*** *Retrosynthetic analysis of dolabriferol* (**10**)

### 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**.

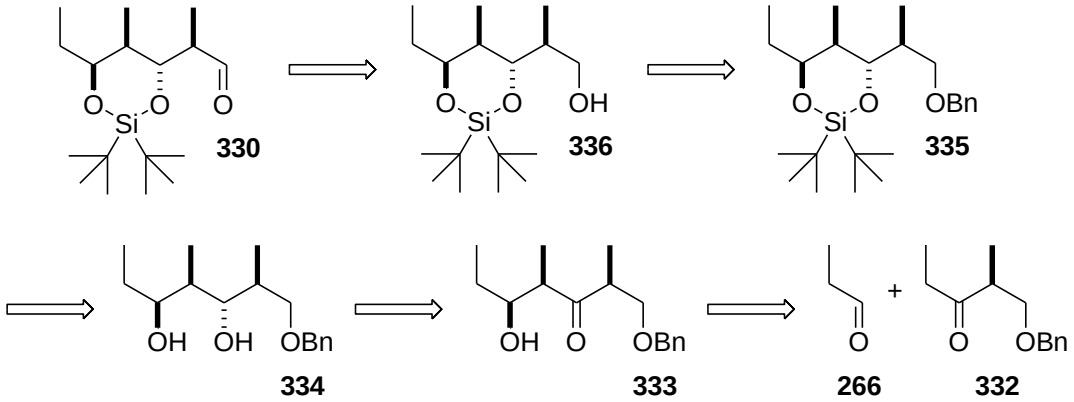
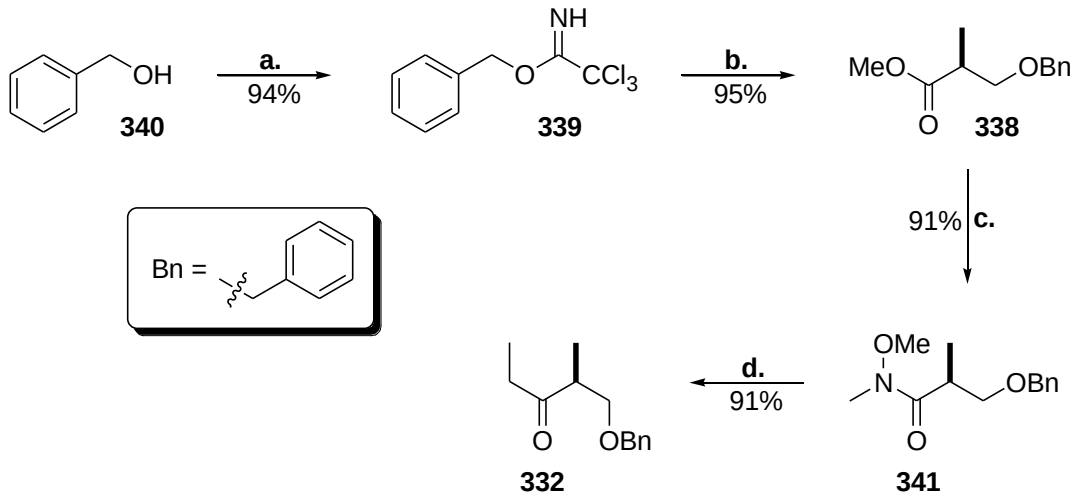



***Figure 4.17:*** *Retrosynthesis of the aldehyde* **330** *fragment*

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 $CH_2Cl_2$ at room temperature with a catalytic amount of triflic acid (TfOH).[21,22] The benzyl-acetimidate **339**[23] 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,[24] followed by subsequent addition of ethyl magnesium bromide[25] 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.



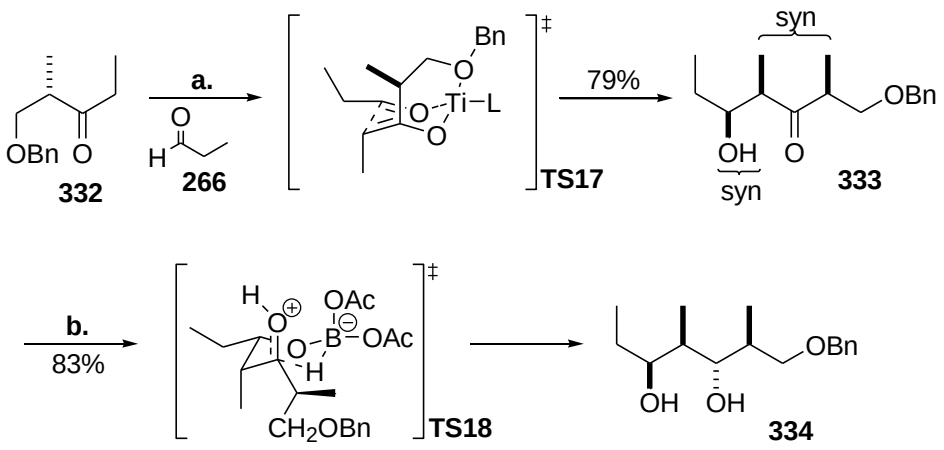

**Reagents and Conditions: a.** 50% KOH aq Solution (w/w), $CH_2Cl_2$, tetrabutylammonium hydrogen sulphate (cat), then benzyl alcohol (**340**), $Cl_3CCN$ (1.0eq), 0°C to RT, 2 hrs; **b.** Ester **337**, $CH_2Cl_2$, RT, then TfOH (10mol%), RT, 15-18 hrs; **c.** MeNH(OMe).HCl (2.5eq), $Et_2O$:THF (1:1), $^{i}$PrMgCl (5.0eq), -20°C 1 hr to 0°C 1 hr; **d.** EtMgBr (3.0eq), 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 muamvatin[26] beginning with a modified titanium based aldol reaction,[27] followed by an Evans-Saksena reduction[28,29] 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($^{i}$OPr)$Cl_3$ chelate complex, which was then added to the newly prepared ketone **332** in $CH_2Cl_2$ at -78°C followed by $^{i}Pr_2NEt$ 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 triacetoxyborohydride[28] also proceeds through a six-membered ring transition state **TS18** which forces the intramolecular boron hydride

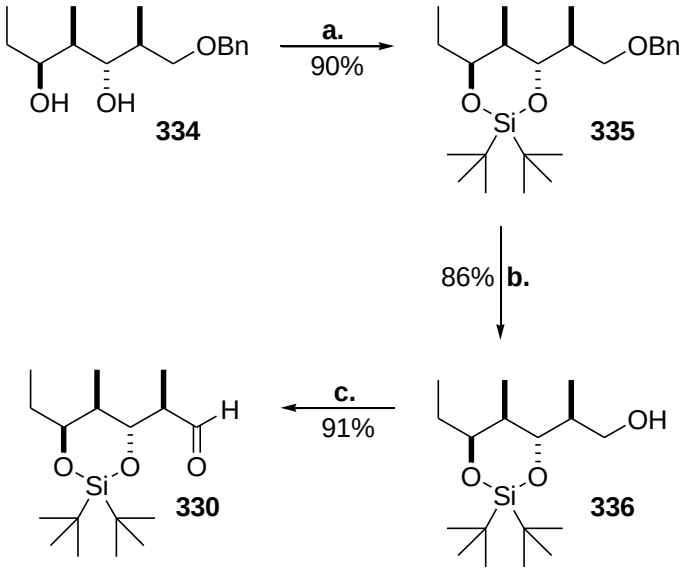
delivery to occur from the opposite face of the chelated β-alcohol to give the desired 2,3-*anti*-3,4-*anti*-4,5-*syn*-diol **334**.




**Reagents and Conditions: a.** $TiCl_4$ (1.0eq), $Ti(^iOPr)_4$ (0.3eq), $CH_2Cl_2$, 0°C, 30 minutes then, $^iPr_2NEt$ (1.2eq) at -78°C, 30 minutes; propionaldehyde (**266**) (1.5eq), $CH_2Cl_2$, -78°C, 2 hrs; **b.** $(Me)_4NBH(OAc)_3$ (8.0eq), $CH_3COOH$, $CH_3CN$, -20°C, 48 hrs.

***Scheme 4.2:*** *Synthesis of benzyl protected diol* **334**

The di-*tert*-butylsilylene diol protecting group[30-32] was selected to protect the 3,5-*anti*-diol **334** due to its robustness and ease of removal under mild acidic conditions.[33] The protection of the diol **334** 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.[26,34] 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**.[34,35] The alcohol **336** was then oxidised as required to the desired aldehyde **330** fragment using Swern conditions (Scheme 4.3).[36] The required aldehyde **330** was synthesised in 46% yield over five linear steps from ketone **332** and completed the construction of the $C_3$-$C_6$ stereochemical array of dolabriferol (**10**).




**Reagents and Conditions: a.** Di-*tert*-butylsilyl bistriflate (2.2eq), 2,6-lutidine (2.5eq), $CH_2Cl_2$, RT, 6 hrs; **b.** $H_2$, Pd/C, EtOH, RT, 6 hrs; **c.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (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 $^{13}C$ 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.

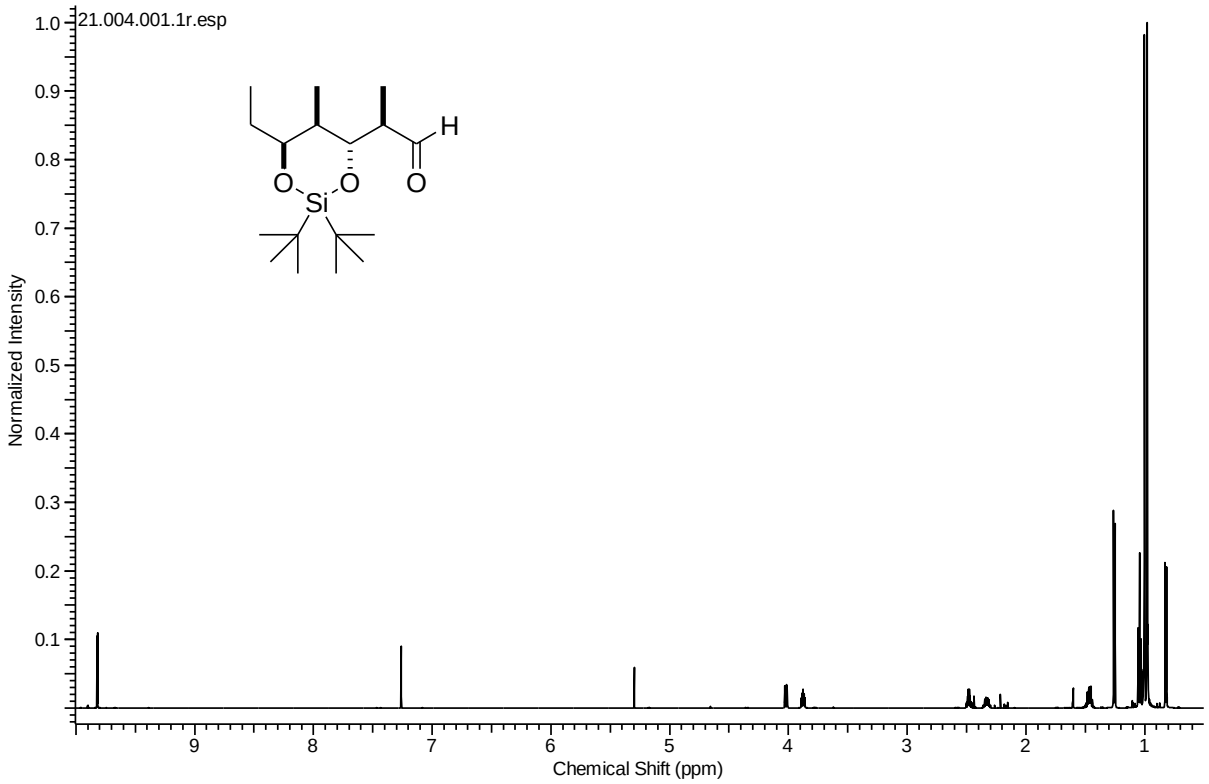



***Figure 4.18:*** *The $^{1}H$ NMR spectrum of aldehyde* **330** *in $CDCl_3$*

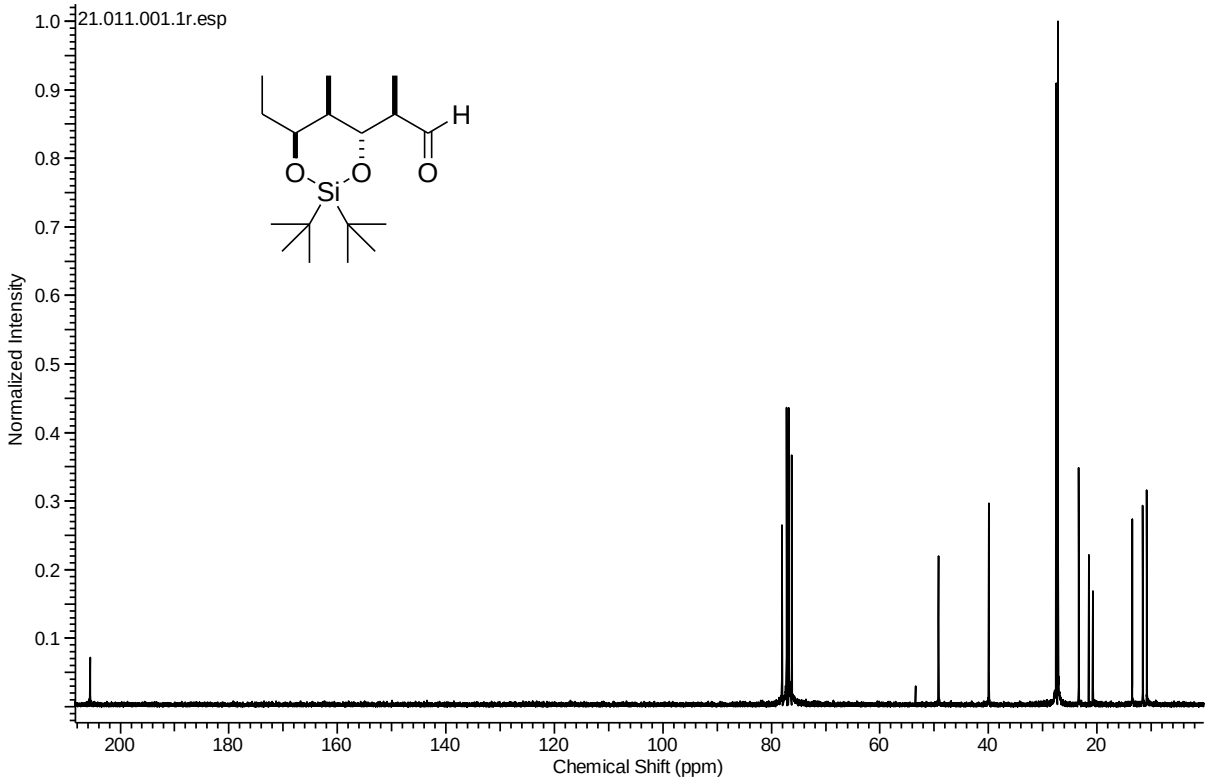
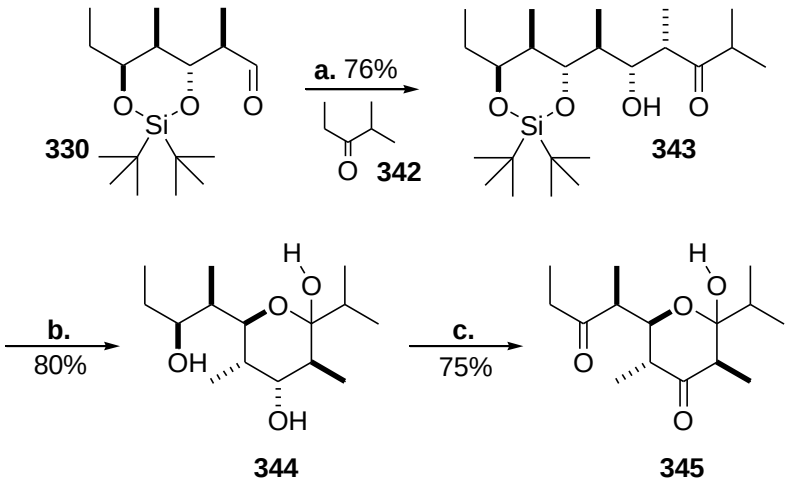



***Figure 4.19:*** *The $^{13}C$ NMR spectrum of aldehyde* **330** *in $CDCl_3$*

### 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 $C_5$ 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[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.[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 $C_9$-OH for the following double oxidation using Swern conditions[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.




**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), $CH_2Cl_2$, $NEt_3$ (12.0eq), -78°C, 2 hrs.

***Scheme 4.4:*** *Synthesis of model diketone hemiacetal* **345**

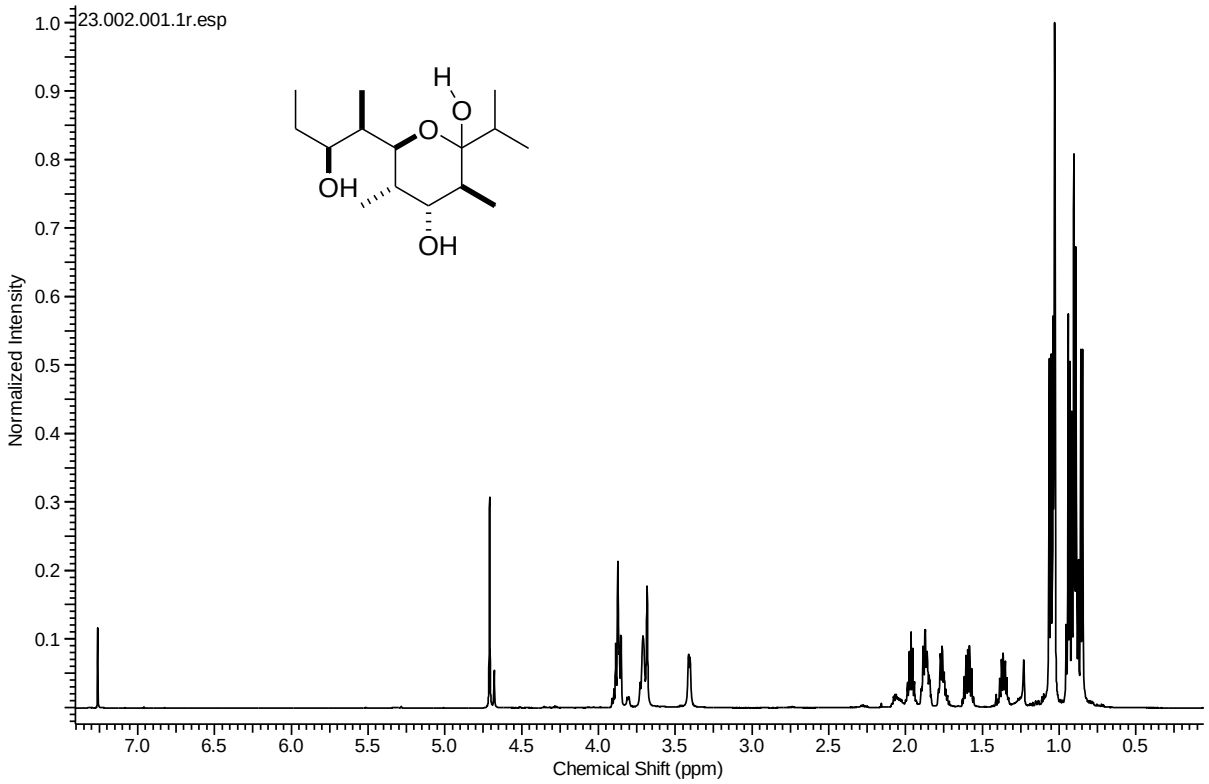



***Figure 4.20:*** *The $^{1}H$ NMR spectrum of hemiacetal* **344** *in $CDCl_3$*

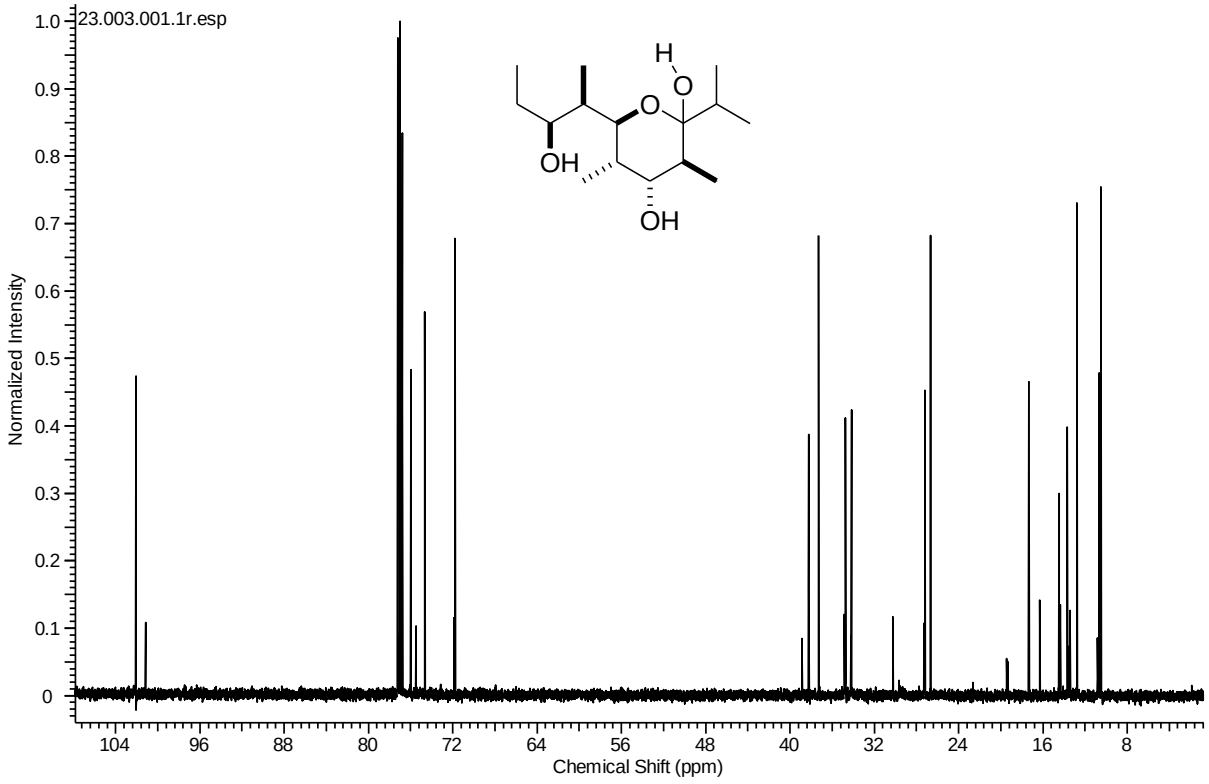



***Figure 4.21:*** *The $^{13}C$ NMR spectrum of hemiacetal* **344** *in $CDCl_3$*

### 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).

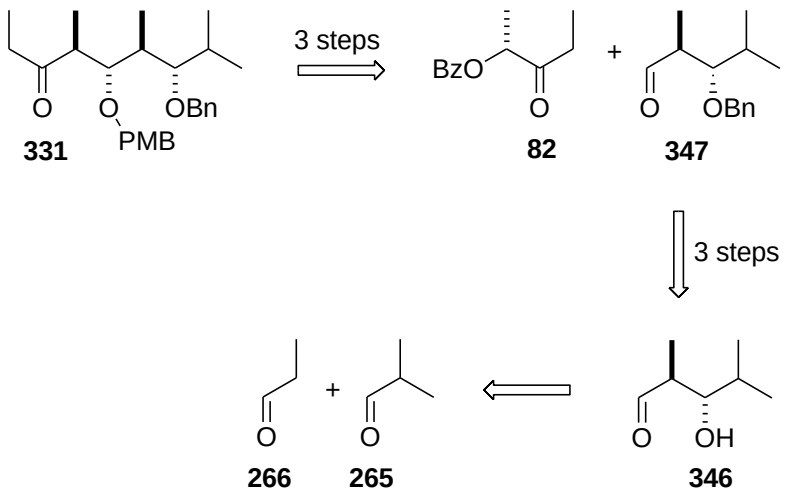
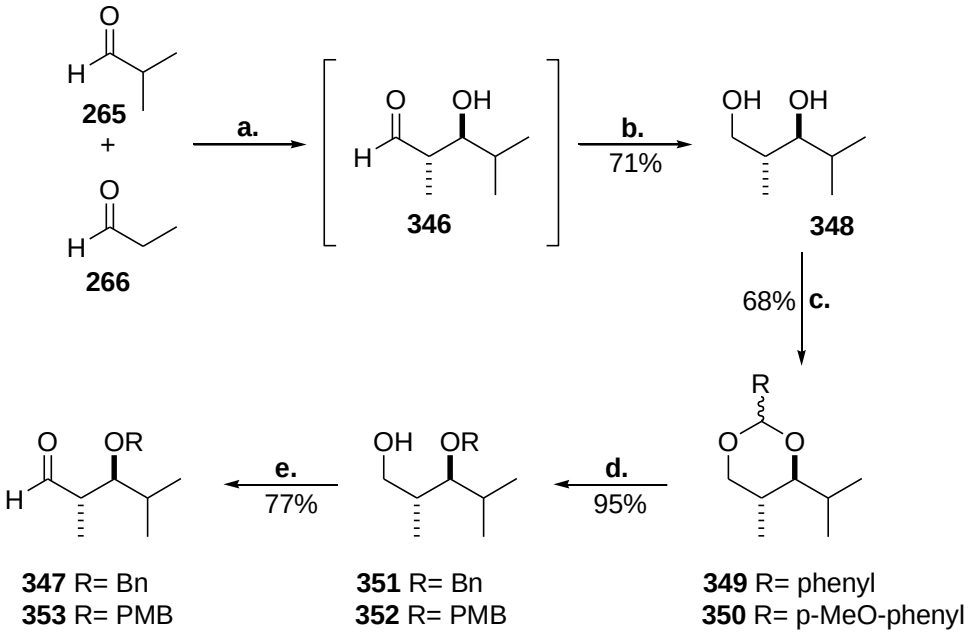



***Figure 4.22:*** *Retrosynthesis of the ketone* **331** *fragment*

It was recognised that β-benzyloxy 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.[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**[42-44] in 52% yield over two steps. This diol **348** could then be protected as either the benzylidene acetal **349**[45] or the *p*-methoxy-benzylidene acetal **350**[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.[42,44,46]

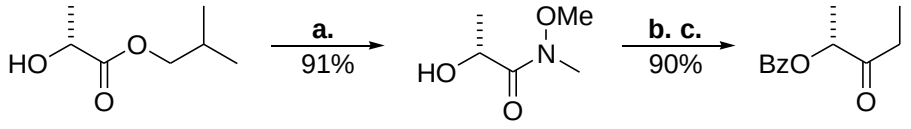
Oxidation to aldehydes **347** and **353** (Scheme 4.5) was performed under general Swern oxidation conditions as required[44,47,48] for the following *anti*-dicyclohexylboron mediated aldol addition.




**Reagents and Conditions: a.** Isobutyraldehyde (**265**) (2.0eq), L-proline (0.1eq), DMF, 0°C, then propionaldehyde (**266**) (1.1eq), 0°C, 15-24 hrs; **b.** $NaBH_4$ (2.0eq), THF, 0°C, 2 hrs; **c.** Benzaldehyde dimethyl acetal or anisaldehyde dimethyl acetal (1.2eq), $CH_2Cl_2$, CSA, RT, 48 hrs; **d.** DiBALH (1.5eq), $CH_2Cl_2$, -78°C to 0°C 3 hrs; **e.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hrs.

***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 **82** boron mediated *anti*-aldol reaction. The synthesis of Paterson's lactate ketone[49] **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.[50,51]

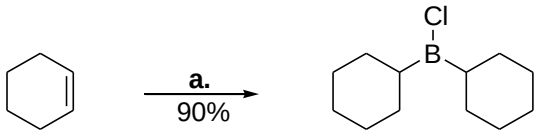



**138** **354** **82**

**Reagents and Conditions: a.** MeNH(OMe).HCl (2.5eq), $^{i}$PrMgCl (5.0eq), 1:1 THF/$Et_2O$, -20°C, 1 hr, then 0°C, 1 hr; **b.** EtMgBr (3.0eq) THF, 0°C to RT, 2 hrs; **c.** $Bz_2O$ (1.5eq), 4-DMAP (0.1eq), $^{i}Pr_2NEt$ (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.



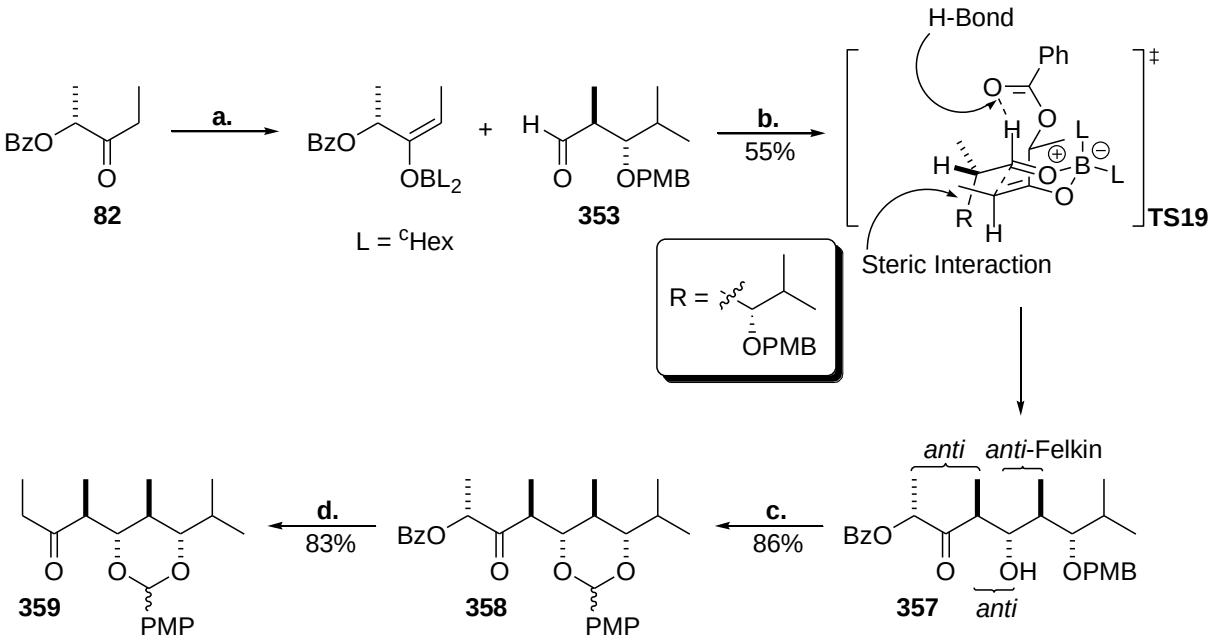

**356** **355**

**Reagents and Conditions: a.** Cyclohexene (**356**) (2.0eq), $Et_2O$, $BH_2Cl.SMe_2$ (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 benzoate[57] 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.




**Reagents and Conditions: a.** $^{c}Hex_2BCl$ (**357**) (1.5eq), $^{i}Pr_2NEt$ (1.8eq), $Et_2O$, -78°C-0°C, 2 hrs; **b.** Aldehyde **353** (1.0eq), $Et_2O$, -78°C, 3 hrs then -20°C, 15 hrs; **c.** DDQ (1.2eq), $CH_2Cl_2$, pH 7 Buffer, RT, 3 hrs; **d.** $SmI_2$ (4.0eq), THF, 0°C.

***Scheme 4.8:*** *Synthesis of PMB-acetal ketone* **359**

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 synthesied 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*[10] on removal of the final $C_{13}$ 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 $C_5$ and $C_{11}$ hydroxyl groups upon the $C_9$ carbonyl with the loss of $H_2O$ would most likely produce spiroacetal **325**.

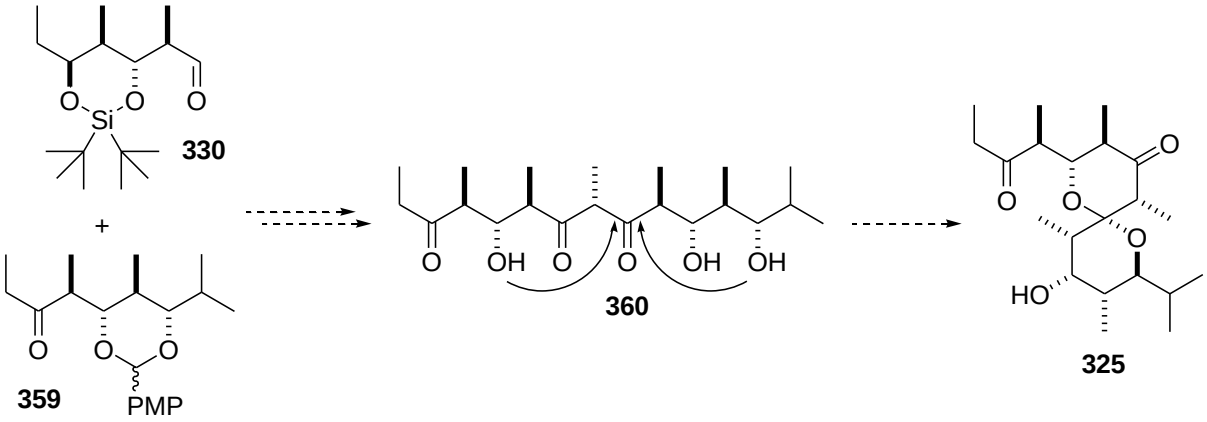
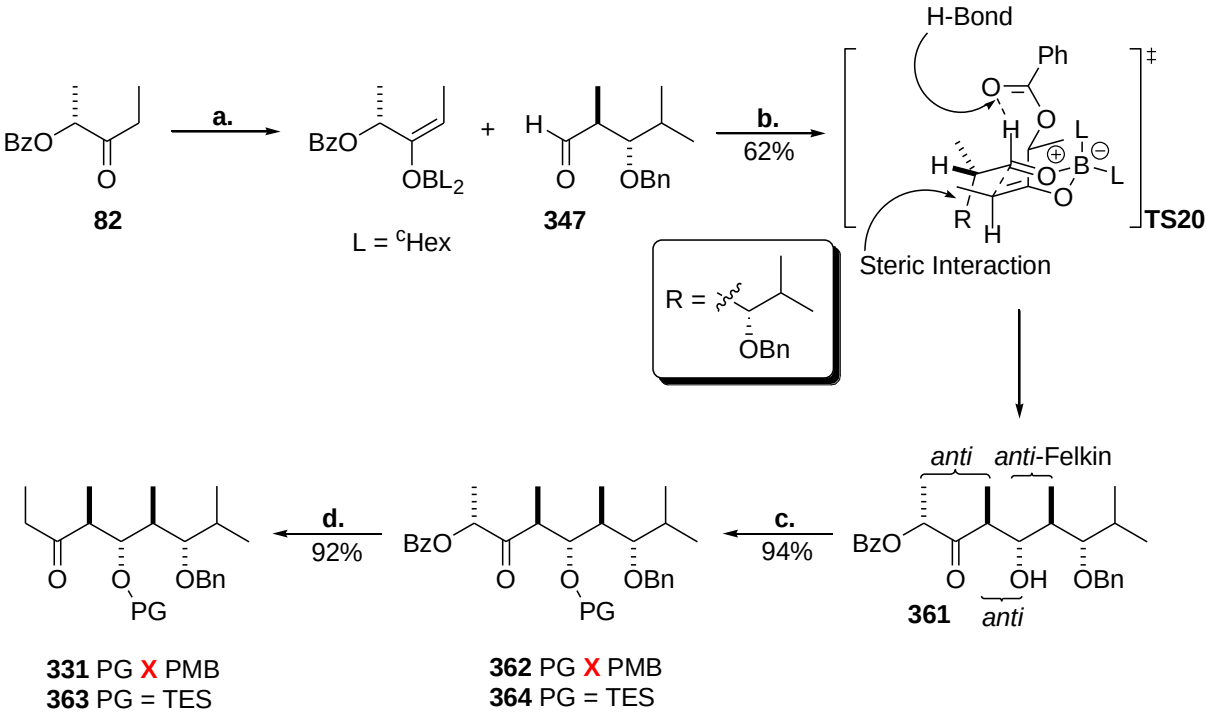



***Figure 4.23:*** *Potential formation of spiroacetal* **325** *from an unprotected linear precursor* **360**

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 (*E*)-enolate geometry. The enolate was then reacted with the newly constructed β-benzyloxy aldehyde **347** through **TS20** to give the *anti*-aldol adduct **361** in 62% yield. The yield obtained from this reaction was lower than other boron mediated *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[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[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[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.[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 $SmI_2$[49,51,57] afforded the desired ethyl ketone **363** in an excellent 92% yield.




**Reagents and Conditions: a.** $^{c}Hex_2BCl$ (**355**) (1.5eq), $^{i}Pr_2NEt$ (1.8eq), $Et_2O$, -78°C-0°C, 2 hrs; **b.** Aldehyde **347** (1.0eq), $Et_2O$, -78°C, 3 hrs then -20°C, 15 hrs; **c.** 2,6-lutidine (2.0eq), $CH_2Cl_2$, -78°C, TESOTf (1.5eq), 1.5 hrs; **d.** $SmI_2$ (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 δ 4.09 (J = 8.3, 1.9 Hz) and δ 3.33 (9.7, 2.2 Hz), respectively. The TES oxymethine proton displays coupling to the methyl methine resonance at δ 2.97 (J = 7.1 Hz), which also shows coupling to the methyl doublet at δ 1.06 (J = 7.1 Hz), and the two hydrogen multiplet at δ 1.95-1.85. This multiplet has additional coupling to the benzyl oxymethine signal at δ 3.33 and the methyl doublets at δ 0.95, δ 0.94 and δ 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 δ 2.37 (J = 18.5, 7.3 Hz) and δ 2.27 (J = 18.5, 7.3 Hz) and show coupling to the methyl triplet at δ 0.93 (J = 7.3 Hz) in addition to reciprocal coupling. The signals present at δ 7.37-7.25, δ 4.74 (J = 11.6 Hz) and δ 4.63 (J = 11.6) Hz are consistent with benzyl ether protecting groups, while the signals at δ 0.93 (J = 8.0 Hz) and δ 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 δ 215, the four signals for the benzyl aromatic group appear at δ 139, δ 128, δ 127, and δ 126 and the two oxymethine carbons resonate at δ 85 and δ 77. The carbons associated with the TES protecting group resonate at δ 7.0 and δ 5.0.

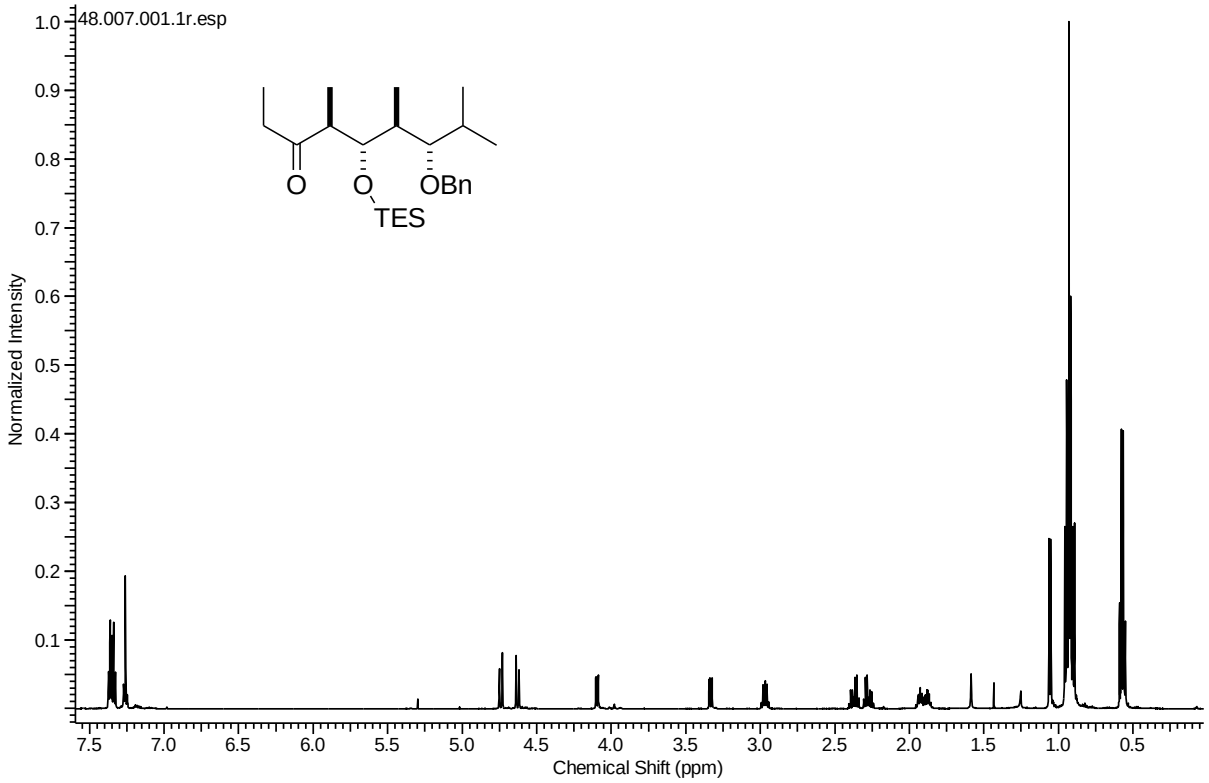



***Figure 4.24:*** *The $^{1}H$ NMR spectrum of ketone* **363** *in $CDCl_3$*

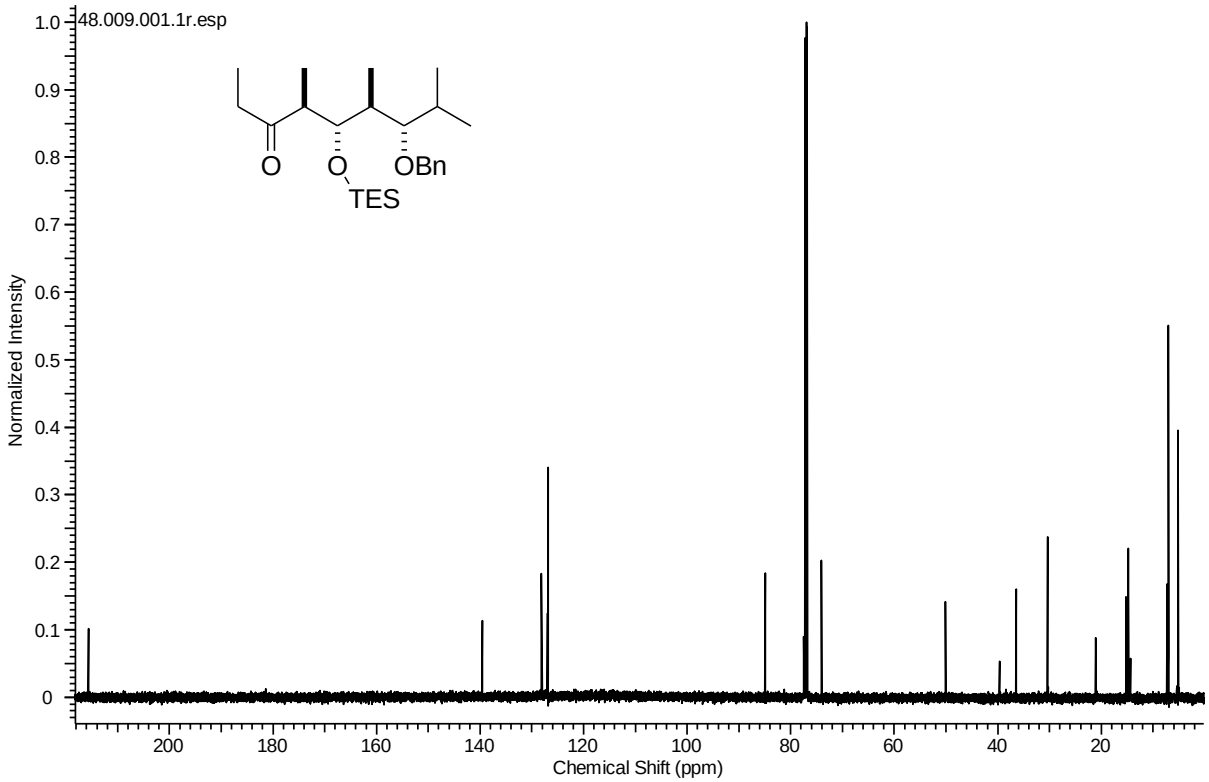



***Figure 4.25:*** *The $^{13}C$ NMR spectrum of ketone* **363** *in $CDCl_3$*

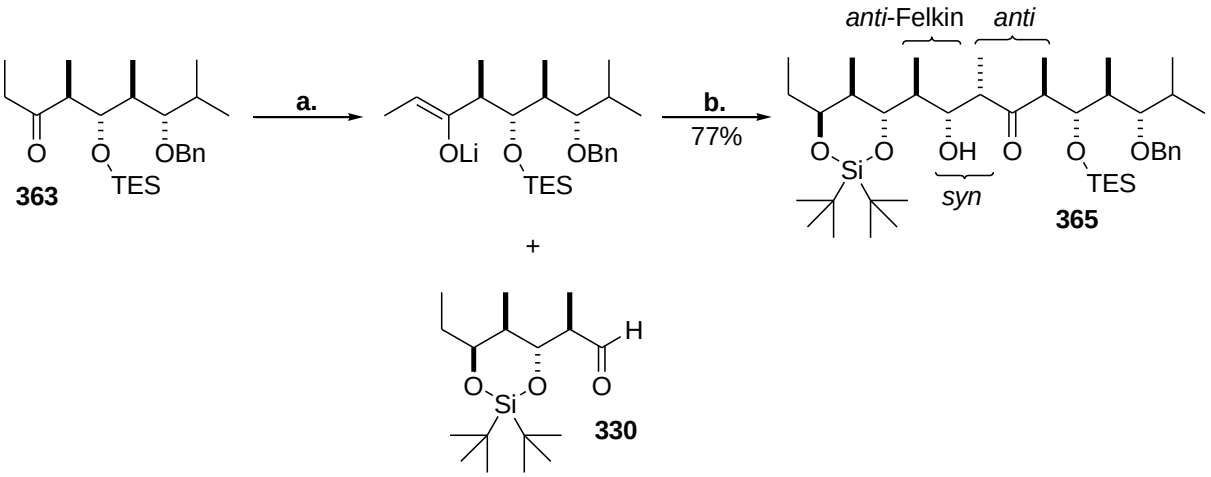
This short linear sequence afforded the amended major ketone fragment **363** in 21% yield over eight linear steps where the required $C_{10}$-$C_{13}$ *anti-anti* stereochemistry was created exploiting cross aldol asymmetric organocatalysis and lactate derived ketone aldol methodology.

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 studes[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)[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.




**Reagents and Conditions: a.** LiHMDS (1.2eq), THF, -78°C, 1 hr then -50°C, 1 hr; **b.** Aldehyde **330** (1.0eq), THF, -78°C, 2hrs.

***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 *anti*-Felkin preference[63,64] usually exhibited by α-methyl aldehydes in aldol reactions with (*Z*)-enolates. The *anti*-8,10 stereochemistry displayed across the carbonyl attributed to the preferred sense of induction of lithium based enolates was also satisfied.[38] 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 hexamethyldisilylazide 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**.

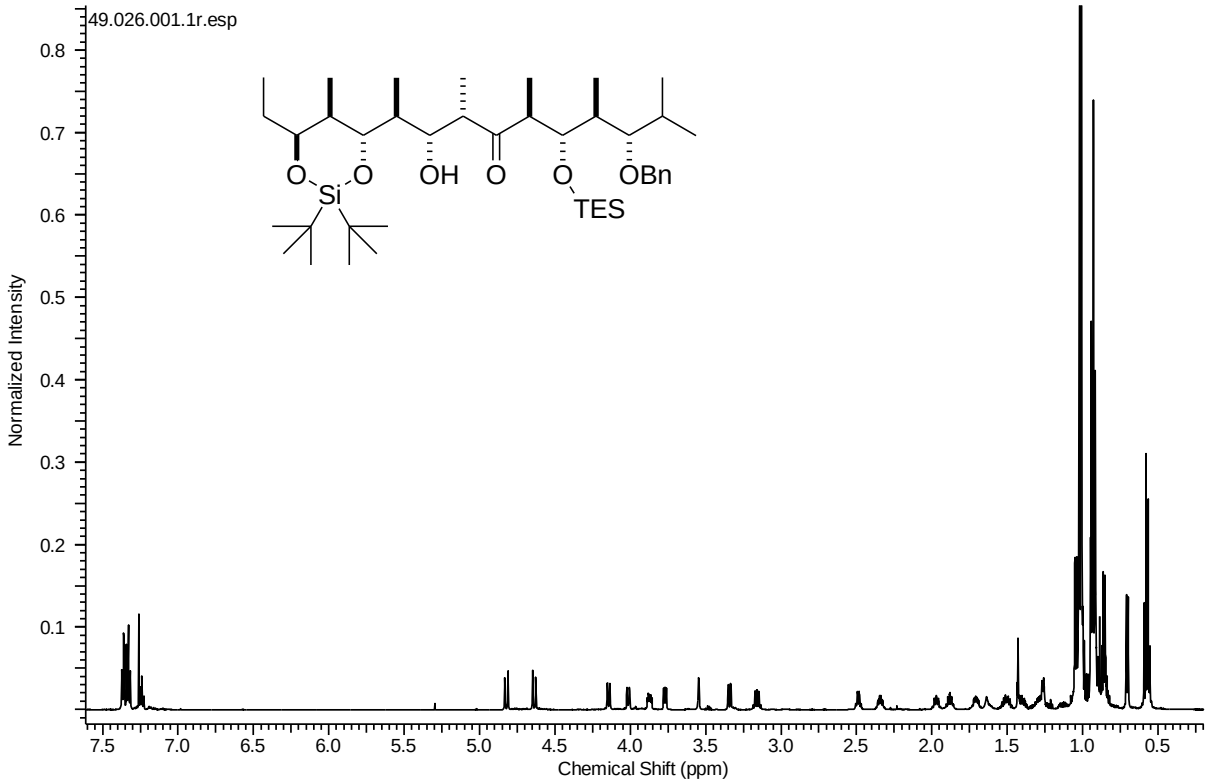



***Figure 4.26:*** *The $^{1}H$ NMR of aldol adduct* **365** *in $CDCl_3$*

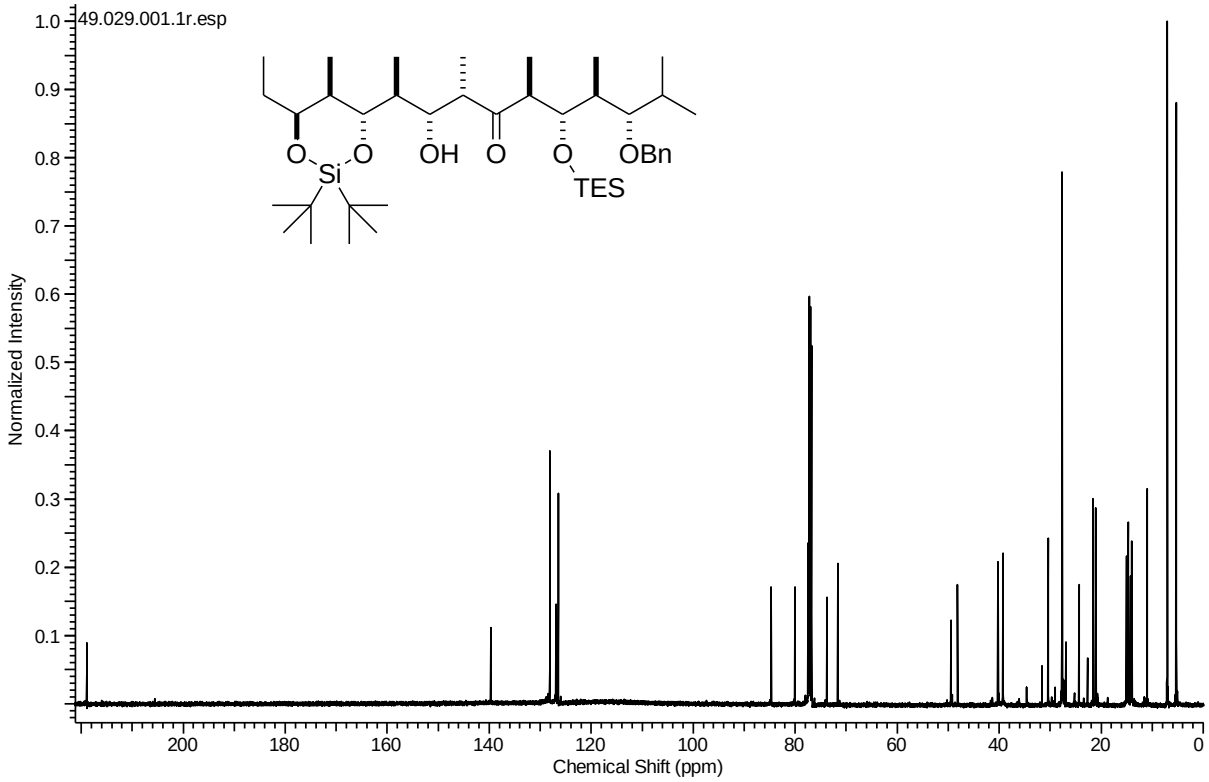


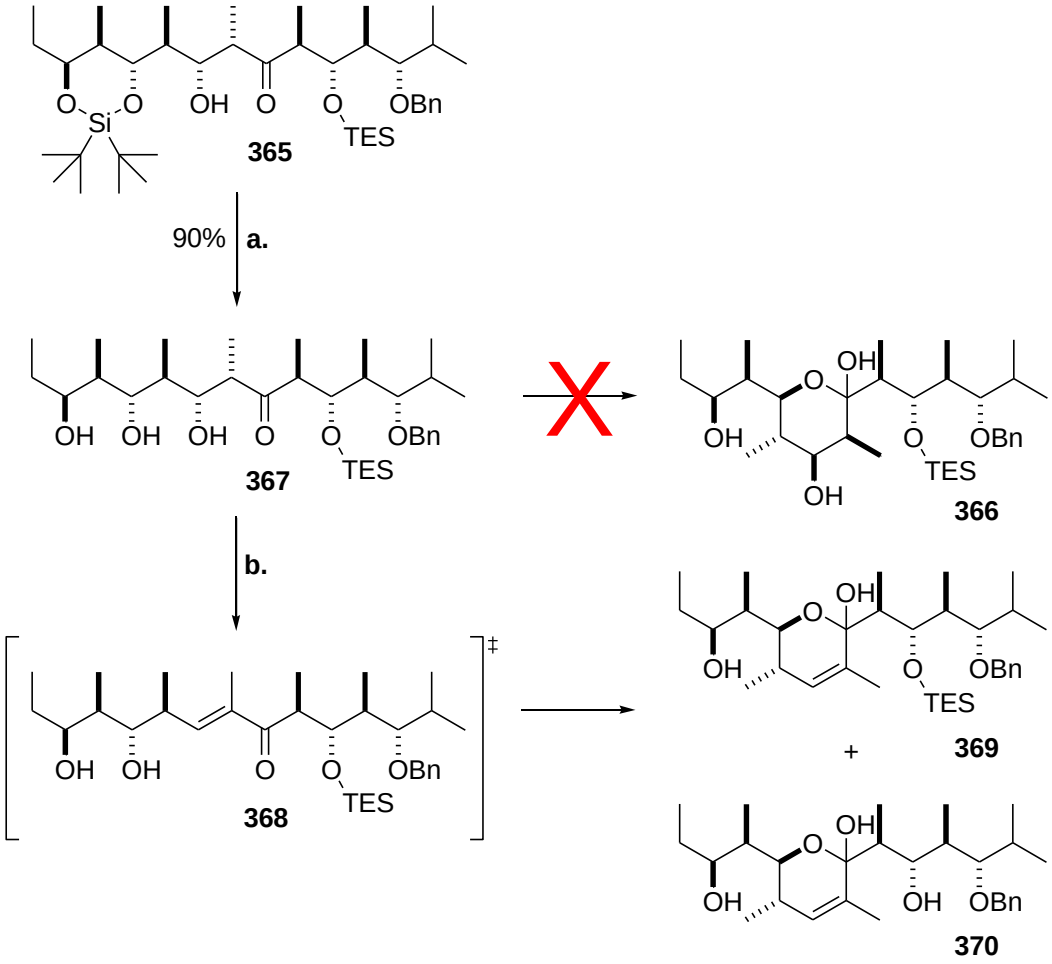

***Figure 4.27:*** *The $^{13}C$ NMR of aldol adduct* **365** *in $CDCl_3$*

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 δ 4.01 (dd, J = 9.3, 1.3 Hz) which shows coupling to the methyl methine resonance at δ 2.48 (dq, J = 7.2, 1.3 Hz). This methyl methine also shows coupling to the 24H multiplet at δ 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 δ 1.02-0.99, the methylene quartet from the TES protecting group at δ 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 δ 218 and the required six oxygen bearing carbon resonances between δ 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*[65] 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 and 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 δ 3.16 and δ 2.52 adjacent to the carbonyl. The presence of the carbonyl at δ 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

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 β-hydroxy ketone into conjugation of the carbonyl to give intermediate compound **368** as indicated by only one α-methine proton at δ 2.73, the vinyl methyl at δ 1.57 and the corresponding vinylic proton at δ 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: $NH_4Cl$, 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 β-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 β-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**).




**Reagents and Conditions: a.** HF/pyr/pyr (1.2eq), THF, 0°C, 6 hrs; **b.** PPTS (0.01eq), $CDCl_3$ 1 to 2 hrs.

***Scheme 4.11:*** *Silyl acetal deprotection and attempted cyclisations of triol* **367**

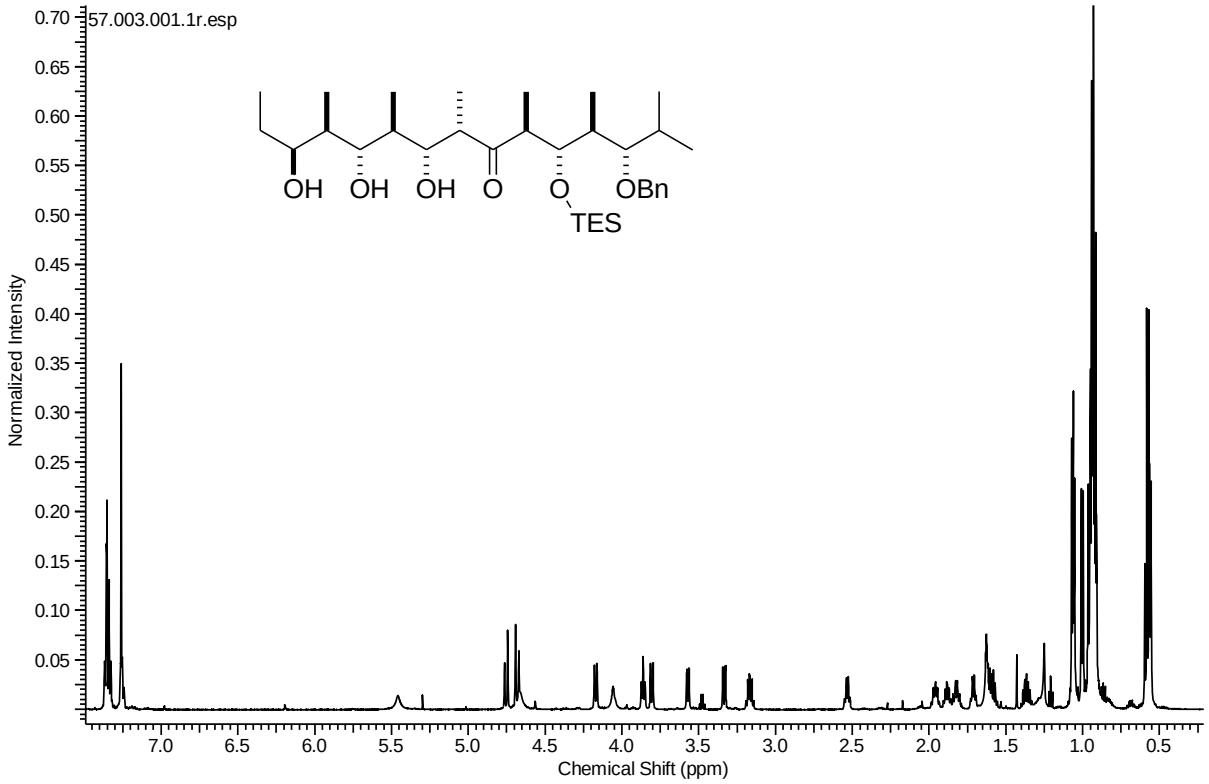



***Figure 4.28:*** *The $^{1}H$ NMR spectrum of triol* **367** *in $CDCl_3$*

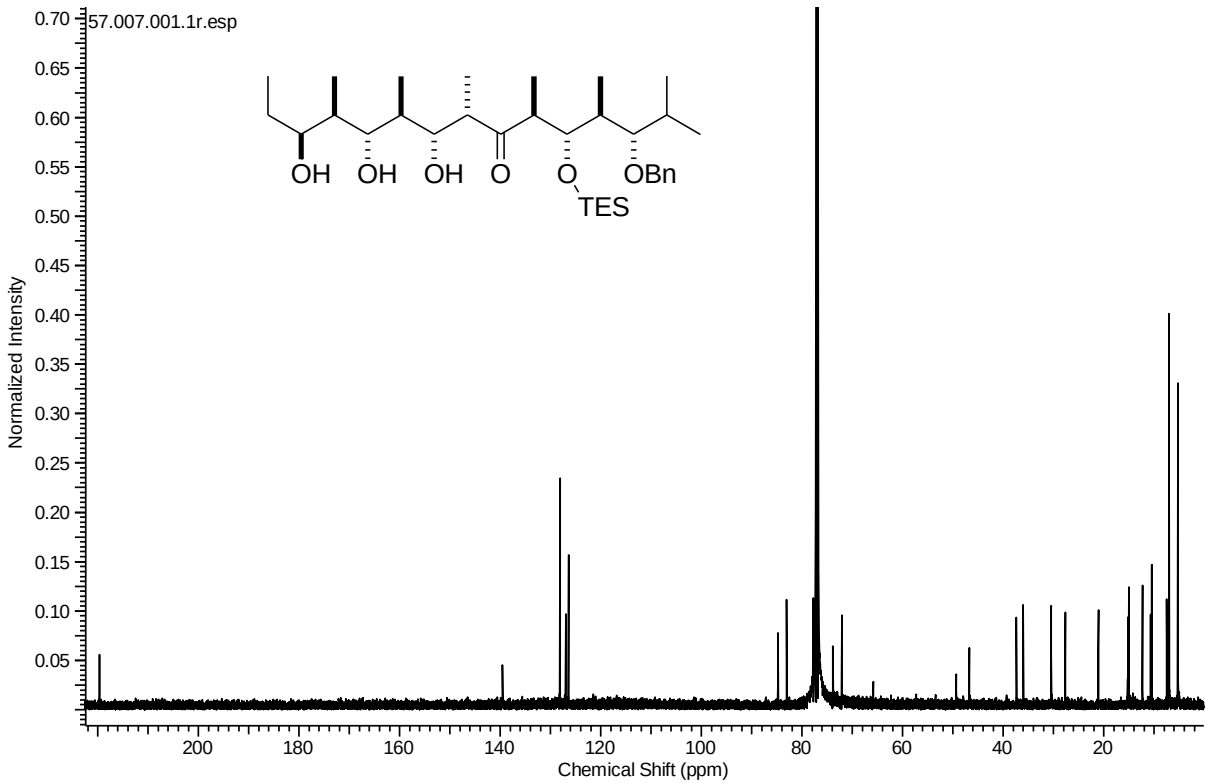
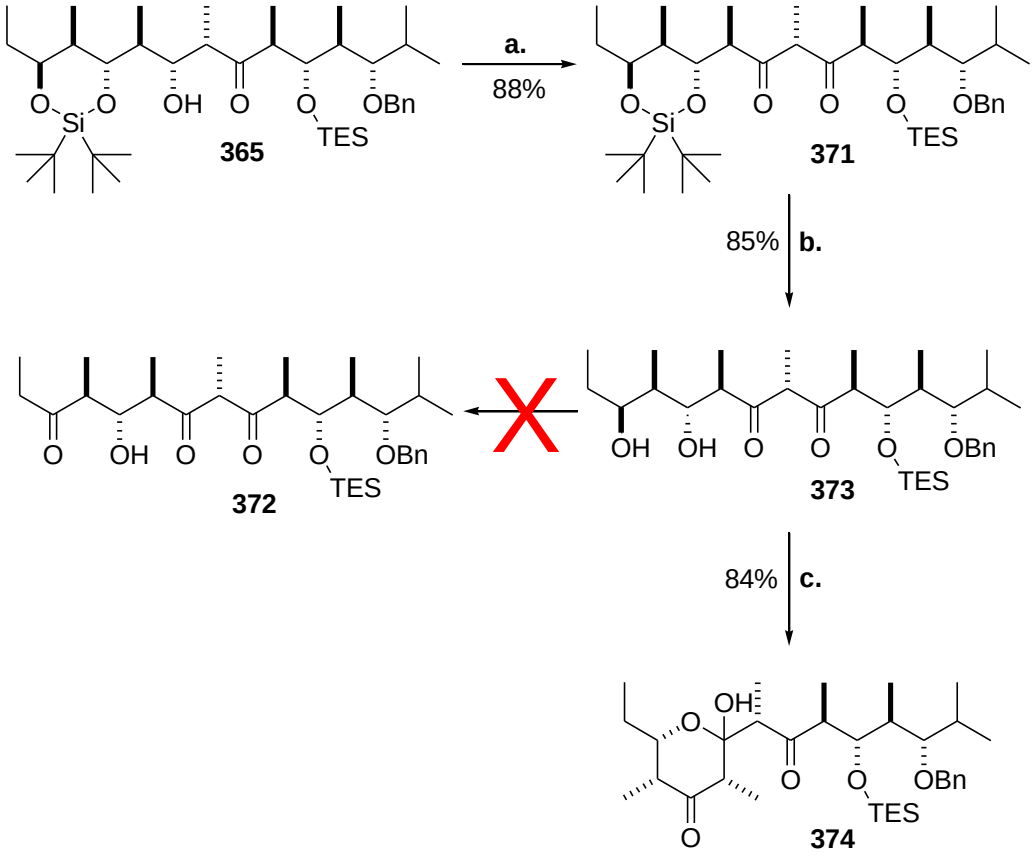



***Figure 4.29:*** *The $^{13}C$ NMR spectrum of triol* **367** *in $CDCl_3$*

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 $C_3$ 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 $C_2$ 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.

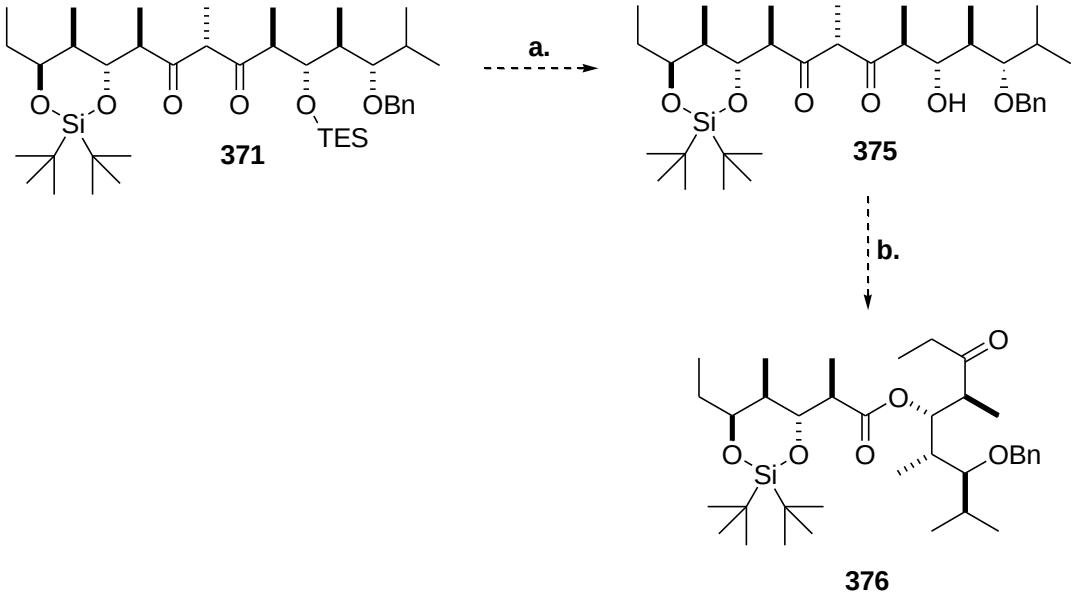



**Reagents and Conditions: a.** DMP (1.5eq), $NaHCO_3$, $CH_2Cl_2$, RT, 1.5 hrs; **b.** HF/pyr/pyr (1.2eq), THF, 0°C, 6 hrs; **c.** DMP (1.5eq), $NaHCO_3$, $CH_2Cl_2$, RT, 1.5 hrs.

***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.




**Reagents and Conditions: a.** *p*-TsOH (cat), 1:1 MeOH/$CH_2Cl_2$, 0°C, 1 hr. **b.** DBU (cat), $C_6D_6$, 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 $C_3$ hydroxyl would be protected as the PMB ether,[10] making the selective reduction of the primary benzyl ether complicated in its presence. Due to the success had in previous studies[10] with the protection of the $C_3$ alcohol as a PMB ether and the $C_5$ 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,[67] which could then be oxidised to the newly proposed aldehyde **377**.

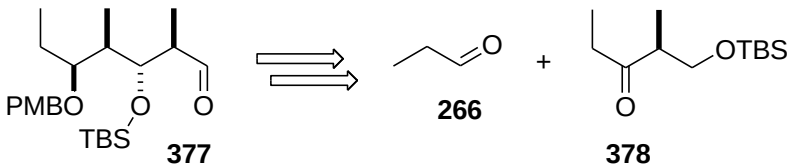
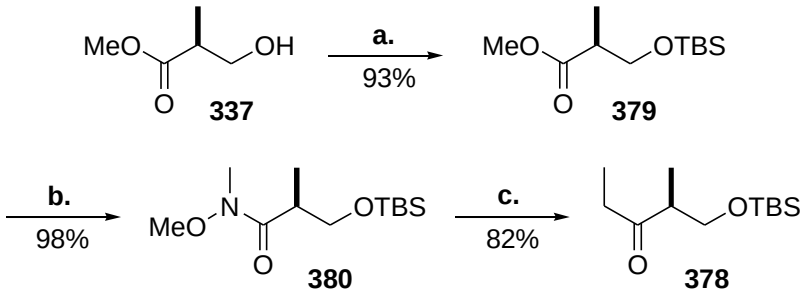



***Figure 4.30:*** *Alternate aldehyde* **377** *synthesis from ethyl ketone* **378** *and propionaldehyde* (**266**)

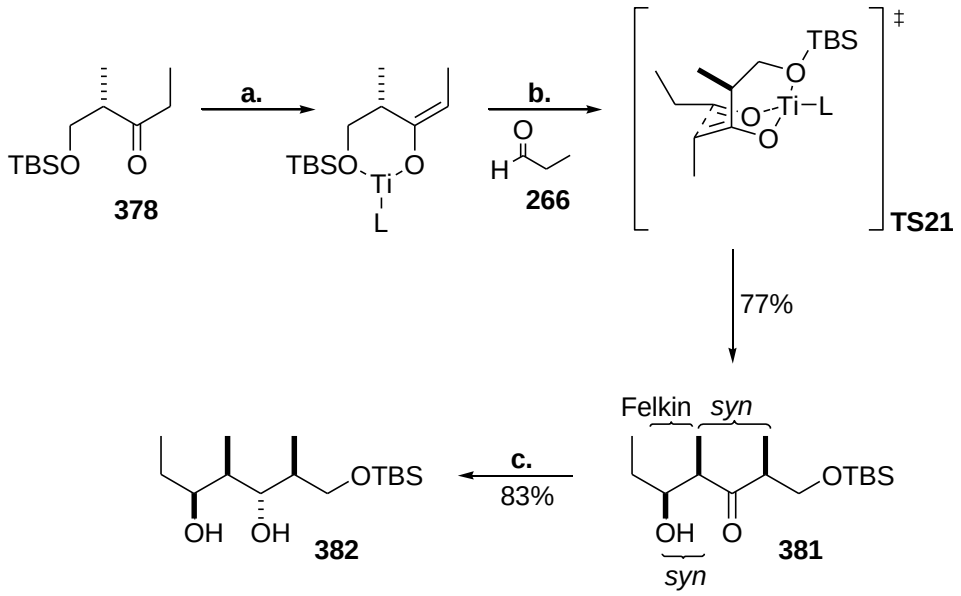
Synthesis of the ethyl ketone **378** (Scheme 4.14) began with the well established TBS-Cl/imidazole procedure[25,68,69] of (*S*)-roche ester **337** to give TBS-protected methyl ester **379** in 93% yield. Conversion of the methyl ester **379** to the corresponding Weinreb amide **380**[24] was achieved in 98% yield, and then addition of ethylmagnesium bromide at 0°C afforded the TBS-protected ethyl ketone **378**[25] in 74% yield, obtained over 3 linear steps.




**Reagents and Conditions: a.** Imidazole (2.0eq), $CH_2Cl_2$, TBS-Cl (1.8eq), RT, 15 hrs; **b** MeNH(OMe).HCl (2.5eq), $^{i}$PrMgCl (5.0eq), 1:1 THF/$Et_2O$, -20°C, 1 hr, then 0°C, 1 hr; **c.** EtMgBr (3.0eq) THF, 0°C to RT, 2 hrs.

***Scheme 4.14:*** *Synthesis of TBS-protected ethyl ketone* **378** *from roche ester* **337**

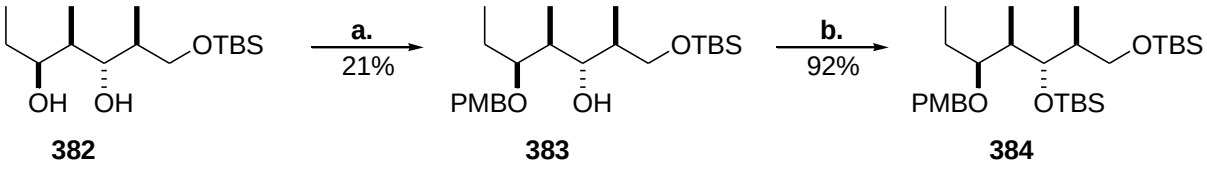
With the TBS-protected ethyl ketone **378** in hand, attention turned to inducing the *syn-syn* stereochemistry of aldol product **381**. This was achieved through use of the modified titanium aldol procedure[27] seen in Scheme 4.15, where titanium tetrachloride was reacted with titanium tetraisopropoxide at 0°C to form the mild Ti($^{i}$OPr)$Cl_3$ chelate complex, which was then added to the newly prepared TBS-protected ketone **378** in $CH_2Cl_2$ at -78°C, followed by $^{i}Pr_2NEt$ 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[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.




**Reagents and Conditions: a.** $TiCl_4$ (1.0eq), $Ti(^iOPr)_4$ (0.3eq), $CH_2Cl_2$, 0°C, 30 minutes then, $^iPr_2NEt$ (1.2eq) at -78°C, 30 minutes; **b.** Propionaldehyde (**266**) (1.5eq), $CH_2Cl_2$, -78°C, 2 hrs; **c.** $(Me)_4NBH(OAc)_3$ (8.0eq), $CH_3COOH$, $CH_3CN$, -20°C, 48 hrs.

***Scheme 4.15:*** *Synthesis of TBS-protected diol* **382**

Protection of the $C_3$ alcohol as the PMB-ether firstly required the synthesis of PMB-imidate **147**,[23] (see Chapter two Scheme 2.5) 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 $C_3$ alcohol as the *p*-methoxy benzyl ether was achieved through reaction triflic acid (0.001M in $Et_2O$) 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 $C_5$ alcohol to also be protected as the PMB-ether. Even though conversion of the free $C_5$ 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.




**382** **383** **384**

**Reagents and Conditions: a.** PMB-imidate **147** (1.5eq), $CH_2Cl_2$, TfOH (cat), RT, 48 hrs; **b.** 2,6-lutidine (2.0eq), $CH_2Cl_2$, TBSOTf (1.5eq), -78°C, 2 hrs.

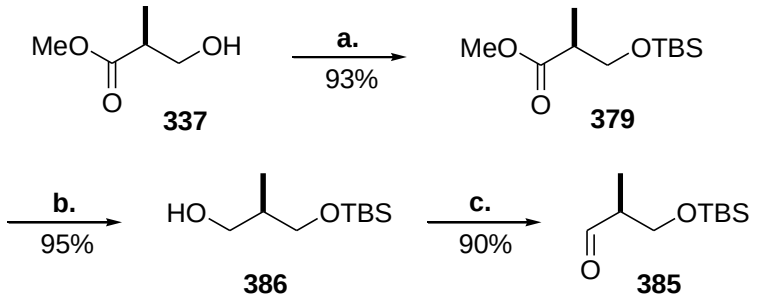
***Scheme 4.16:*** *Synthesis of protected adduct* **384**

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 borohydride reduction of the $C_3$ 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 $C_3$-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 susbstituent and reduction of the $C_3$ 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,[25,68,70] above in Scheme 4.14. The methyl ester was completely reduced to corresponding primary alcohol **386**[70,71] 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

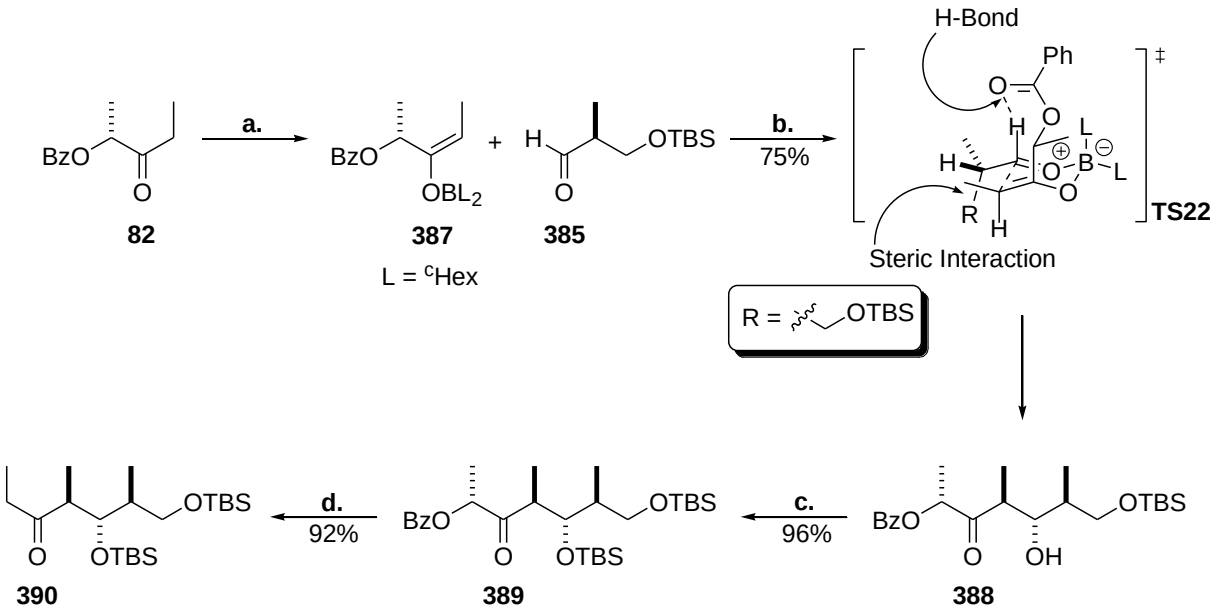
potassium tartrate solution). The alcohol **386** was then oxidised under Swern conditions[48,70] to the (*S*)-TBS-protected aldehyde **385** in 79% yield over 3 linear steps.




**Reagents and Conditions: a.** Imidazole (2.0eq), $CH_2Cl_2$, TBS-Cl (1.8eq), RT, 15 hrs; **b.** DiBALH (1.5eq), $CH_2Cl_2$, -78°C, 2 hrs; **c.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hrs.

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

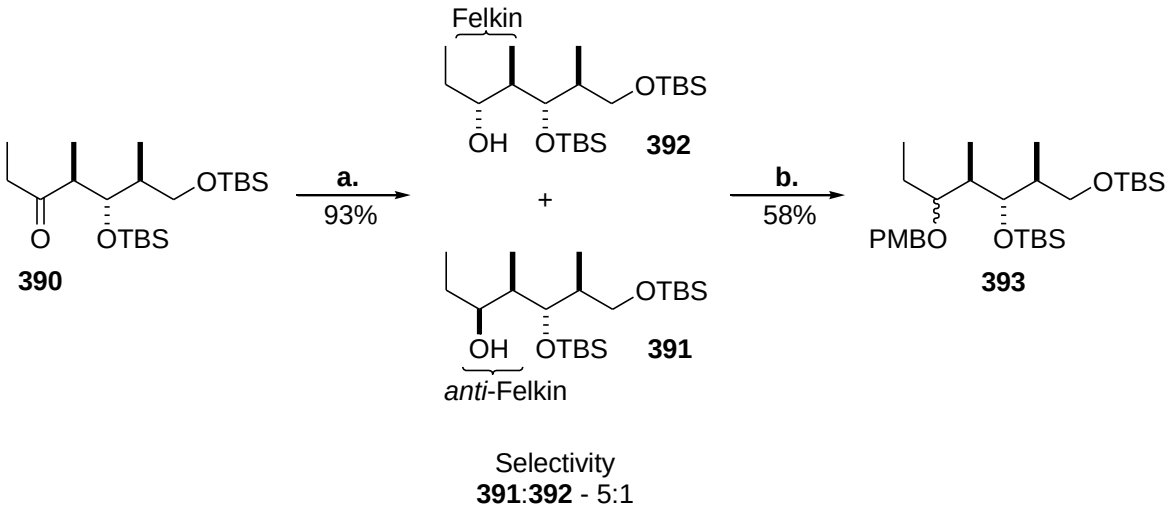
Addition of the newly prepared (*S*)-TBS-aldehyde **385** to a solution of the (*E*)-enolate **387** formed by the addition of dicyclohexylboron chloride (**355**) and triethylamine to ethyl ketone **82** in $Et_2O$ at -78°C,[53,54] followed by stirring at -20°C overnight gave the 2,4-*anti*-4,5-*anti*-5,6-*anti*-Felkin 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[49,51,57] 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).




**Reagents and Conditions: a.** $^{c}Hex_2BCl$ (**355**) (1.5eq), $^{i}Pr_2NEt$ (1.8eq), $Et_2O$, -78°C to 0°C, 2 hrs; **b.** Aldehyde **385** (1.0eq), $Et_2O$, -78°C, 3 hrs then -20°C, 15 hrs; **c.** 2,6-lutidine (2.0eq), $CH_2Cl_2$, TBSOTf (1.8eq), -78°C, 2 hrs; **d.** $SmI_2$ (3.0eq), THF, 0°C.

***Scheme 4.18:*** *Preparation of bis-TBS-protected ketone* **390**

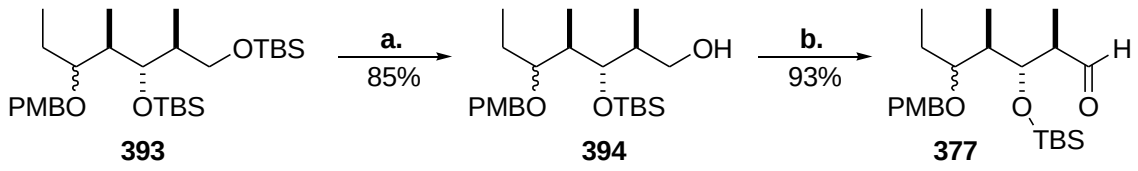
As mentioned above, it was planned that the $C_3$ carbonyl be reduced and protected as *p*-methoxy benzyl ether to avoid potential cyclisation modes encountered at various stages of the synthesis, mainly upon removal of the primary TBS group as a lead up to the acquisition of the key aldehyde **377** fragment. As a result, ketone **390** was reduced with $NaBH_4$[10,73] 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[63,64] 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 $C_3$ 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 $Et_2O$ at room temperature for 48 hours.[37,74] This process was completed after two recycles of starting material to give PMB ether **393** in 58% yield.




**Reagents and Conditions: a.** $NaBH_4$ (2.5eq), EtOH, 0°C to RT, 6 hrs; **b.** PMB-imidate **147** (3.0eq), $Et_2O$, TfOH (cat), RT, 48 hrs.

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

The decision to install the secondary TBS-ether at $C_5$ was made with the anticipation that the $C_7$ primary TBS-ether would be selectively cleaved in its presence.[25,67] In practice this proved correct with application of a procedure by Paterson *et al*.[25] 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[48] to provide the targeted key aldehyde **377** fragment in 93% yield (Scheme 4.20).




**Reagents and Conditions: a.** 1%HCl/EtOH, 0°C, 30 minutes; **b.** DMSO (3.0eq), $(COCl)_2$ (1.5eq), $CH_2Cl_2$, $NEt_3$ (6.0eq), -78°C, 2 hrs.

***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.

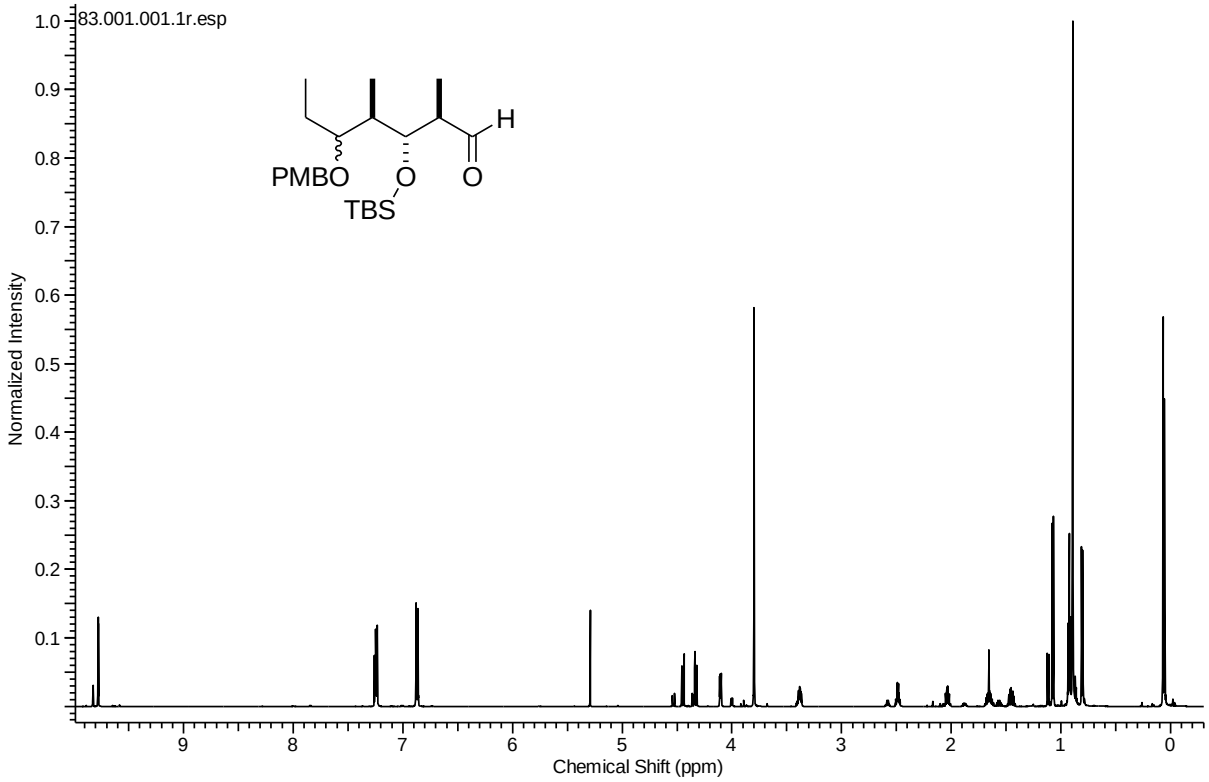



***Figure 4.31:*** *The $^{1}$H NMR spectrum of aldehyde* **377** *in $CDCl_3$*

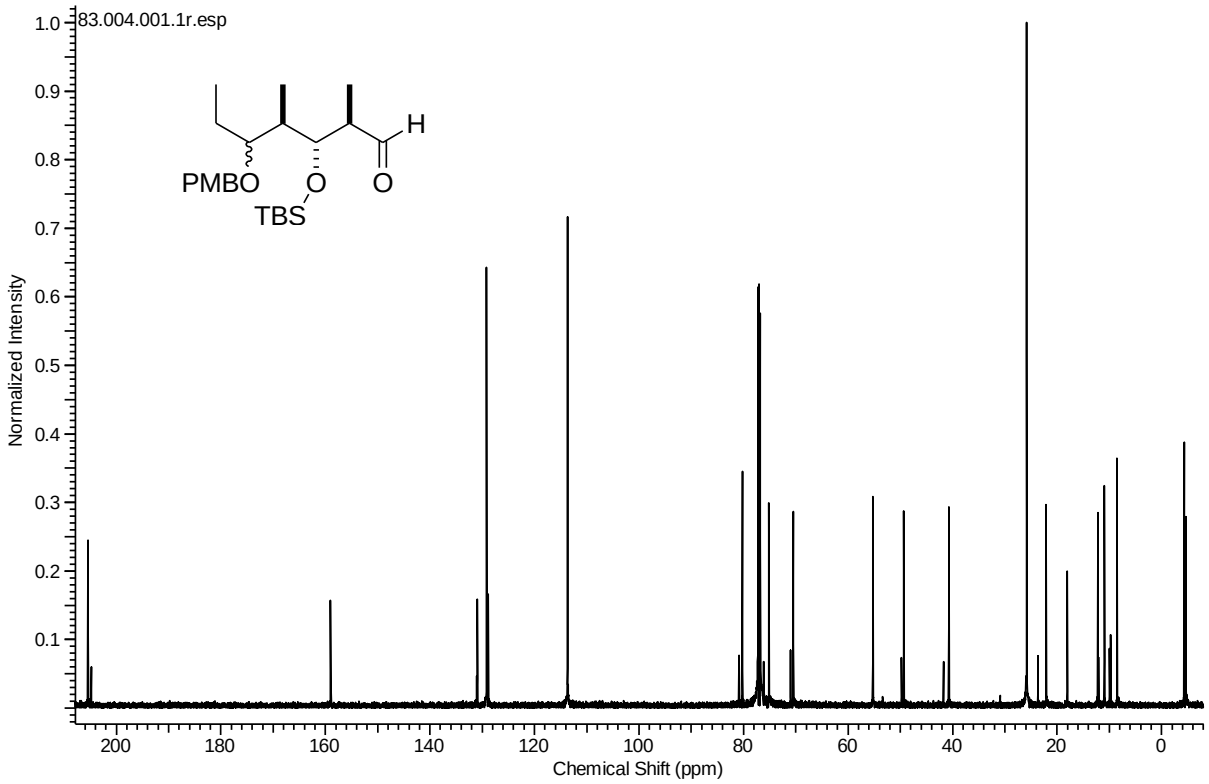


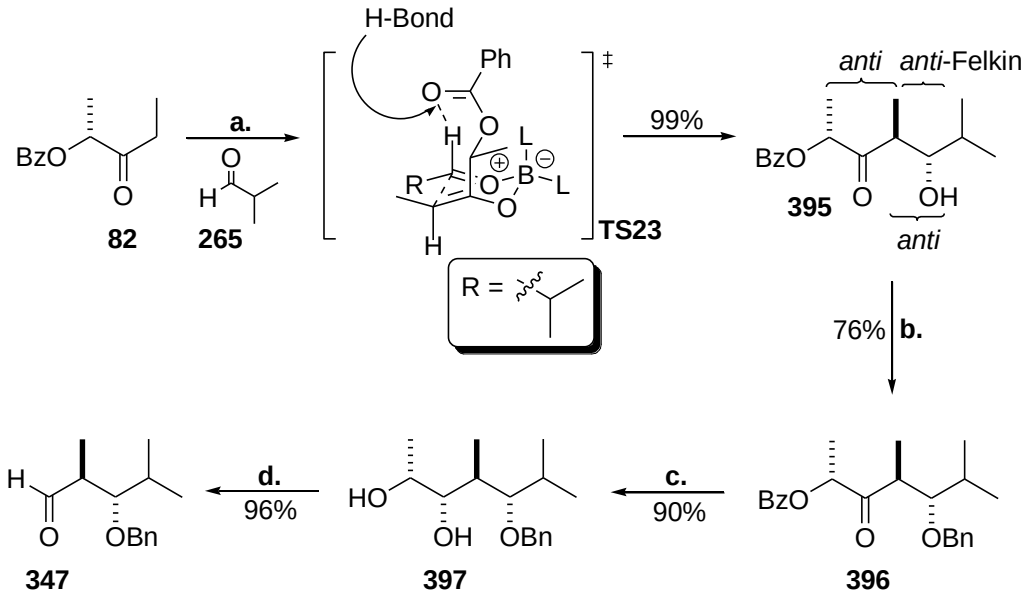

***Figure 4.32:*** *The $^{13}C$ NMR spectrum of aldehyde* **377** *in $CDCl_3$*

### 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[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*-$C_{12}$ and $C_{13}$ stereochemistry using another lactate derived ketone **82** dicyclohexylboron aldol with isobutyraldehyde (**265**) following a known protocol.[49,51] The (*E*)-enolate was prepared under standard conditions ($^{c}Hex_2BCl/NEt_3$),[49] and was reacted with freshly distilled isobutyraldehyde (**265**) to give 11,12-*anti*-12,13-*anti*-aldol adduct **395** as a single observable isomer in almost quantitative yield. The *anti*-*anti*-stereocontrol observed[49,51] for this aldol addition primarily comes from the strong diastereofacial preference of the (*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 $C_{13}$ 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

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[10,75] using $LiBH_4$ in THF at -78°C, warmed to room temperature for 15 hours to produce diol **396**. Oxidative cleavage[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.



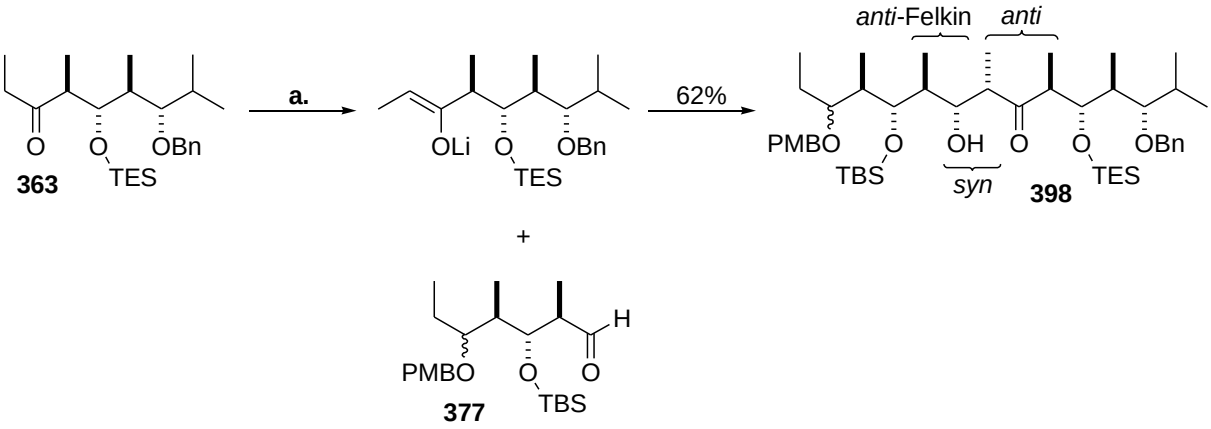

**Reagents and Conditions: a.** $^{c}Hex_2BCl$ (**355**) (1.5eq), $^{i}Pr_2NEt$ (1.8eq), $Et_2O$, -78°C to 0°C, 2 hrs, Isobutyraldehyde (**265**) (3.0eq), $Et_2O$, -78°C, 3 hrs then -20°C, 15 hrs; **b.** Benzyl-imidate **338** (2.0eq), Cyclohexane/$CH_2Cl_2$ (2:1), TfOH (0.1eq), 0°C to RT, 4 hrs; **c.** $LiBH_4$ (5.0eq), THF, -78°C to RT, 15 hrs; **d.** $NaIO_4$ (5.0eq), MeOH, $H_2O$, RT, 15 minutes.

***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 hexamethyldisilylazide in THF

conditions[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[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.




**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.

***Scheme 4.22:*** *Merger of the synthesised aldehyde* **377** *and ketone* **363** *fragments using an LiHMDS aldol*

The $^{1}$H NMR and $^{13}$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 $^{1}$H NMR spectrum indicates the presence of the new hydroxymethine resonance as a doublet at δ 3.93 (10.3 Hz) which couples to the methyl methine resonance at δ 2.55 (qd, J = 6.9, 1.5 Hz). The new methyl methine in turn also couples to the doublet observed at δ 1.04 (J = 6.9 Hz). Also readily apparent are the two methyl singlets between δ 0.07 and δ 0.05 accounting for the methyl groups attached to the TBS protecting group. The TES methylene quartet at δ 0.53 (J = 7.8 Hz), the aromatic signals associated with benzyl and *p*-methoxy benzyl at δ 7.37 and δ 6.87 and their corresponding diastereotopic oxybenzylic protons between δ 4.82 and δ 4.35.

The $^{13}$C NMR displays the correct number of unique carbon resonances in their expected regions. The ketone carbonyl resonance at δ 217, the seven oxycarbon resonances at δ 84.98, δ 80.40, δ

77.20, δ 76.26, δ 74.16, δ 72.46, δ 69.89, and the eight $sp^2$ 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.

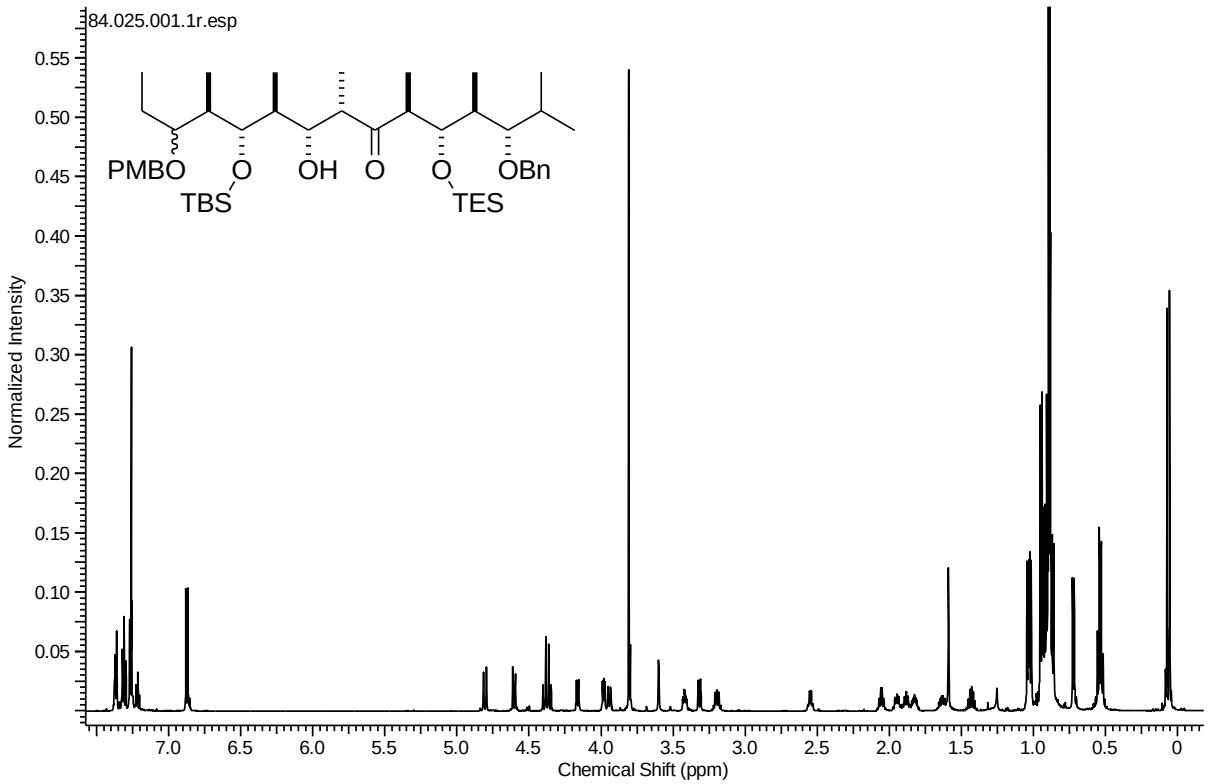



***Figure 4.33:*** *The $^1H$ NMR spectrum of aldol adduct* **398** *in $CDCl_3$*

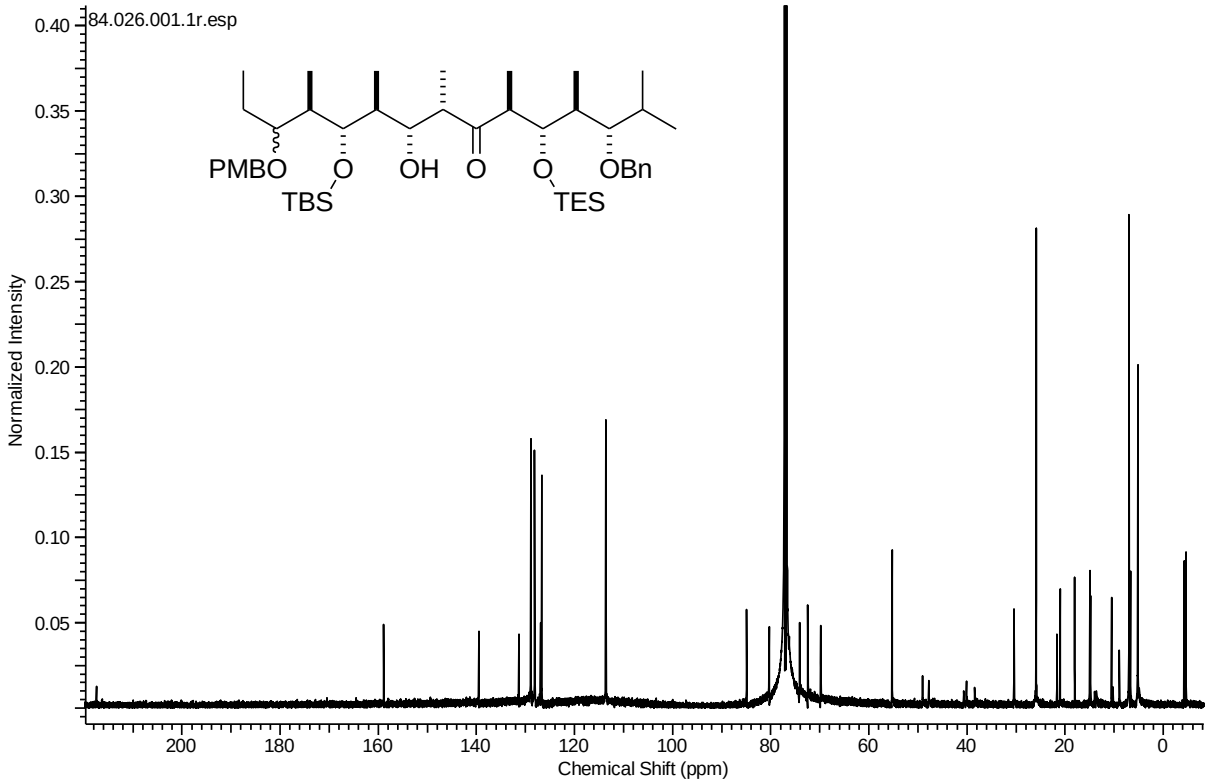


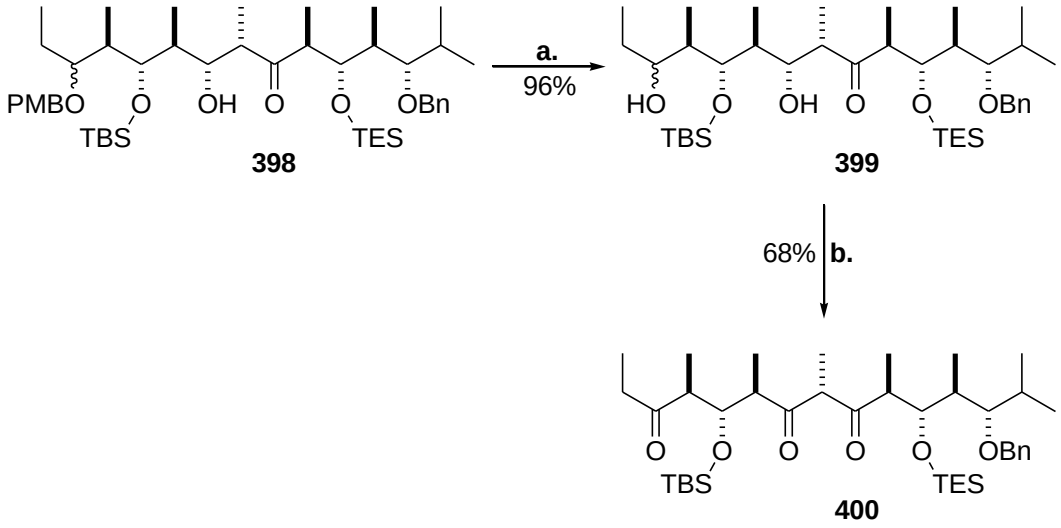

***Figure 4.34:*** *The $^{13}C$ NMR spectrum of aldol adduct* **398** *in $CDCl_3$*

### 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 $C_3$ and $C_7$ 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,[56] at the $C_3$ position, to produce the diol **399** in 96% yield. The diol **399** was then exposed to double the equivalents used for traditional Swern oxidations[10,48] to effect the oxidation of both the $C_3$ and $C_7$ 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), $CH_2Cl_2/H_2O$ (9:1), 0°C, 1 hr; **b.** DMSO (6.0eq), $(COCl)_2$ (3.0eq), $CH_2Cl_2$, $NEt_3$ (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

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 $sp^2$ carbons at δ 139, δ 128, δ 127, and δ 126 confirming the trione's **399** assigned structure.

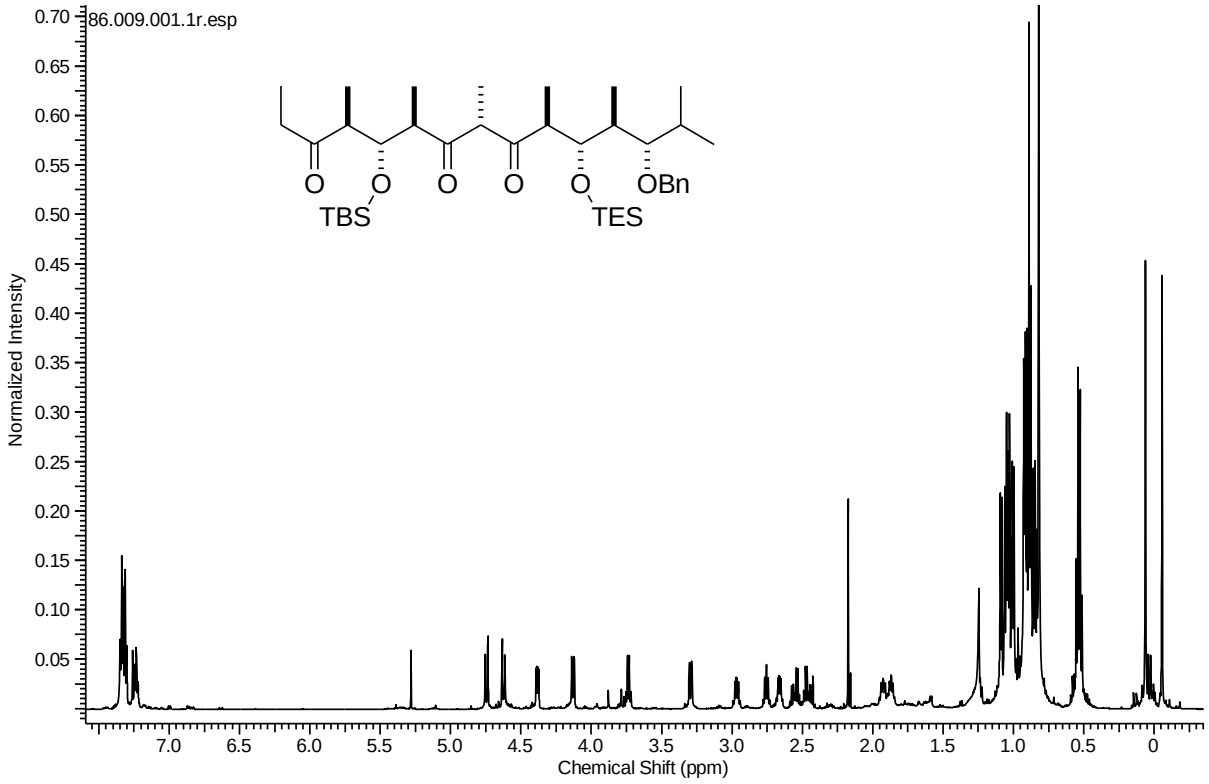



***Figure 4.35:*** *The $^1H$ NMR spectrum of trione* **400** *in $CDCl_3$*

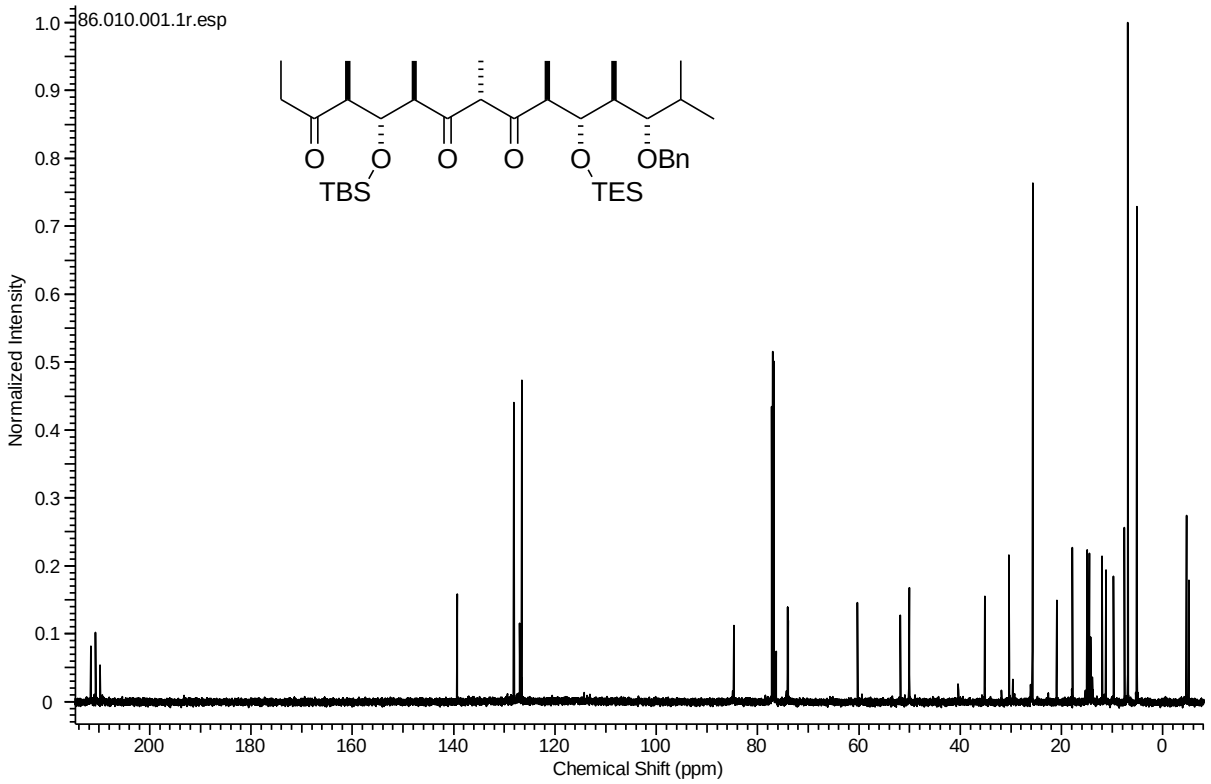


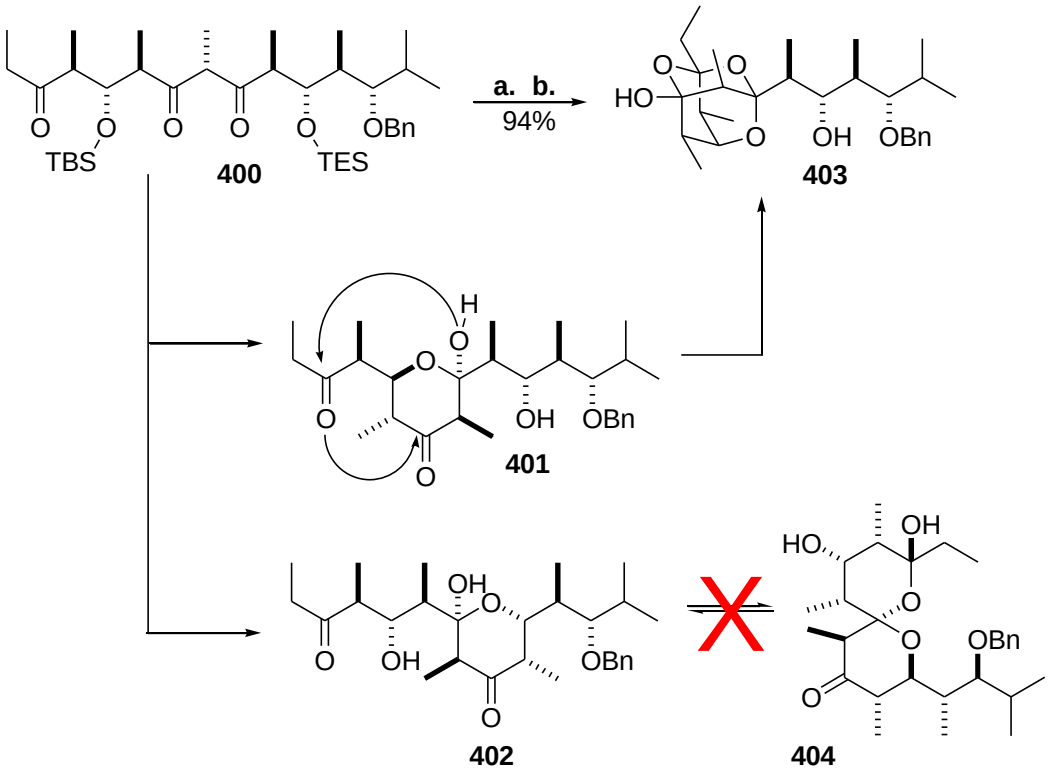

***Figure 4.36:*** *The $^{13}C$ NMR spectrum of trione* **400** *in $CDCl_3$*

### 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*,[76] 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 $C_5$ and $C_{11}$ 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 $^1$H 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.[57] Amazingly, this resulted in the rapid conversion of the complex mixture into one single observable compound by $^1$H NMR. This product was isolated by column chromatography in 94% yield and confirmed as 2,4,6-trioxaadamantane **403** by spectroscopic analysis.[10,26,78-80] This unique compound results from the removal of the $C_5$ and $C_{11}$ 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 $C_3$ carbonyl, which in turn reacts with the $C_7$ carbonyl in a cascade cyclisation leading to the formation of the trioxaadamantane **403**. Surprisingly, the desired hemiacetal **402**, which results from the cyclisation of the free $C_{11}$ alcohol onto the $C_7$ carbonyl, or the potential spiroacetal **404**, which is a further cyclisation of the hemiacetal alcohol on the $C_3$ carbonyl were not observed.




**Reagents and Conditions: a.** TAS-F (5.0eq), $H_2O$ (10.0eq), DMF, RT, 2 hrs; **b.** DBU (cat), $C_6D_6$, 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 $C_6D_6$ (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.

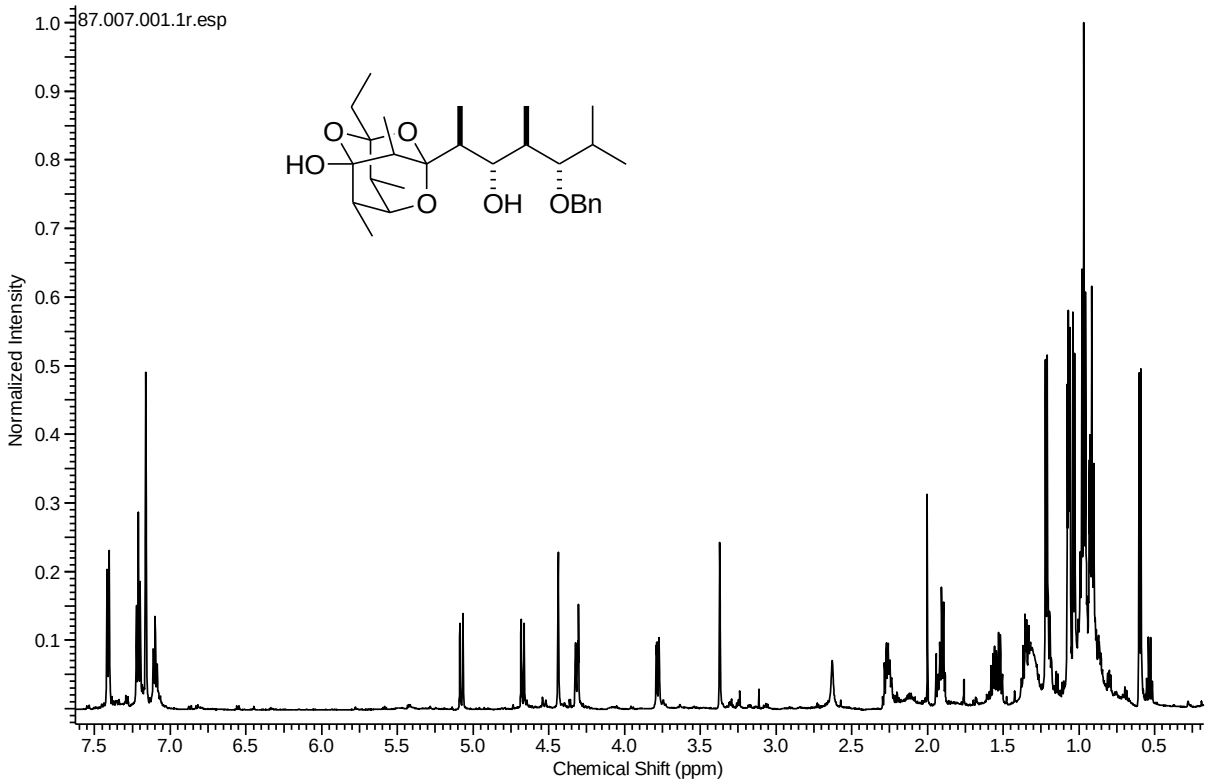



***Figure 4.37:*** *The $^{1}H$ NMR spectrum of 2,4,6-trioxaadamantane* **403** *in $C_6D_6$*

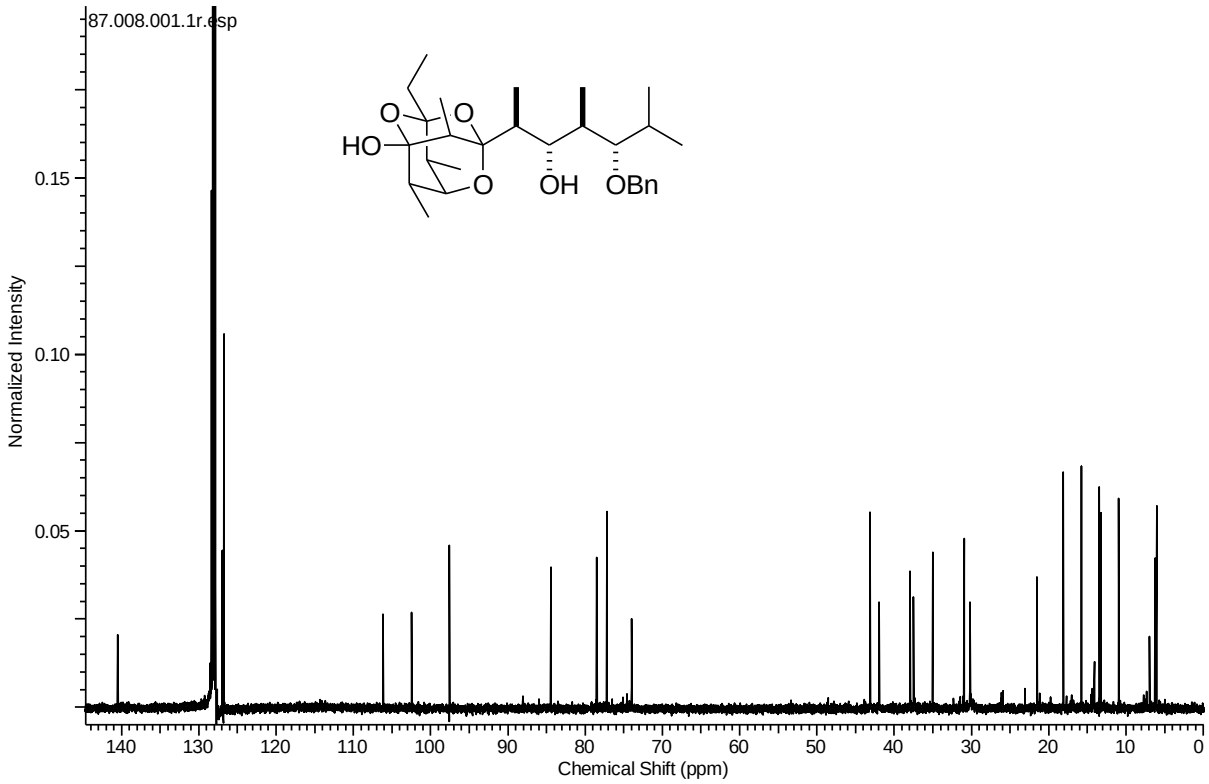


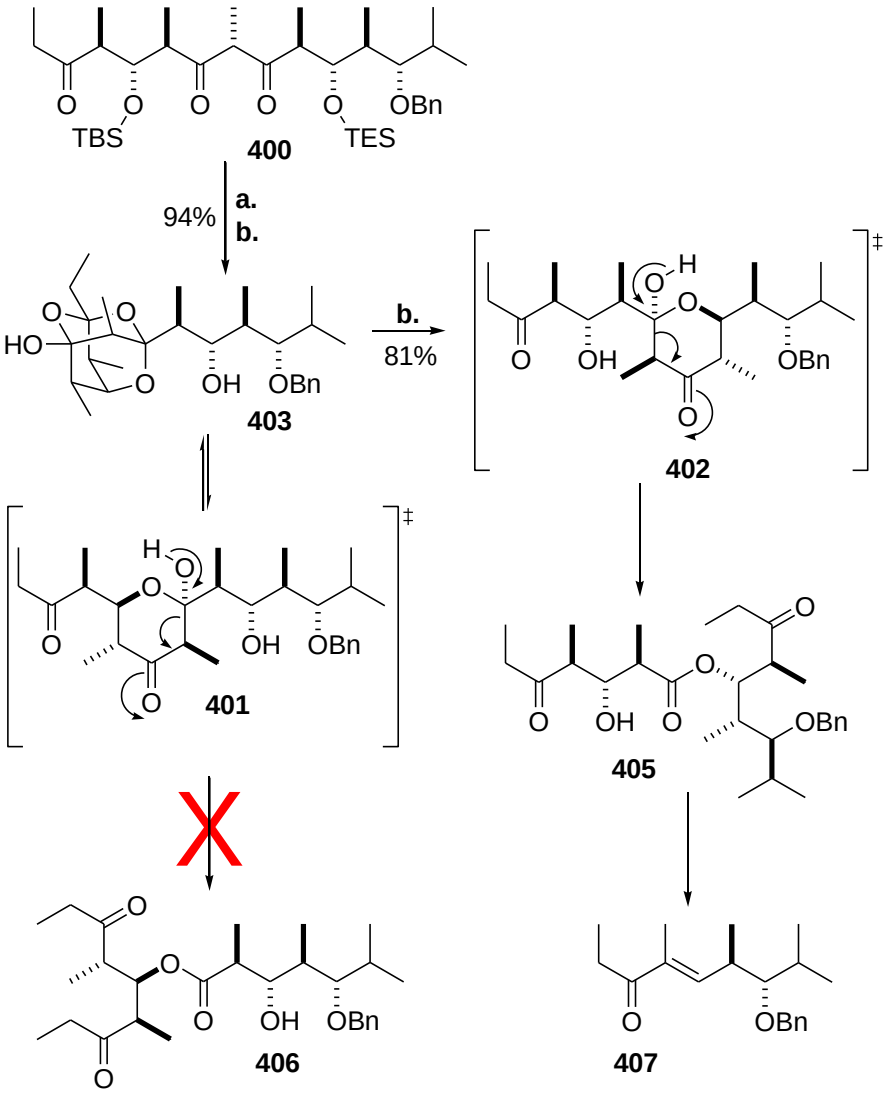

***Figure 4.38:*** *The $^{13}C$ NMR spectrum of 2,4,6-trioxaadamantane* **403** *in $C_6D_6$*

**4.3.11 Retro-Claisen Rearrangement towards the Acquisition of Ester 405**

Although the formation of an analogue of 2,4,6-trioxaadamantane **403** was seen in the previous work of Lister and Perkins,[10] 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[10] that prolonged exposure of 2,4,6-trioxaadamantane (cf-**403**) to DBU did achieve the desired retro-Claisen rearrangement.

In this work when the purified trioxaadamantane **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 trioxaadamantane **403** starting material was consumed the ester **405** product was observed to undergo partial β-elimination[79] 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 trioxaadamantane **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 trioxaadamantane **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 trioxaadamantane **403** preventing an analogous retro-Claisen rearrangement of this acetal **401** to produce ester **406**. The thermodynamic stability of the trioxaadamantane **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), $H_2O$ (10.0eq), DMF, RT, 2 hrs; **b.** DBU (cat), $C_6D_6$, RT, 8 hrs, then purified and recycled.

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

The $^1$H NMR spectrum of ester **405** (Figure 4.39) shows an oxymethine 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 oxymethine resonance at δ 5.45 is indicative of an ester moiety. The methyl methine at δ 2.10 also shows additional coupling to the benzyloxymethine proton resonance at δ 3.19 (dd, J = 7.1, 3.9 Hz). The benzyloxymethine also displays the predicted coupling to the dimethyl methine resonance at δ 1.82 (apt qn d, 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 oxymethine 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.

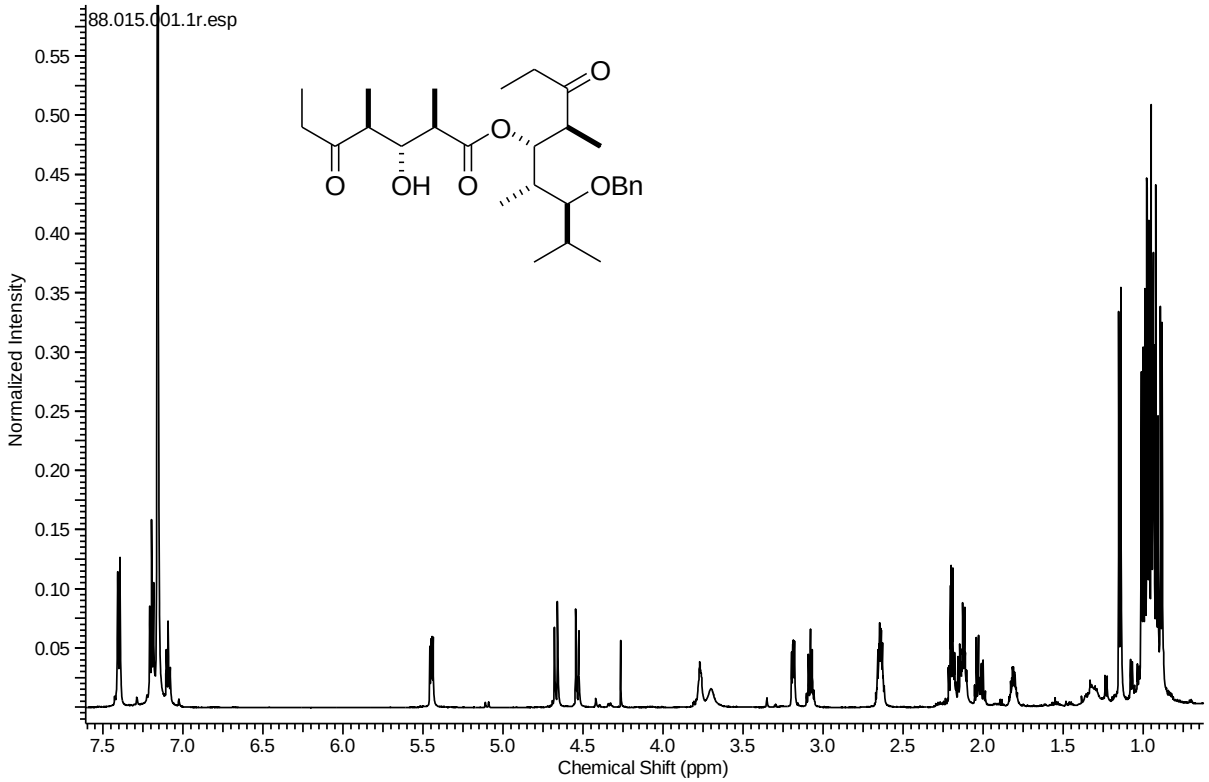



***Figure 4.39:*** *The $^{1}H$ NMR spectrum of acyclic ester* **405** *precursor in $C_6D_6$*

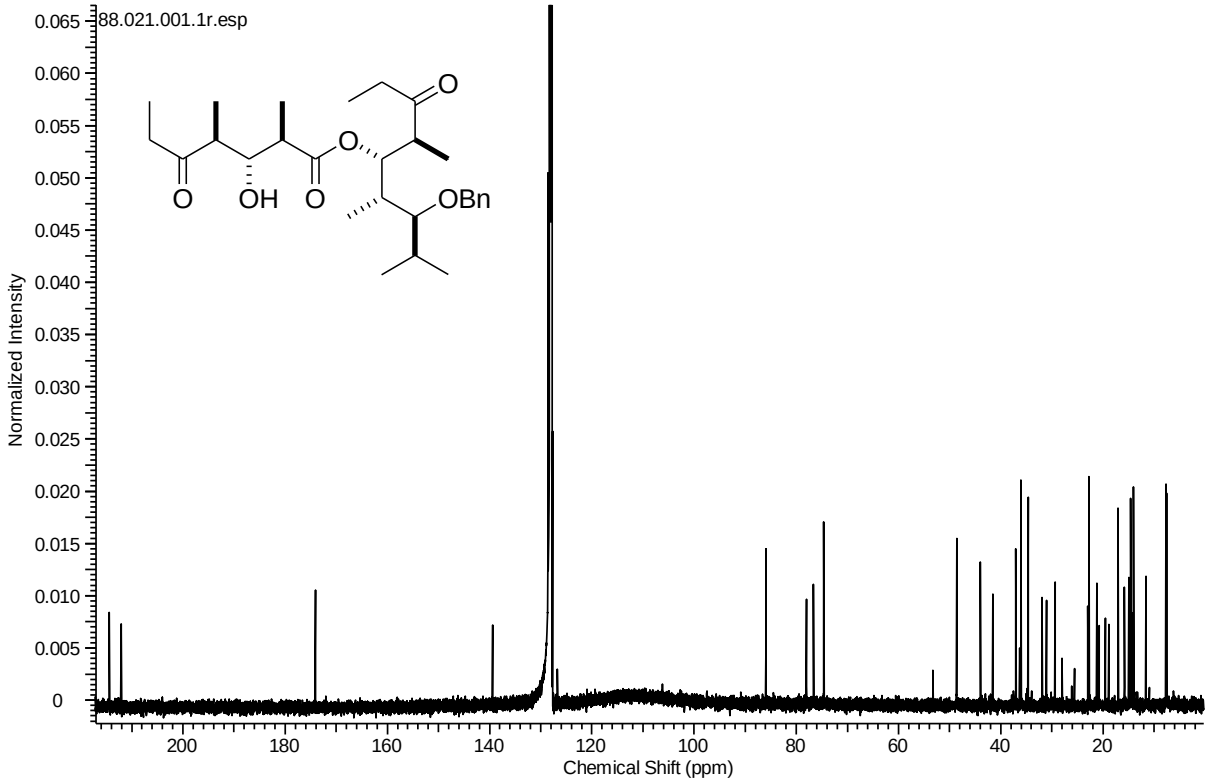
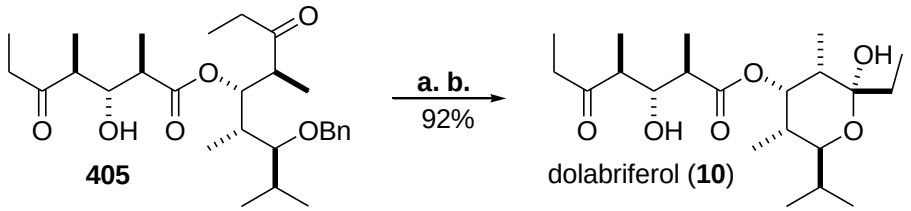



***Figure 4.40:*** *The $^{13}C$ NMR spectrum of acyclic ester* **405** *precursor in $C_6D_6$*

### 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 $C_{13}$ benzyl ether protecting group by hydrogenolysis.[60,81] (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.




**Reagents and Conditions: a.** $H_2$, Pd/C (excess), EtOH, RT, 6 hrs; **b.** $CDCl_3$, RT, 12 hrs.

***Scheme 4.26:*** *Deprotection and cyclisation of acyclic ester* **405** *to give dolabriferol* (**10**)

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

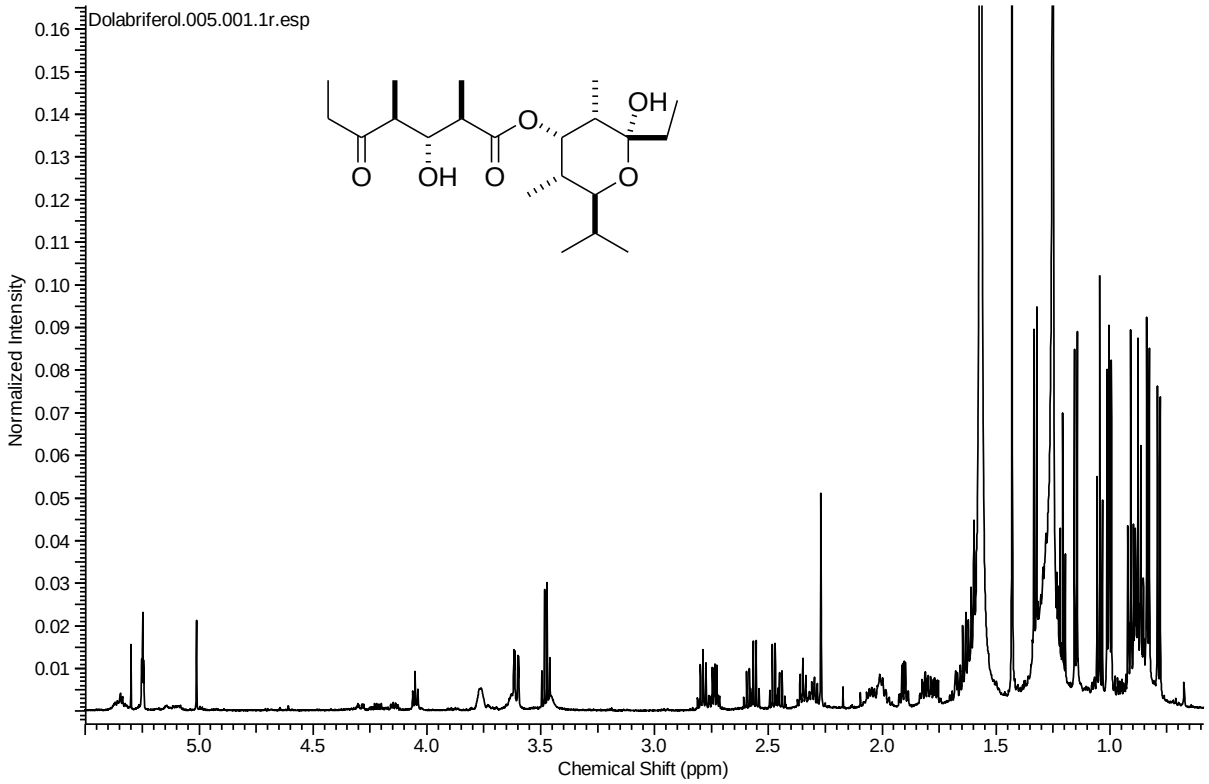



***Figure 4.41:*** *The $^{1}H$ NMR spectrum of dolabriferol* (**10**) *in CDCl*

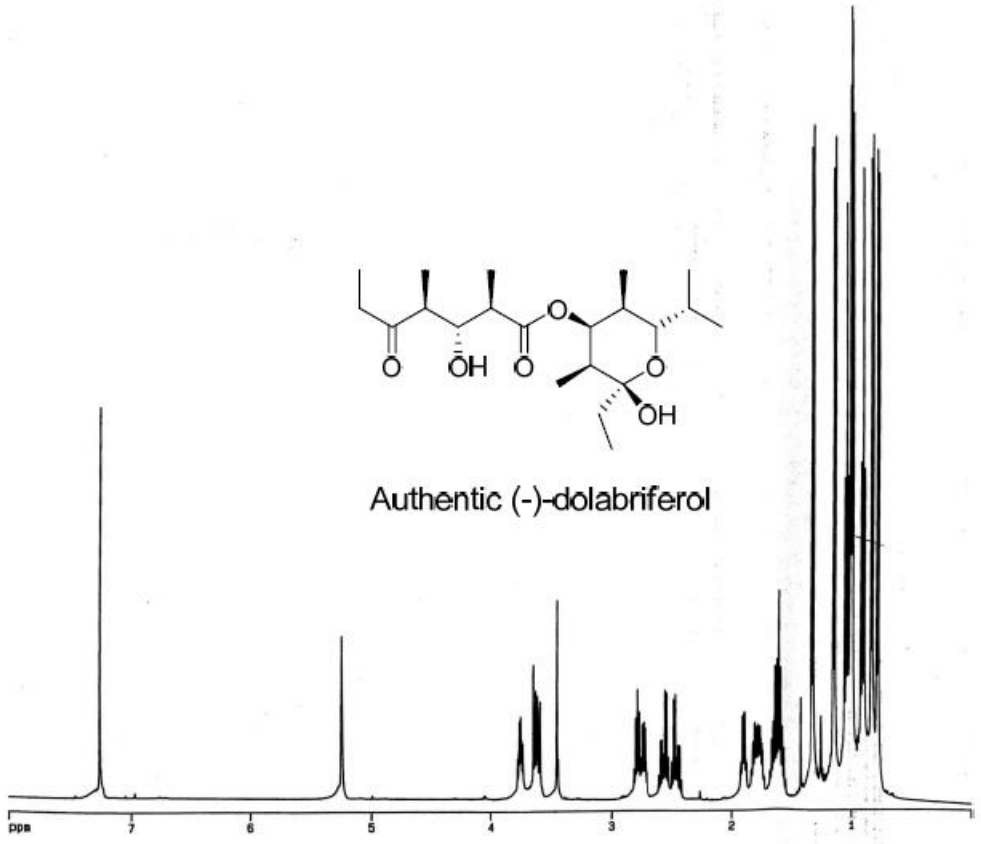



***Figure 4.42:*** *The $^{1}H$ NMR spectrum of authentic dolabriferol* (**10**) *in $CDCl_3$*

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.[8,9] This in turn matches the data published (Table 4.1) of the authentic isolated dolabriferol (**10**) sample by Ciavatta and co-workers.[2] 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**).

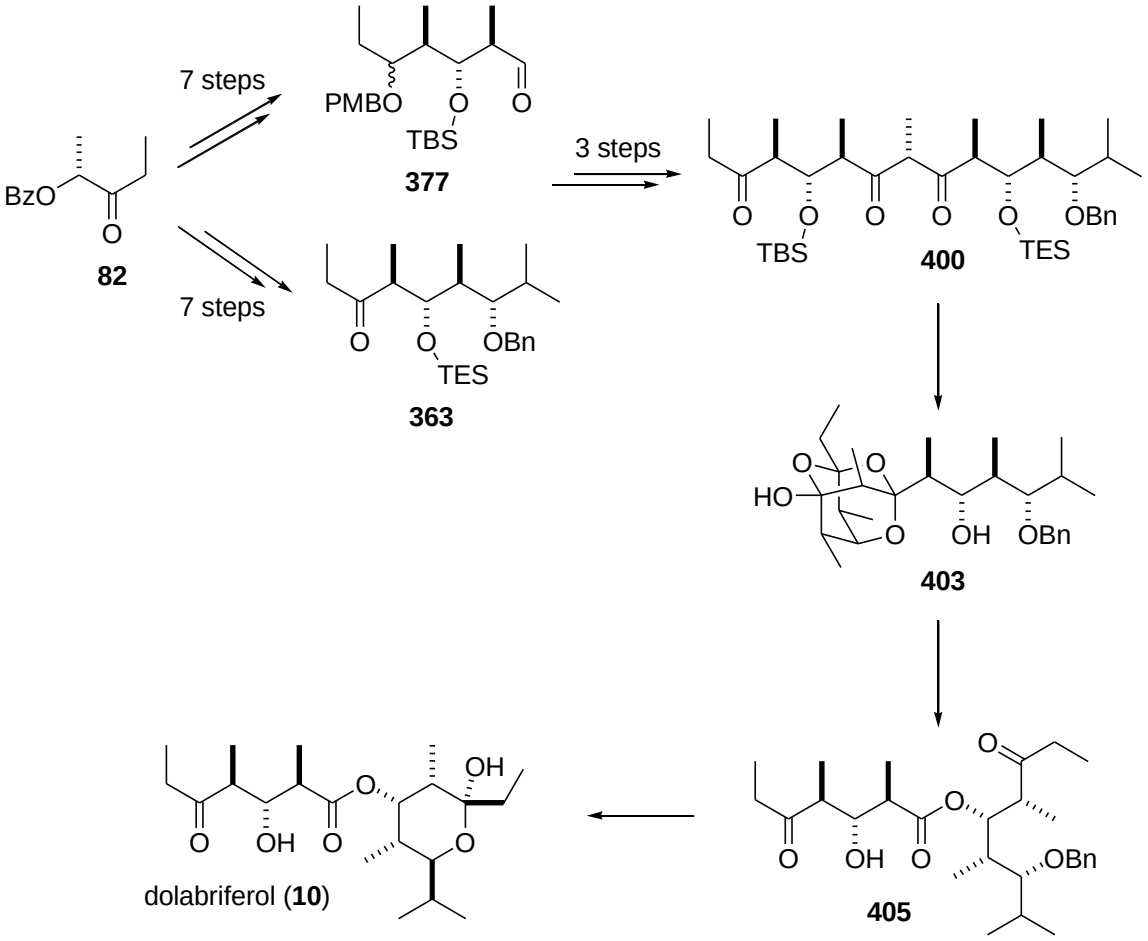
| Position | δ $^{1}$H Natural | M | (Hz) | δ$^{1}$H Synthetic | M | (Hz) |
|---|---|---|---|---|---|---|
| **1** | 1.04 | t | 7.2 | 1.04 | t | 7.2 |
| **2** | 2.46 | dq | 14.5, 7.2 | 2.46 | dq | 14.5, 7.2 |
| | 2.57 | dq | 14.5, 7.2 | 2.57 | dq | 14.5, 7.2 |
| **3** | - | - | - | | | |
| **4** | 2.78 | dq | 7.1, 7.1 | 2.79 | dq | 7.2, 7.2 |
| **5** | 1.14 | d | 7.1 | 1.15 | d | 7.2 |
| **6** | 3.75 | m | - | 3.76 | m | |
| **7** | 2.73 | dq | 4.3, 7.1 | 2.73 | dq | 4.8, 7.1 |
| **8** | 1.32 | d | 7.1 | 1.33 | d | 7.1 |
| **9** | - | - | - | | | |
| **10** | 1.60 | m | - | 1.62 | m | |
| **11** | 0.91 | t | 7.4 | 0.91 | t | 7.3 |
| **12** | - | - | - | | | |
| **13** | 1.90 | dq | 2.5, 7.2 | 1.91 | dq | 2.8, 7.2 |
| **14** | 0.99 | d | 7.2 | 1.00 | d | 7.2 |
| **15** | 5.24 | dd | 2.7, 2.5 | 5.24 | t | 2.7 |
| **16** | 1.78 | ddq | 2.7, 7.0, 10.5 | 1.79 | dqd | 2.7 6.9 10.5 |
| **17** | 0.78 | d | 7.0 | 0.78 | d | 6.9 |
| **18** | 3.60 | dd | 2.0, 10.5 | 3.60 | dd | 2.2, 10.5 |
| **19** | 1.83 | dqq | 2.0, 6.8, | 1.83 | dqq | 2.0, 6.9, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 6.8 | | | 6.9 |
| **20** | 1.00 | d | 6.8 | 1.01 | d | 6.9 |
| **21** | 0.83 | d | 6.8 | 0.83 | d | 6.9 |
| **OH-6** | 3.65 | | | 3.61 | br | |
| **OH-12** | 3.45 | | | 3.46 | br | |

***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 contolled *anti*-boron mediated aldol reactions to install all but the $C_6$ 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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# Chapter Five

# Experimental Procedures for Chapters Two to Four

## 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 ($KMnO_4$, 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 δ 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 $CHCl_3$ (δ 7.26) was used as internal reference, and the spectra recorded in $C_6D_6$, the peak due to residual $C_6H_6$ (δ 7.15) was used as internal reference. $^1H$ NMR data were recorded as follows: chemical shift (δ), 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 (δ 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 (δ 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.

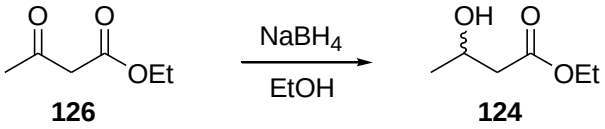
Most starting materials and reagents were available from the Sigma Aldrich Chemical Company and were used as supplied, or dried and distilled using standard procedures. Triethylamine ($NEt_3$), pyridine and commercially available aldehydes were distilled from calcium hydride under nitrogen prior to use. 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 ($Et_2O$) were dried using sodium metal, and then distilled as required from sodium-benzophenone ketyl under nitrogen. Dichloromethane ($CH_2Cl_2$) 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

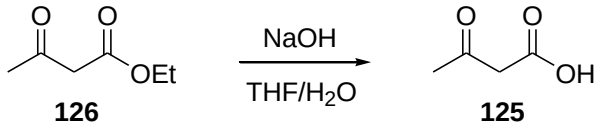
**3-Hydroxy-butyric acid ethyl ester (124)**




**126** **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 $NH_4Cl$ solution (100 mL), extracted with $Et_2O$ (3*100 mL), washed with brine (100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% $Et_2O/CH_2Cl_2$) 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, C*H*(OH)) 4.15 (2H, q, 7.2 Hz, OC*H*$_2$CH$_3$) 3.09 (1H, brs, CH(O*H*)) 2.46 (1H, dd, 16.4, 3.4 Hz, CH(OH)C*H*$_A$CH$_B$C(=O)) 2.40 (1H, dd, 16.4, 8.8 Hz, CH(OH)CH$_A$C*H*$_B$C(=O)) 1.25 (3H, t, 7.2 Hz, OCH$_2$C*H*$_3$) 1.20 (3H, d, 6.4 Hz, C*H*$_3$CH(OH)) $^{13}$C NMR (150MHz; $CDCl_3$) δ 172.91, 64.17, 60.61, 42.69, 22.34, 14.10.

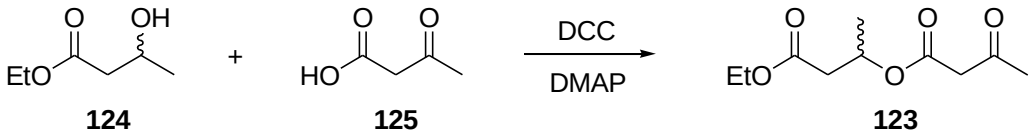
**3-Oxo-butanoic acid (125)**




**126** **125**

To a solution of ethyl acetoacetate (**126**) (2.0 g; 15.5 mmol) in THF (12 mL) and $H_2O$ (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 ($Na_2SO_4$) 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, COO*H*) 3.49 (2H, s, C(=O)C*H*$_2$COOH) 2.26 (3H, s, C*H*$_3$C(=O)) $^{13}$C NMR (150MHz; $CDCl_3$) δ 201.17, 172.52, 49.26, 30.14.

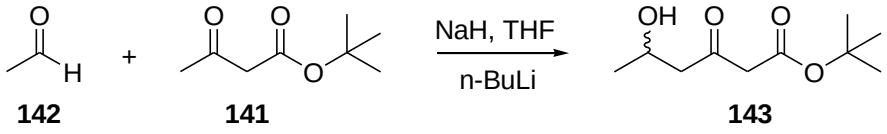
**3-Oxo-butyric acid 2-ethoxycarbonyl-1-methyl-ethyl ester (123)**




**124** **125** **123**

To a stirring solution of β-hydroxy-ester **124** (1.0 g; 7.6 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (3*10 mL) and the filtrated concentrated *in vacuo*. The mixture was purified by column chromatography (5% $Et_2O/CH_2Cl_2$) to yield diester **123** (1.23 g; 75%) as yellow oil. $R_F$ = 0.30, $^1$H NMR (600MHz; $CDCl_3$) δ 5.27 (1H, m, $CH_3CHO$) 4.07 (2H, q, 7.2 Hz, $OCH_2CH_3$) 3.35 (2H, s, $C(=O)CH_2C(=O)$) 2.58 (1H, dd, 15.7, 7.7 Hz, $C(=O)CH_ACH_B$) 2.45 (1H, dd, 15.7, 5.5 Hz, $C(=O)CH_ACH_B$) 2.19 (3H, s, $CH_3C(=O)$) 1.25 (3H, d, 6.4 Hz, $CH_3CHO$) 1.18 (3H, t, 7.2 Hz, $OCH_2CH_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 200.30, 169.86, 166.15, 68.33, 60.54, 50.07, 40.45, 29.88, 19.58, 13.97.

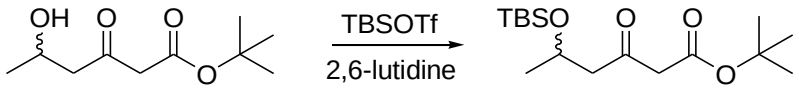
**5-Hydroxy-3-oxo-hexanoic acid tert-butyl ester (143)**




**142** **141** **143**

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 $NH_4Cl$ (70 mL), extracted with $Et_2O$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give the acetate-aldol product **143** (2.03 g) as a yellow oil which contained a minor amount of residual solvent that was used without further purification. $R_F$ = 0.1 (10% $Et_2O/CH_2Cl_2$), $^1$H NMR (200MHz, $CDCl_3$) δ 4.22 (1H, m, $CH_3CH(OH)CH_2$) 3.38 (1H, d, 15 Hz, $C(=O)CH_2C(=O)$) 3.34 (1H, d, 15 Hz, $C(=O)CH_2C(=O)$) 2.66 (1H, dd, 12, 4 Hz, $CH(OH)CCH_2C(=O)$) 2.61 (1H, dd, 12, 4 Hz, $CH(OH)CCH_2C(=O)$) 1.44 (9H, s, $C(CH_3)_3$) 1.18 (3H, d, 6.4 Hz, $CH_3CH(OH)$) $^{13}$C NMR (50MHz, $CDCl_3$) δ 204.13, 166.15, 82.21, 63.68, 51.40, 51.02, 27.85, 22.31

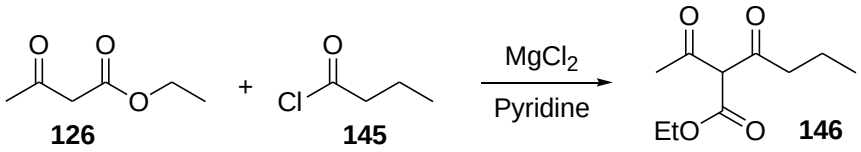
**5-(tert-Butyl-dimethyl-silanyloxy)-3-oxo-hexanoic acid tert-butyl ester (144)**




**143** **144**

To a stirred solution of β-ketoester **143** (0.30 g; 14.8 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ (50 mL) extracted with $CH_2Cl_2$ (3*20 mL) washed with brine (10 mL) dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50%$CH_2Cl_2$/hexanes) gave the TBS-protected β-Keto-ester **144** (0.40 g; 84%) as a clear yellow oil. $R_F$ = 0.33, $^1$H NMR (200MHz, $CDCl_3$) δ 4.29 (1H, m, $CH_3CH$(OTBS)$CH_2$) 3.36 (2H, s, C(=O)C$H_2$C(=O)) 2.70 (1H, dd, 7, 15 Hz, CH(OTBS)CC$H_2$C(=O)) 2.53 (1H, dd, 7, 15 Hz, CH(OTBS)CC$H_2$C(=O)) 1.45 (9H, s, C(C$H_3$)$_3$) 1.17 (3H, d, 6 Hz, C$H_3$CH(OTBS)$CH_2$) 0.85 (9H, s, OSi($CH_3$)$_2$C(C$H_3$)$_3$) 0.05 (3H, s, OSi(C$H_3$)$_2$C($CH_3$)$_3$) 0.03 (3H, s, OSi(C$H_3$)$_2$C($CH_3$)$_3$) $^{13}$C NMR (50MHz, $CDCl_3$) 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)**

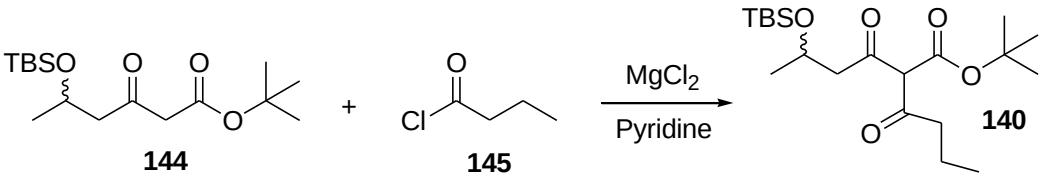



**126** **145** **146**

Dry magnesium chloride (0.93 g; 10 mmol) in $CH_2Cl_2$ (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 $Et_2O$ (3*20 mL), dried ($MgSO_4$) 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), $^1$H NMR (200MHz, $CDCl_3$) δ 17.8 (1H, s, C=C(O*H*)) 4.26 (2H, m, 7 Hz, $CH_3CH_2O$) 2.62 (2H, t, 7.3 Hz , (C=O)C$H_2CH_2CH_3$) 2.34 (3H, s, C$H_3$(C=O)) 1.65 (2H, m, 7.3 Hz, $CH_3CH_2CH_2$) 1.34 (3H, t, 7 Hz,

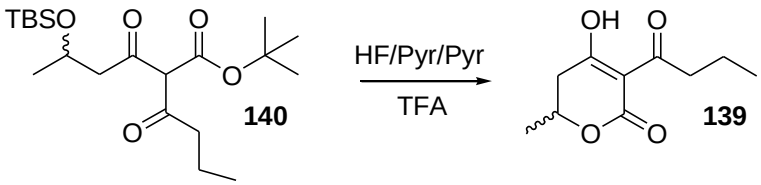
$OCH_2CH_3$) 0.96 (3H, t, 7.3 Hz, $CH_2CH_2CH_3$); $^{13}C$ NMR (50MHz, $CDCl_3$) δ 198.55, 195.66, 167.16, 108.56, 60.60, 39.51, 25.58, 19.11, 14.01, 13.71

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




Dry magnesium chloride (45 mg; 0.78 mmol) in $CH_2Cl_2$ (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 $Et_2O$ (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 ($CH_2Cl_2$) yielded the TBS protected acylated product **140** (121 mg; 66%) as a clear oil. $R_F$ = 0.53, $^1H$ NMR (200MHz, $CDCl_3$) δ 17.40 (1H, s, C=C(O*H*)) 4.33 (1H, m, $CH_3CH$(OTBS)$CH_2$) 2.80 (1H, dd, 7, 15 Hz, CH(OTBS)$CCH_2$C(=O)) 2.63 (1H, dd, 7, 15 Hz, CH(OTBS)$CCH_2$C(=O)) 2.54 (2H, m, C(=O)$CH_2CH_2CH_3$) 1.66 (2H, m, C(=O)$CH_2CH_2CH_3$) 1.55 (9H, s, $C(CH_3)_3$), 1.19 (3H, d, 6 Hz, $CH_3$CH(OTBS)$CH_2$) 0.96 (3H, t, 7.2 Hz, C(=O)$CH_2CH_2CH_3$) 0.84 (9H, s, $OSi(CH_3)_2C(CH_3)_3$) 0.03 (3H, s, $OSi(CH_3)_2C(CH_3)_3$) -0.01 (3H, s, $OSi(CH_3)_2C(CH_3)_3$) $^{13}C$ 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.

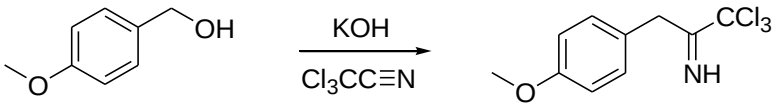
**3-Butyryl-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one (139)**




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 $H_20$ (86 µL) at RT. The reaction was stirred at RT for one

day then diluted with $Et_2O$ (10 mL) and quenched with $NaHCO_3$ (20 mL). The organic extractwas washed with $CuSO_4$ (20 mL), brine (20 mL), dried ($Na_2SO_4$) and concentrated in vacuo. The deprotected TBS compound (20 mg; 0.07 mmol) was redissolved in $CH_2Cl_2$ (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 ($CH_2Cl_2$) yielded the model compound **139** (8 mg; 57%) as a clear oil, $R_F$ = 0.60, $^1$H NMR (200MHz, $CDCl_3$) δ 13.17 (1H, bs, C=C(O*H*)) 4.62 (1H, m, OC*H*($CH_3$)$CH_2$) 3.03 (2H, m, OCH($CH_3$)C*H*$_2$C(=O) 2.63 (2H, t, 5.6 Hz, C(=O)C*H*$_2$$CH_2CH_3$) 1.70 (2H, m, C(=O)$CH_2$C*H*$_2$$CH_3$) 1.54 (3H, d, 6 Hz, OCH(C*H*$_3$)$CH_2$) 0.99 (3H, t, 7.2 Hz, C(=O)$CH_2CH_2$C*H*$_3$) $^{13}$C NMR (50MHz, $CDCl_3$) δ 195.36, 192.93, 164.60, 106.04, 75.60, 41.16, 37.04, 20.46, 19.82, 13.96

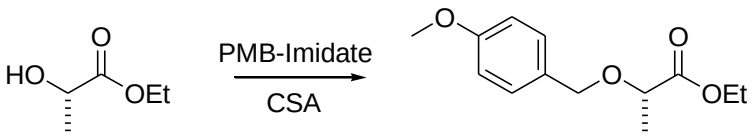
**Para-methoxybenzyl trichloroacetimidate (147)**




**148** **147**

To a solution of p-methoxy benzyl alcohol (**148**) (18 mL; 0.14 mol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (3* 50 mL), dried ($Na_2SO_4$) 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. $^1$H NMR (400MHz, $CDCl_3$) δ 8.39 (1H. s, N*H*) 7.39 (2H, d, 8.6 Hz, Ar*H*) 6.92 (2H, d, 8.6 Hz, Ar*H*) 5.29 (2H, s, OC*H*$_2$PMP) 3.82 (3H, s, OC*H*$_3$) $^{13}$C NMR (100MHz; $CDCl_3$) δ 207.33, 162.64, 159.78, 129.75, 127.56, 113.94, 70.77, 55.25.

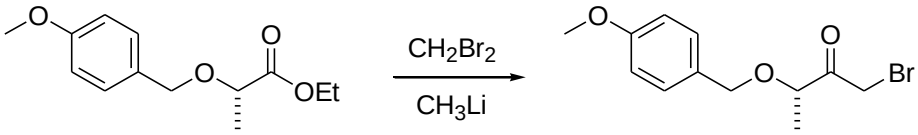
**(*S*)-Ethyl 2-(4-methoxybenzyloxy) propanoate (133)**




**132** **133**

To a solution of ethyl-(*S*)-lactate (**132**) (10.0 mL; 0.07 mol) in $CH_2Cl_2$ (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 $NaHCO_3$ (200 mL) and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3*100 mL). Organic extracts were combined, dried ($Na_2SO_4$) and concentrated in vacuo. The slurry produced was triturated (25% $CH_2Cl_2$/hexanes) and concentrated *in vacuo*. Purification by column chromatography (2% $Et_2O/CH_2Cl_2$) gave the protected hydroxy-ester **133** (11.84g, 71%) as yellow oil. $R_F$ = 0.23 ($CH_2Cl_2$), $^1$H NMR (600MHz, $CDCl_3$) δ 7.26 (2H, d, 8.2 Hz, Ar*H*) 6.85 (2H, d, 8.2 Hz, Ar*H*) 4.60 (1H, d, 11.1 Hz, OC$H_A$CH$_B$PMP) 4.36 (1H, d, 11.1 Hz, OCH$_A$C$H_B$PMP) 4.19 (2H, q, 7 Hz, OC$H_2$CH$_3$) 3.99 (1H, q, 6.8 Hz, C*H*(CH$_3$)OPMB) 3.77 (3H, s, OC$H_3$) 1.39 (3H, d, 6.8 Hz, CH(C$H_3$)OPMB) 1.28 (3H, t, 7 Hz, OCH$_2$C$H_3$) $^{13}$C NMR (150MHz, $CDCl_3$) 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)**

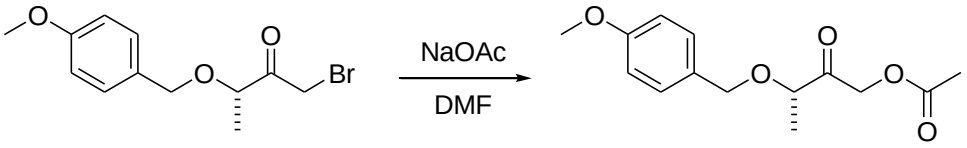



**133** **134**

To a solution of stirring hydroxy-ester **133** (5.0 g; 21 mmol) and $CH_2Br_2$ (2.95 mL; 42 mmol) in THF (38mL) $CH_3Li$ (26.5 mL of a 1.6 M solution in $Et_2O$; 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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the brominated-ketone **134** (4.76 g, 79%) as a yellow oil. $R_F$ = 0.40, $^1$H NMR (600MHz, $CDCl_3$) δ 7.27 (2H, d, 7.2 Hz, Ar*H*) 6.89 (2H, d, 7.2 Hz, Ar*H*) 4.55

(1H, d, 11 Hz, OC$H_A$CH$_B$PMP) 4.50 (1H, d, 11 Hz, OCH$_A$C$H_B$PMP) 4.18 (1H, q, 6.8 Hz, C*H*OPMB) 4.15 (2H, s, C$H_2$Br) 3.80 (3H, s, OC$H_3$) 1.38 (3H, d, 6.8 Hz, CH(C$H_3$)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

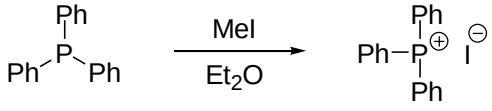
**(*S*)-1-Acetoxy-3-(p-methoxybenzyloxy)-butan-2-one (135)**




**134** **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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) 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, Ar*H*) 6.85 (2H, d, 8.3 Hz, Ar*H*) 4.90 (1H, d, 17.6 Hz, OC$H_A$CH$_B$C(=O)) 4.84 (1H, d, 17.6 Hz, OCH$_A$C$H_B$C(=O)) 4.50 (1H, d, 11 Hz, OC$H_A$CH$_B$PMP) 4.45 (1H, d, 11 Hz, OCH$_A$C$H_B$PMP) 3.99 (1H, q, 6.8 Hz, C*H*(CH$_3$)OPMB) 3.75 (3H, s, OC$H_3$) 2.10 (3H, s, C$H_3$C(=O)) 1.32 (3H, d, 6.8 Hz, CH(C$H_3$)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.

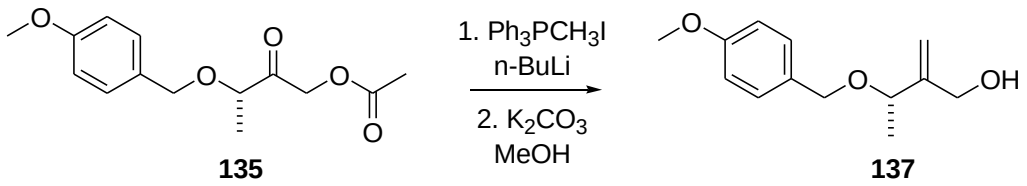
**Methyl triphenylphosphonium Iodide (149)**




**149**

To a solution of triphenylphosphine (20.0 g; 76.3 mmol) in $Et_2O$ (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 $Et_2O$ (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, Ar*H*) 3.25 (3H, d, 13.2 Hz, PC$H_3$).

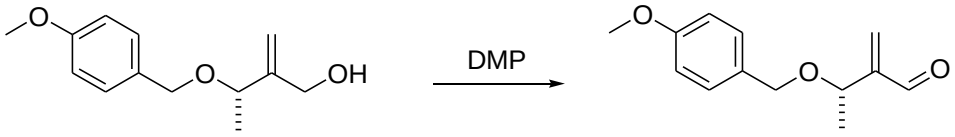
**(*S*)-3-(4-Methoxy-benzyloxy)-2-methylene-butan-1-ol (137)**




**135** **137**

To a stirred suspension of $CH_3Ph_3PI$ (**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 $Et_2O$; 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), $K_2CO_3$ (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% $Et_2O/CH_2Cl_2$) yielded the hydroxy-alkene **137** (0.65 g; 77%) as clear oil. $R_F$ = 0.20, $^1$H NMR (600MHz, $CDCl_3$) δ 7.27 (2H, d, 8.5 Hz, Ar*H*), 6.89 (2H, d, 8.5 Hz, Ar*H*) 5.22 (1H, s, $HOCH_2C=C\mathit{H}_A CH_B$) 5.12 (1H, s, $HOCH_2C=CH_A C\mathit{H}_B$) 4.48 (1H, d, 11.4 Hz, $OC\mathit{H}_A CH_B$PMP) 4.34 (1H, d, 11.4 Hz, $OCH_A C\mathit{H}_B$PMP) 4.29 (1H, d, 13.5 Hz, $C\mathit{H}_A CH_B OH$) 4.17 (1H, d, 13.5 Hz, $CH_A C\mathit{H}_B OH$) 4.10 (1H, q, 6.6 Hz, C*H*($CH_3$)OPMB) 3.81 (3H, s, $OC\mathit{H}_3$) 1.36 (3H, d, 6.6 Hz, CH($C\mathit{H}_3$)OPMB) $^{13}$C NMR (150MHz, $CDCl_3$) 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)**

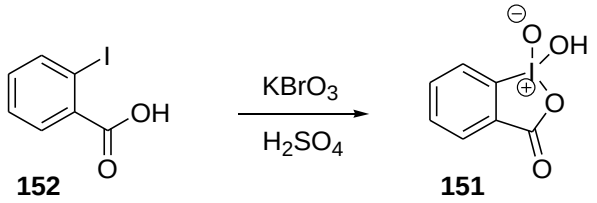



**137** **131**

To a stirring solution of the hydroxy-alkene **137** (0.5 g; 2.24 mmol) in $CH_2Cl_2$ (30 mL) was added DMP (1.25 g; 2.91 mmol). The reaction was stirred for one hour then quenched with $Na_2S_2O_3$ (3.6 g in 60 mL of $NaHCO_3$) diluted with diethyl ether (40 mL) washed with $NaHCO_3$ (30 mL), brine (20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) yielded the α-β-unsaturated aldehyde **131** (0.46 g; 94%) as a clear oil. $R_F$ = 0.33, $^1$H NMR (600MHz; $CDCl_3$) δ 9.66 (1H, s, C*H*(=O)), 7.28 (2H, d, 8.4 Hz, Ar*H*) 6.91 (2H, d, 8.4 Hz, Ar*H*) 6.61 (1H, s, $C=C\mathit{H}_A CH_B$) 6.17 (1H, s, $C=CH_A C\mathit{H}_B$)

4.48-4.35 (1H, m, C*H*($CH_3$)OPMB) 4.44 (1H, d, 11.1 Hz, OC$H_A$$CH_B$PMP) 4.37 (1H, d, 11.1 Hz, OC$H_A$C$H_B$PMP) 3.83 (3H, s, OC$H_3$) 1.35 (3H, d, 6.3 Hz, CH(C$H_3$)OPMB) $^{13}$C (150MHz; $CDCl_3$) δ 193.75, 159.07, 151.70, 133.56, 130.16, 129.10, 113.67, 70.57, 70.46, 55.11, 21.28

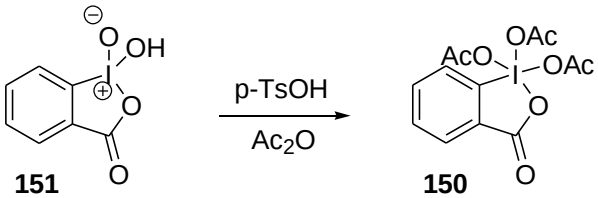
**2-Iodoxybenzoic acid (151)**




**152** **151**

To a mixture of 2-iodobenzoic acid (**152**) (45.8 g; 0.18 mol) in a 0.7 M solution of $H_2SO_4$ (370 mL) at 55°C was added $KBrO_3$ (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 $H_2O$ (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.

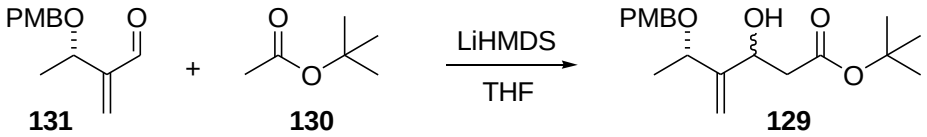
**1,1,1-Triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1H)-one (150)**




**151** **150**

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.$H_2O$ (250 mg; 0.74 mmol). The mixture was heated at 80°C for 2-3hrs then cooled on ice overnight. The solid precipitate was filtered under vacuum and washed with $Et_2O$ (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.

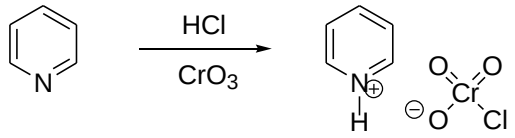
**(*S*)-3-Hydroxy-5-(4-methoxy-benzyloxy)-4-methylene-hexanoic acid tert-butyl ester (129)**




**131** **130** **129**

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 $NH_4Cl$ (100 mL), extracted $Et_2O$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (5% $Et_2O/CH_2Cl_2$) gave the acetate-aldol product **129** (0.72 g; 95%) as a clear oil. $R_F$ = 0.32, $^1$H NMR (600MHz, $CDCl_3$) δ 7.26 (2H, d, 8.1 Hz, Ar*H*) 6.87 (2H, d, 8.1 Hz, Ar*H*) 5.30 (1H, s, $CH_3CHC(=CH_ACH_B)$) 5.21 (1H, s, $CH_3CHC(=CH_ACH_B)$) 4.60 (1H, m, C*H*OH) 4.44 (1H, d, 12 Hz, $OCH_ACH_BPMP$) 4.30 (1H, d, 12 Hz, $OCH_ACH_BPMP$) 4.08 (1H, q, 6.6 Hz, C*H*OPMB) 3.80 (3H, s, $OCH_3$) 2.59 (2H, m, $C(=O)CH_2C(=O)$) 1.46 (9H, s, $C(CH_3)_3$) 1.36 (3H, d, 6.6 Hz, $CH_3CHOPMB$) $^{13}$C NMR (150MHz, $CDCl_3$) δ 172.08, 159.10, 150.41, 130.50, 129.21, 113.76, 112.13, 81.30, 75.97, 69.80, 67.87, 55.21, 41.82, 28.04, 20.74

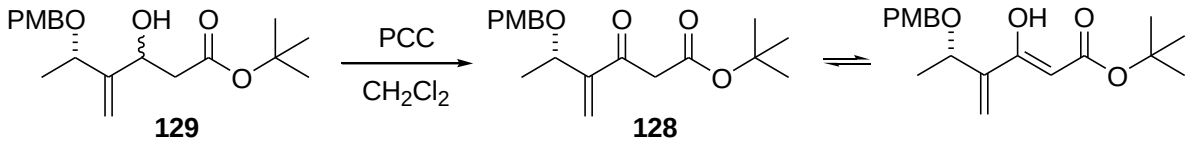
**Pyridinium chlorochromate (153)**




**153**

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 $CrO_3$ (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.

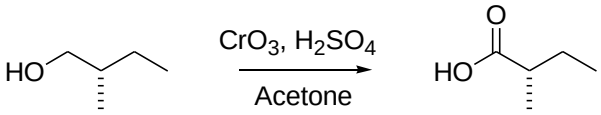
**(*S*)-5-(4-Methoxy-benzyloxy)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (128)**




**129** **128**

To a stirring solution of β-hydroxy ester **129** (500 mg; 1.5 mmol) in $CH_2Cl_2$ (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 ($CH_2Cl_2$) produced the β-keto ester **128** (375 mg; 75%) as clear oil. $R_F$ = 0.60, **Ketone:** $^1$H NMR (600MHz, $CDCl_3$) δ 7.23 (2H, d, 8.6 Hz, Ar*H*) 6.88 (2H, d, 8.6Hz, Ar*H*) 6.24 (1H, s, $CH_3CHC(=CH_AH_B)$) 6.15 (1H, s, $CH_3CHC(=CH_AH_B)$) 4.44 (1H, q, 6.6 Hz, C*H*OPMB) 4.36 (1H, d, 12 Hz, $OCH_AH_BPMP$) 4.32 (1H, d, 12 Hz, $OCH_AH_BPMP$) 3.80 (3H, s, $OCH_3$) 3.68 (1H, d, 15 Hz, $C(=O)CH_AH_BC(=O)$) 3.62 (1H, d, 15 Hz, $C(=O)CH_AH_BC(=O)$) 1.45 (9H, s, $C(CH_3)_3$) 1.28 (3H, d, 6.6 Hz, $CH_3CHOPMB$) $^{13}$C NMR (150MHz, $CDCl_3$) 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; $CDCl_3$) δ 12.35 (1H, s, CO*H*) 7.25 (2H, d, 8.6 Hz, Ar*H*) 6.93 (2H, d, 8.6Hz, Ar*H*) 6.01 (1H, s, $CH_3CHC(=CH_AH_B)$) 5.62 (1H, s, $CH_3CHC(=CH_AH_B)$) 5.27 (1H, s, C(OH)=C*H*C(=O)) 4.52 (1H, q, 6.6 Hz, C*H*OPMB) 4.45 (1H, d, 12 Hz, $OCH_AH_BPMP$) 4.25 (1H, d, 12 Hz, $OCH_AH_BPMP$) 3.81 (3H, s, $OCH_3$) 1.43 (9H, s, $C(CH_3)_3$) 1.36 (3H, d, 6.6 Hz, $CH_3CHOPMB$)

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

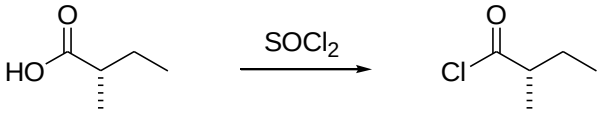



**154** **155**

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 $CrO_3$ (10 g; 0.1 M), $H_2SO_4$ (8.6 mL) and $H_2O$ (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 $Et_2O$ (2*100 mL) and the combined organic extracts were washed with a solution of saturated sodium bicarbonate solution (100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Distillation

of the concentrated mixture gave (*S*)-2-methyl-butanoic acid (**155**) (4.92 g; 85%) as a clear oil. b.p. 78°C; 15mmHg, $^{1}$H NMR (600MHz; $CDCl_3$) δ 2.38 (1H, qn, 7.0 Hz, C*H*$CH_3$) 1.69 (1H, dqn, 14.2, 7.7 Hz, C$H_A$$CH_B$$CH_3$) 1.48 (1H, dqn, 14.2, 7.7 Hz, $CH_A$C$H_B$$CH_3$) 1.15 (3H, d, 7.0 Hz, CHC$H_3$) 0.92 (3H, t, 7.7 Hz, $CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 183.49, 40.85, 26.45, 16.25, 11.43.

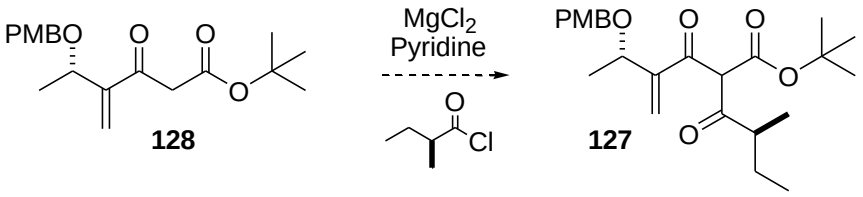
**(*S*)-2-Methyl-butyryl chloride (120)**




**155** **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 $SOCl_2$ (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, $^{1}$H NMR (600MHz; $CDCl_3$) δ 2.80 (1H, qn, 6.9 Hz, C*H*$CH_3$) 1.82 (1H, dqn, 14.2, 7.7 Hz, C$H_A$$CH_B$$CH_3$) 1.60 (1H, dqn, 14.2, 7.7 Hz, $CH_A$C$H_B$$CH_3$) 1.27 (3H, d, 6.9 Hz, CHC$H_3$) 0.97 (3H, t, 7.7 Hz, $CH_2$C$H_3$) $^{13}$C NMR (150MHz; CDCl3) δ 177.72, 52.94, 26.58, 16.53, 11.17.

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

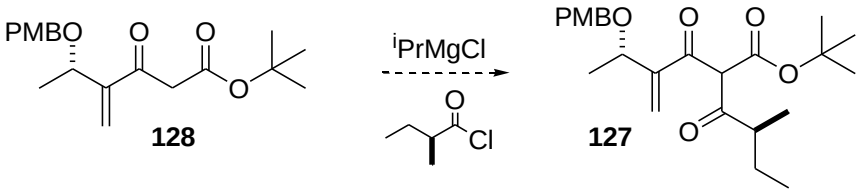



**128** **127**

Dry magnesium chloride (15 mg; 0.16 mmol) in $CH_2Cl_2$ (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 $Et_2O$ (3*10 mL). The organic extracts were washed with $CuSO_4$ solution (5 mL), then dried ($Na_2SO_4$) and

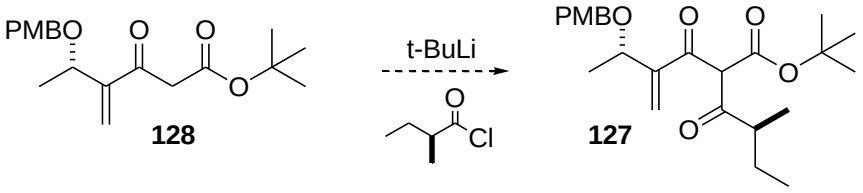
concentrated *in vacuo*. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had occurred and that β-keto ester **128** was recovered following purification by column chromatography.

**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** (100 mg; 0.30 mmol) in THF (1 mL) at -78°C was added $^i$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 $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) 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.

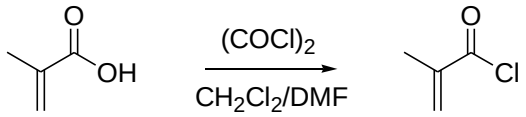
**5-(4-Methoxy-benzyloxy)-2-(2-methyl-butyryl)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (127)**




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 $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) 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.

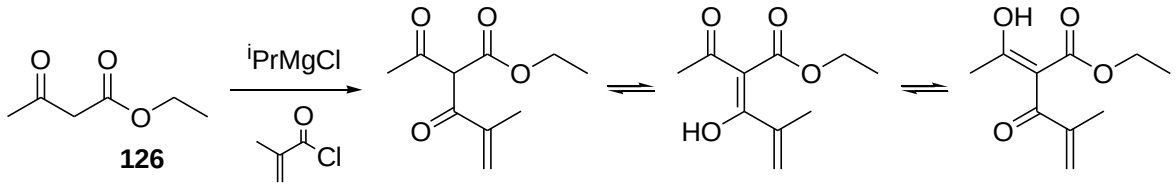
**Methylacryloyl chloride (158)**




**159** **158**

To a solution of methylacrylic acid (**159**) (5.0 g; 5.8 mmol) in $CH_2Cl_2$ (30 mL) at 0°C was added DMF (5 drops) and oxalyl chloride (3 mL of a 2 M solution in $CH_2Cl_2$; 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; $C_6D_6$) δ 6.14 (1H, s, C=C*H*$_A$CH$_B$) 5.20 (1H, s, C=CH$_A$C*H*$_B$) 1.71 (3H, s, CC*H*$_3$) $^{13}$C NMR (100MHz; $C_6D_6$) δ 174.18, 136.71, 128.30, 18.27.

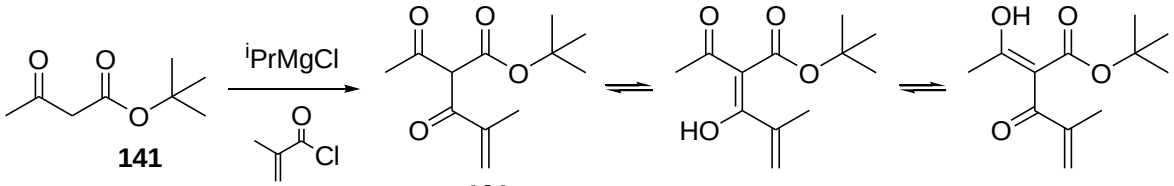
**2-Acetyl-4-methyl-3-oxo-pent-4-enoic acid ethyl ester (160)**




To a solution of ethyl acetoacetate (**126**) (75 µL; 0.76 mmol) in THF (5 mL) at -78°C was added $^i$PrMgCl (0.45 mL of a 2 M solution in THF; 0.9 mmol) dropwise. The mixture was stirred for 30 minutes then methacroloyl 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 $NH_4Cl$ solution (10 mL), extracted with $Et_2O$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) 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*H*$_A$CH$_B$) 5.11 (1H, s, C=CH$_A$C*H*$_B$) 4.24 (2H, q, 7.3 Hz, OC*H*$_2$CH$_3$) 3.71 (1H, s, C(=O)C*H*C(=O)) 2.28 (1H, s, C(=O)C*H*$_3$) 1.92 (3H, brs, C*H*$_3$C=CH$_2$) 1.27 (3H, t, 7.3 Hz, OCH$_2$C*H*$_3$), **Enol:** $^1$H NMR (600MHz; $CDCl_3$) δ 16.85 (1H, s, CO*H*) 5.77 (1H, s, C=C*H*$_A$CH$_B$) 5.22 (1H, s, C=CH$_A$C*H*$_B$) 4.15 (2H, q, 7.3 Hz, OC*H*$_2$CH$_3$) 2.31 (3H, s, C(=O)C*H*$_3$) 1.96 (3H, brs, C*H*$_3$C=CH$_2$) 1.25

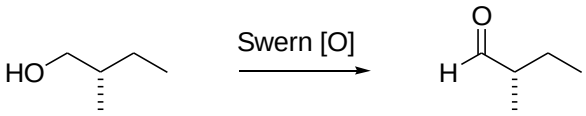
(3H, t, 7.3 Hz, $OCH_2CH_3$) **Enol 1:** $^1$H NMR (600MHz; $CDCl_3$) δ 12.86 (1H, s, CO*H*) 5.77 (1H, s, C=C$H_A$$CH_B$) 5.24 (1H, s, C=$CH_A$C$H_B$) 4.18 (2H, q, 7.3 Hz, OC$H_2$$CH_3$) 2.27 (3H, s, C(=O)C$H_3$) 1.93 (3H, brs, C$H_3$C=$CH_2$) 1.21 (3H, t, 7.3 Hz, $OCH_2CH_3$)

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




To a solution of t-butyl acetoacetate (**141**) (104 µL; 0.63 mmol) In THF (5 mL) at -78°C was added $^i$PrMgCl (0.38 mL of a 2 M solution in THF; 0.75 mmol) dropwise. The mixture was stirred for 30 minutes then methacroloyl 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 $NH_4Cl$ solution (10 mL), extracted with $Et_2O$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the tricarbonyl adduct **161** (101 mg; 71%) as clear oil. $R_F$ = 0.71, **Ketone:** $^1$H NMR (600MHz; $CDCl_3$) δ 6.03-5.99 (1H, m, C=C$H_A$$CH_B$) 5.84-5.80 (1H, m, C=$CH_A$C$H_B$) 4.85 (1H, s, C(=O)C*H*C(=O)) 2.18 (3H, s, C$H_3$C(=O)) 2.00-1.91 (3H, m, C$H_3$C=$CH_2$) 1.47 (9H, s, OC(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 199.18, 192.41, 164.55, 144.18, 126.84, 83.23, 69.02, 29.22, 27.97, 19.05. **Enol 1:** $^1$H NMR (600MHz; $CDCl_3$) δ 16.69 (1H, s, CO*H*) 5.70-5.67 (1H, m, C=C$H_A$$CH_B$) 5.25-5.22 (1H, m, C=$CH_A$C$H_B$) 2.28 (3H, s, C(=O)C$H_3$) 1.95 (3H, brs, C$H_3$C=$CH_2$) 1.44 (9H, s, OC(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 196.24, 176.60, 170.67, 146.64, 124.52, 105.98, 82.54, 27.98, 24.25, 17.22. **Enol 2:** $^1$H NMR (600MHz; $CDCl_3$) δ 12.99 (1H, s, CO*H*) 5.88-5.86 (1H, m, C=C$H_A$$CH_B$) 5.71-5.68 (1H, m, C=$CH_A$C$H_B$) 2.25 (3H, s, C(=O)C$H_3$) 1.89 (3H, brs, C$H_3$C=$CH_2$) 1.40 (9H, t, 7.3 Hz, OC(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 193.81, 192.80, 166.77, 142.53, 118.16, 109.97, 81.42, 27.72, 19.55, 17.44.

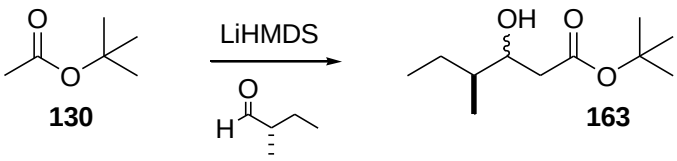
**(*S*)-2-Methyl butyraldehyde (162)**




**151** **162**

To a solution of DMSO (5 mL; 72 mmol) in $CH_2Cl_2$ (180 mL) at -78°C was added oxalyl chloride (18 mL of a 2 M solution in $CH_2Cl_2$; 36 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **151** (2.0 g; 24 mmol) in $CH_2Cl_2$ (20 mL) was added *via* cannula. This mixture was stirred for a further 30 minutes then $NEt_3$ (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 $NH_4Cl$ (200 mL) then extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and carefully concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the desired aldehyde **162** (1.86 g; 90%) as a colourless oil. $R_F$ = 0.55, $^1$H NMR (600MHz; $CDCl_3$) δ 9.63 (1H, d, 1.9 Hz, C*H*O), 2.33-2.18 (1H, m, C*H*$CH_3$), 1.85-1.64 (1H, m, C$H_A$$CH_B$$CH_3$) 1.54-1.33 (1H, m, $CH_A$C$H_B$$CH_3$) 1.09 (3H, d, 7.0 Hz, CHC$H_3$) 0.95 (3H, t, 7.3 Hz, $CH_2$C$H_3$) $^{13}$C NMR (100MHz; $CDCl_3$) δ 205.52, 47.74, 23.58, 12.85, 11.33.

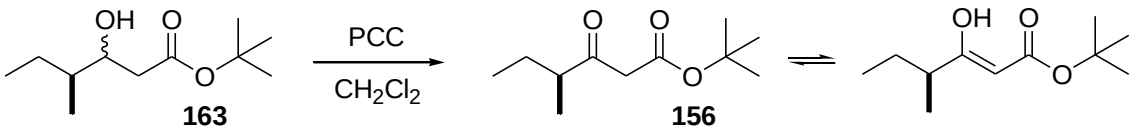
**3-Hydroxy-4-methyl-hexanoic acid tert-butyl ester (163)**




**130** **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 $NH_4Cl$ (80 mL), extracted $Et_2O$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% $Et_2O$/hexanes) gave the acetate-aldol products **163** (1.78 g; 76%) as a mixture of inseparable isomers. $R_F$ = 0.24, $^1$H NMR (400MHz; $CDCl_3$) δ 3.93-3.77 (1H, m, C*H*OH) 2.81 (1H, brs, CHO*H*) 2.45-2.30 (2H, m, C(OH)C$H_2$C(=O)) 1.58-1.71 (11H, m, C*H*$CH_3$, C$H_A$$CH_B$$CH_3$, OC(C$H_3$)$_3$) 1.22-1.09 (1H, m, C$H_A$$CH_B$$CH_3$) 0.94-0.86 (6H, m, CHC$H_3$, $CH_2$C$H_3$) $^{13}$C NMR (100MHz; $CDCl_3$) δ 172.89, 80.94, 71.52, 39.69, 38.87, 27.97, 25.38, 14.31, 11.61.

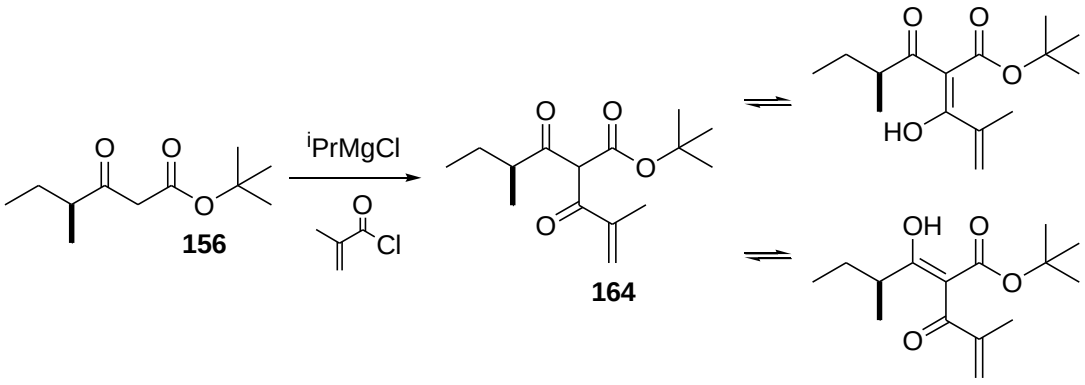
**4-Methyl-3-oxo-hexanoic acid tert-butyl ester (156)**




**163** **156**

To a stirring solution of β-hydroxy ester **163** (1.0 g; 5.0 mmol) in $CH_2Cl_2$ (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 ($CH_2Cl_2$) produced the β-keto ester **156** (0.82 g; 82%) as clear oil. $R_F$ = 0.43, **Ketone:** $^1$H NMR (600MHz; $CDCl_3$) δ 3.37 (2H, s, C(=O)C$H_2$C(=O)) 2.56 (1H, dq, 6.9, 6.6 Hz, C$H$CH$_3$) 1.73-1.66 (1H, m, C$H_A$CH$_B$CH$_3$) 1.45 (9H, s, OC(C$H_3$)$_3$) 1.43-1.37 (1H, m, CH$_A$C$H_B$CH$_3$) 1.08 (3H, d, 6.9 Hz, CHC$H_3$) 0.88 (3H, t, 7.3 Hz, CH$_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 206.78, 166.46, 81.61, 49.00, 47.85, 27.87, 25.49, 15.37, 11.36. **Enol:** $^1$H NMR (600MHz; $CDCl_3$) δ 12.46 (1H, s, CH=CO$H$) 4.86 (1H, C$H$=COH) 2.09 (1H, dq, 6.9, 6.6 Hz, C$H$CH$_3$) 1.67-1.61 (1H, m, C$H_A$CH$_B$CH$_3$) 1.48 (9H, s, OC(C$H_3$)$_3$) 1.44-1.38 (1H, m, CH$_A$C$H_B$CH$_3$) 1.10 (3H, d, 6.9 Hz, CHC$H_3$) 0.89 (3H, t, 7.3 Hz, CH$_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

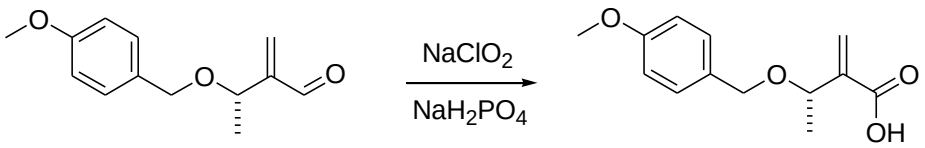



**156** **164**

To a solution of (*S*)-β-ketoester **156** (200 mg; 1 mmol) In THF (8 mL) at -78°C was added $^i$PrMgCl (0.6 mL of a 2 M solution in THF; 1.2 mmol) dropwise. The mixture was stirred for 30 minutes then methacroloyl 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 $NH_4Cl$ solution (15 mL), extracted with $Et_2O$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in*

*vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the tricarbonyl adduct **164** (196 mg; 73%) as clear oil. $R_F$ = 0.68, **Ketone:** $^1$H NMR (600MHz; $CDCl_3$) δ 5.51 (1H, s, C=C$H_A$CH$_B$) 5.29 (1H, m, C=CH$_A$C$H_B$) 4.87 (1H, s, C(=O)C*H*C(=O)) 2.59-2.53 (1H, m, C*H*CH$_3$) 1.93 (3H, brs, C$H_3$C=CH$_2$) 1.75-1.65 (1H, m, C$H_A$CH$_B$CH$_3$) 1.45 (9H, s, OC(C$H_3$)$_3$) 1.33-1.25 (1H, m, CH$_A$C$H_B$CH$_3$) 1.08 (3H, d, 6.9 Hz, CHC$H_3$) 0.87 (3H, t, 7.3 Hz, CH$_2$C$H_3$) **Enol 1:** $^1$H NMR (600MHz; $CDCl_3$) δ 16.88 (1H, s, CO*H*) 5.78 (1H, s, C=C$H_A$CH$_B$) 5.73 (1H, s, C=CH$_A$C$H_B$) 2.30-2.25 (1H, m, C*H*CH$_3$) 1.99 (3H, brs, C$H_3$C=CH$_2$) 1.75-1.65 (1H, m, C$H_A$CH$_B$CH$_3$) 1.42 (9H, s, OC(C$H_3$)$_3$) 1.30-1.23 (1H, m, CH$_A$C$H_B$CH$_3$) 1.11 (3H, d, 6.9 Hz, CHC$H_3$) 0.89 (3H, t, 7.3 Hz, CH$_2$C$H_3$) **Enol 2:** $^1$H NMR (600MHz; $CDCl_3$) δ 12.97 (1H, s, CO*H*) 5.31 (1H, s, C=C$H_A$CH$_B$) 5.25 (1H, s, C=CH$_A$C$H_B$) 2.11-2.07 (1H, m, C*H*CH$_3$) 2.00 (3H, brs, C$H_3$C=CH$_2$) 1.72-1.61 (1H, m, C$H_A$CH$_B$CH$_3$) 1.45 (9H, s, OC(C$H_3$)$_3$) 1.31-1.22 (1H, m, CH$_A$C$H_B$CH$_3$) 1.15 (3H, d, 6.9 Hz, CHC$H_3$) 0.85 (3H, t, 7.3 Hz, CH$_2$C$H_3$)

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

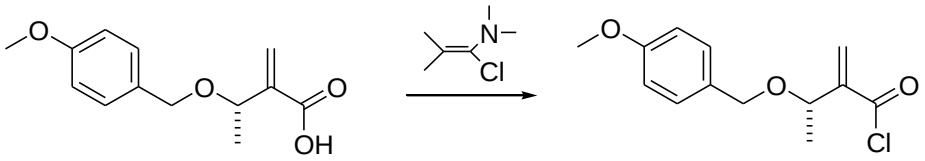



**131** **166**

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 $NaClO_2$ (0.56 g; 6.25 mmol) and $NaH_2PO_4.2H_2O$ (0.6 g; 5 mmol) in water (5 mL) dropwise. The reaction mixture was stirred for two hours before being diluted with $CH_2Cl_2/H_2O$ (150 mL; 2:1) and acidified with TFA to pH 3. The phases were separated and the aqueous phase extracted with $CH_2Cl_2$ (3*75 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$ + 0.5% AcOH) gave the acid **166** (265 mg; 90%) as a colourless oil. $R_F$ = 0.6, $^1$H NMR (600MHz; $CDCl_3$) δ 7.26 (2H, d, 8.8 Hz, Ar*H*) 6.88 (2H, d, 8.8 Hz, Ar*H*) 6.48 (1H, s, C=C$H_A$CH$_B$) 6.06 (1H, s, C=CH$_A$C$H_B$) 4.49 (1H, d, 11.4 Hz, OC$H_A$CH$_B$PMP) 4.42 (1H, q, 6.6 Hz, C*H*OPMB) 4.35 (1H, d, 11.4 Hz, OCH$_A$C$H_B$PMP) 3.80 (3H, s, OC$H_3$) 1.36 (3H, d, 6.6 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 159.16, 141.71, 132.32, 130.12, 129.29, 127.03, 113.79, 72.74, 70.50, 55.22, 21.77.

$^1$H NMR (600MHz; $C_6D_6$) δ 7.17 (2H, d, 8.8 Hz, Ar*H*) 6.77 (2H, d, 8.8 Hz, Ar*H*) 6.40 (1H, s, C=C$H_A$CH$_B$) 5.91 (1H, s, C=CH$_A$C$H_B$) 4.44 (1H, q, 6.6 Hz, C*H*OPMB) 4.30 (1H, d, 11.4 Hz, OC$H_A$CH$_B$PMP) 4.16 (1H, d, 11.4 Hz, OCH$_A$C$H_B$PMP) 3.29 (3H, s, OC$H_3$) 1.32 (3H, d, 6.6 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $C_6D_6$) δ 160.27, 143.11, 131.46, 129.95, 128.88, 127.55, 114.63, 73.44, 71.17, 55.31, 22.61.

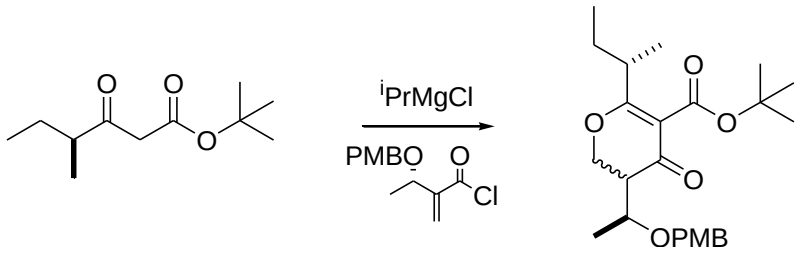
**3-(4-Methoxy-benzyloxy)-2-methylene-butyryl chloride (165)**



**166** **165**

To a solution of acid **166** (50 mg; 0.21mmol) in $CH_2Cl_2$ (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. $^1$H NMR (600MHz; $C_6D_6$) δ 7.09 (2H, d, 8.7 Hz, Ar*H*) 6.76 (2H, d, 8.7 Hz, Ar*H*) 6.30 (1H, s, C=C$H_A$CH$_B$) 5.97 (1H, s, C=CH$_A$C$H_B$) 4.21 (1H, q, 6.4 Hz, C*H*OPMB) 4.10 (1H, d, 11.3 Hz, OC$H_A$CH$_B$PMP) 3.99 (1H, d, 11.3 Hz, OCH$_A$C$H_B$PMP) 3.30 (3H, s, OC$H_3$) 1.12 (3H, d, 6.4 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $C_6D_6$) δ 168.03, 160.38, 148.13, 133.77, 129.95, 128.90, 114.66, 73.79, 71.34, 55.36, 22.18.

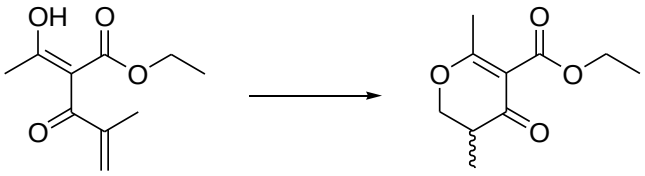
**5-[1-(4-Methoxy-benzyloxy)-ethyl]-4-oxo-2-propyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester (167)**



To a solution of β-ketoester **156** (40 mg; 0.20 mmol) In THF (5 mL) at -78°C was added $^i$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 $NH_4Cl$ solution (15 mL), extracted with $Et_2O$ (3*15 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the γ-lactone **167** (59 mg; 71%) as clear oil. $R_F$ = 0.64, $^1$H NMR (600MHz; $CDCl_3$) δ 7.23 (2H, d, 8.8 Hz, Ar*H*) 6.86 (2H, d, 8.8 Hz, Ar*H*) 4.61 (1H, dd, 11.7, 8.1 Hz, OC$H_A$CH$_B$CHC(=O)) 4.52 (1H, d, 11.0 Hz, OC$H_A$CH$_B$PMP) 4.49 (1H, dd, 11.7, 4.8 Hz, OCH$_A$C$H_B$CHC(=O)) 4.35 (1H, d, 11.0 Hz, OCH$_A$C$H_B$PMP) 4.32 (1H, q, 6.4 Hz, C*H*OPMB) 3.80 (3H, s, OC$H_3$) 2.45-2.37 (2H, m,

C*H*($CH_3$)$CH_2CH_3$, C(=O)C*H*$CHCH_3$OPMB) 1.67-1.58 (2H, m, $CH_2CH_2CH_3$) 1.45 (9H, s, OC($CH_3$)$_3$) 1.26 (3H, d, 6.4 Hz, $CHCH_3$OPMB) 1.13 (3H, dd, 6.9, 3.1 Hz, CH($CH_3$)$CH_2CH_3$) 0.93 (3H, t, 7.4 Hz, $CH_2CH_2CH_3$) $^{13}$C NMR (100MHz; $CDCl_3$) 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

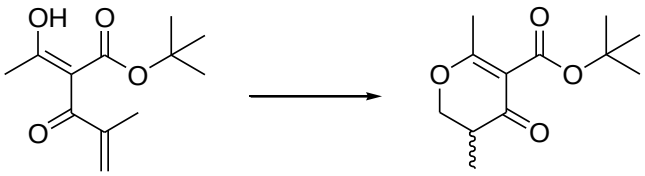
**2,5-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester (168)**



**160** **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. $^1$H NMR (400MHz; $CDCl_3$) δ 4.38 (1H, dd, 11.4, 5.4 Hz, $OCH_ACH_BCHCH_3$) 4.16 (2H, q, 7.1 Hz, $OCH_2CH_3$) 3.98 (1H, t, 11.4 Hz, $OCH_ACH_BCHCH_3$) 2.54-2.48 (1H, m, C(=O)C*H*$CH_3$) 2.07 (3H, s, C=C$CH_3$) 1.21 (3H, t, 7.1 Hz, $OCH_2CH_3$) 1.00 (3H, d, 7.0 Hz, C(=O)CH$CH_3$) $^{13}$C NMR (100MHz; $CDCl_3$) δ 190.31, 175.93, 165.45, 111.82, 72.50, 60.72, 37.91, 19.77, 13.89, 10.29.

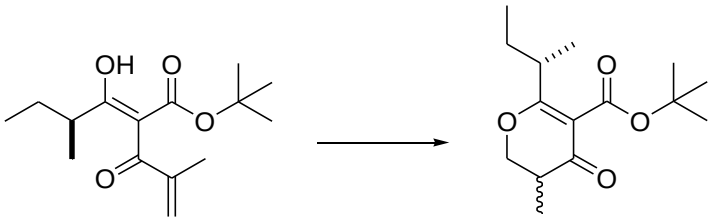
**2,5-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid tert-butyl ester (169)**



**161** **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. $^1$H NMR (400MHz; $CDCl_3$) δ 4.39 (1H, dd, 11.4, 5.4 Hz, $OCH_ACH_BCHCH_3$) 3.99 (1H, t, 11.4 Hz, $OCH_ACH_BCHCH_3$) 2.58-2.50 (1H, m, C(=O)C*H*$CH_3$) 2.08 (3H, s, C=C$CH_3$) 1.46 (9H, s, OC($CH_3$)$_3$) 1.04 (3H, d, 7.0 Hz, C(=O)CH$CH_3$) $^{13}$C NMR (100MHz; $CDCl_3$) δ 190.51, 174.42, 164.90, 113.67, 81.44, 72.55, 37.98, 27.97, 19.58, 10.35.

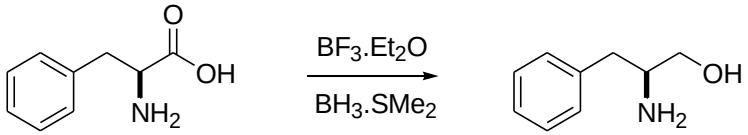
**2-sec-Butyl-5-methyl-4-oxo-5,6-dihydro-4H-pyran-3-carboxylic acid tert-butyl ester (170)**



**164** **170**

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$H_A$$CH_B$$CHCH_3$) 3.99 (1H, td, 11.2, 7.0 Hz, $OCH_ACH_B$$CHCH_3$) 2.63-2.56 (1H, m, C$H$$(CH_3)CH_2CH_3$) 2.55-2.51 (1H, m, C(=O)C$H$$CH_3$) 1.62-1.56 (1H, m, $CH_ACH_BCH_3$) 1.48 (9H, s, $OC(CH_3)_3$) 1.44-1.37 (1H, m, $CH_ACH_BCH_3$) 1.12 (3H, dd, 6.9, 3.1 Hz, $CH(CH_3)CH_2CH_3$) 1.07 (3H, t, 7.1 Hz, $OCH_2CHCH_3$) 0.85 (3H, t, 7.4 Hz, $CH_2CH_3$) $^{13}$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)**

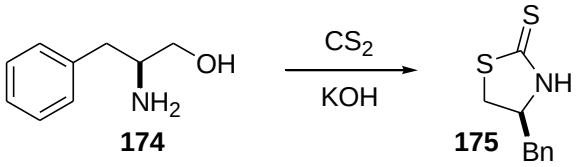


**173** **174**

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/$H_2O$ (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 $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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

7.30 (2H, t, 7.4 Hz, Ar*H*) 7.21 (1H, t, 7.4 Hz, Ar*H*) 7.17 (2H, d, 7.4 Hz, Ar*H*) 3.62 (1H, dd, 10.7, 3.7 Hz, C$H_A$CH$_B$OH) 3.38 (1H, dd, 10.7, 7.2 Hz, CH$_A$C$H_B$OH) 3.10 (1H, m, C*H*NH$_2$) 2.78 (1H, dd, 13.5, 5.1 Hz, C$H_A$CH$_B$Ph) 2.50 (1H, dd, 13.5, 8.7 Hz, CH$_A$C$H_B$Ph) 2.35 (3H, brs, CHN$H_2$, CH$_2$O*H*) $^{13}$C NMR (150MHz; CDCl$_3$) δ 138.59, 129.12, 128.49, 126.32, 65.97, 54.11, 40.58.

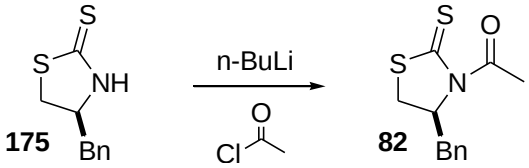
**(*S*)-4-benzyl-1,3-thiazolidinone-2-thione (175)**




**174** **175**

To a stirring solution of β-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 $CH_2Cl_2$ (3*100 mL). The combined organic extracts were dried ($Na_2SO_4$) 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, N*H*) 7.33 (2H, m, Ar*H*) 7.26 (1H, m, Ar*H*) 7.19 (2H, m, Ar*H*) 4.46 (1H, qn, 7.4 Hz, NHC*H*CH$_2$Ph) 3.51 (1H, dd, 11.2, 7.8 Hz, C$H_A$CH$_B$S) 3.27 (1H, dd, 11.2, 6.6 HZ, CH$_A$C$H_B$S) 3.04 (1H, dd, 13.6, 7.2 Hz, C$H_A$CH$_B$Ph) 2.95 (1H, dd, 13.6, 7.1 Hz, CH$_A$C$H_B$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-(*S*)-4-benzyl-1,3-thiazolidinone-2-thione (82)**

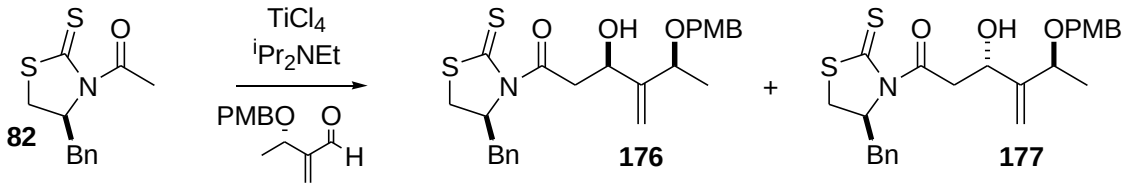



**175** **82**

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% $K_2CO_3$ and extracted first with $Et_2O$ (3*50 mL), then $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the acetyl auxiliary **82** (3.94 g; 94%) as yellow powder. mp. 105°C, $^1$H NMR (600MHz; $CDCl_3$) δ 7.36-7.26 (5H, m, Ar*H*) 5.37 (1H, ddd, 10.6, 7.0, 3.7 Hz, NC*H*$CH_2$Ph) 3.38 (1H, dd, 11.5, 7.0 Hz, C$H_A$$CH_B$S) 3.21 (1H, dd, 13.2, 3.7 Hz, CHC$H_A$$CH_B$Ph) 3.03 (1H, dd, 13.2, 10.6 Hz, $CHCH_A$C$H_B$Ph) 2.88 (1H, d, 11.5 Hz, $CH_A$C$H_B$S) 2.79 (3H, s, C(=O)C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 201.48, 170.62, 136.41, 129.36, 128.81, 127.13, 68.12, 36.56, 31.72, 27.00.

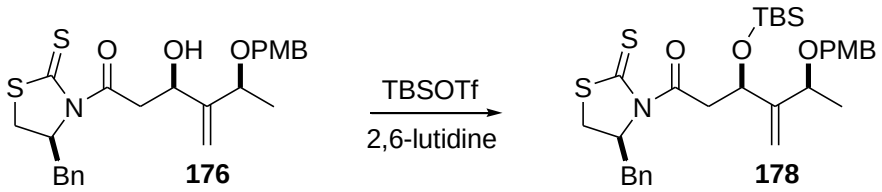
**1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3R-hydroxy-5-(4-methoxy-benzyloxy)-4-methylene-hexan-1-one (176) and 1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3S-hydroxy-5-(4-methoxy-benzyloxy)-4-methylene-hexan-1-one (177)**




To a solution of *N*-acetyl-(4*S*)-benzylthiazolidinethione (**82**) (955 mg; 3.8 mmol) in $CH_2Cl_2$ (30 mL) at -40°C was added dropwise $TiCl_4$ solution (3.85 mL; 1 M solution in $CH_2Cl_2$; 3.85 mmol). The solution was stirred for 30 minutes. $^i$$Pr_2$NEt (0.84 mL; 4.79 mmol) was then added and stirring continued for an additional hour. The mixture was then cooled to -78°C and aldehyde **131** (500 mg; 2.5 mmol) was added *via* cannula (5 mL; $CH_2Cl_2$) and stirring continued at -78°C for a further two hours. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) then quenched by the addition of saturated $NH_4Cl$ solution (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Separation of the two diastereomers was achieved by column chromatography (20% EtOAC/hexanes) to give the major isomer **176** (1.40 g; 78%) and the minor isomer **177** (0.12 g; 7%) as yellow oils. **Major diastereomer:** $R_F$ = 0.1, $^1$H NMR (600MHz; $CDCl_3$) δ 7.36-7.27 (7H, m, Ar*H*) 6.87 (2H, d, 8.6 Hz, Ar*H*) 5.37 (1H, m NC*H*$CH_2$Ph) 5.35 (1H, s, C=C$H_A$$CH_B$) 5.24 (1H, s, C=$CH_A$C$H_B$) 4.83 (1H, d, 9.4 Hz, C*H*OH) 4.47 (1H, d, 11.5 Hz, OC$H_A$$CH_B$PMP) 4.33 (1H, d, 11.5 Hz, $OCH_A$C$H_B$PMP) 4.11 (1H, q, 6.6 Hz, C*H*OPMB) 3.79 (3H, s, OC$H_3$) 3.72 (1H, dd, 18.0, 1.8 Hz, C(=O)C$H_A$$CH_B$CHOH) 3.47 (1H, dd, 18.0, 9.6 Hz, $C(=O)CH_A$C$H_B$CHOH) 3.36 (1H, dd, 11.4, 7.2 Hz, SC$H_A$$CH_B$CHBn) 3.22 (1H, dd, 13.2, 3.6 Hz, CHC$H_A$$CH_B$Ph) 3.03 (1H, dd, 13.2, 10.5 Hz, $CHCH_A$C$H_B$Ph) 2.88 (1H, d, 11.4 Hz, $SCH_A$C$H_B$CHBn) 1.39 (3H, d, 6.6 Hz, CH(C$H_3$)OPMB) $^{13}$C NMR (150MHz;

$CDCl_3$) 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** $R_F$ = 0.15, $^1$H NMR (600MHz; $CDCl_3$) δ 7.38-7.26 (7H, m, Ar*H*) 6.89 (2H, d, 8.6 Hz, Ar*H*) 5.36 (1H, m NC*H*$CH_2$Ph) 5.33 (1H, s, C=C$H_A$$CH_B$) 5.27 (1H, s, C=$CH_A$C$H_B$) 4.70 (1H, d, 9.4 Hz, C*H*OH) 4.50 (1H, d, 11.5 Hz, OC$H_A$$CH_B$PMP) 4.34 (1H, d, 11.5 Hz, $OCH_A$C$H_B$PMP) 4.08 (1H, q, 6.6 Hz, C*H*OPMB) 3.80 (3H, s, OC$H_3$) 3.67 (1H, dd, 18.0, 1.8 Hz, C(=O)C$H_A$$CH_B$CHOH) 3.56 (1H, dd, 18.0, 9.6 Hz, C(=O)$CH_A$C$H_B$CHOH) 3.39 (1H, dd, 11.4, 7.2 Hz, SC$H_A$$CH_B$CHBn) 3.24 (1H, dd, 13.2, 3.6 Hz, CHC$H_A$$CH_B$Ph) 3.04 (1H, dd, 13.2, 10.5 Hz, $CHCH_A$C$H_B$Ph) 2.90 (1H, d, 11.4 Hz, $SCH_A$C$H_B$CHBn) 1.38 (3H, d, 6.6 Hz, CH(C$H_3$)OPMB) $^{13}$C NMR (150MHz; $CDCl_3$) δ 201.41, 172.88, 159.12, 150.39, 136.34, 130.34, 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.

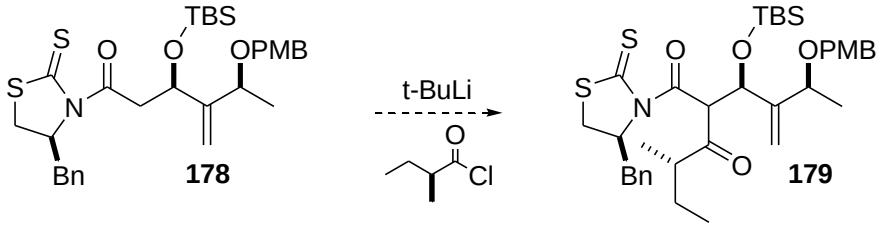
**1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-4-methylene-hexan-1-one (178)**




To a solution of aldol adduct **176** (500 mg; 1.06 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (50 mL) and warmed to ambient temperature for a further hour. The mixture was quenched with $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification of column chromatography ($CH_2Cl_2$) gave the TBS-protected aldol product **178** (571 mg; 92%) as yellow oil. $R_F$ = 0.62, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.26 (7H, m, Ar*H*) 6.87 (2H, 8.6 Hz, Ar*H*) 5.38 (1H, s, C=C$H_A$$CH_B$) 5.23-5.19 (2H, m, C=$CH_A$C$H_B$, NC*H*$CH_2$Ph) 4.46 (1H, dd, 9.5, 2.2 Hz, C*H*OTBS) 4.46 (1H, d, 11.2 Hz, OC$H_A$$CH_B$PMP) 4.30 (1H, d, 11.2 Hz, $OCH_A$C$H_B$PMP) 4.07 (1H, q, 6.4 Hz, C*H*OPMB) 3.79 (3H, s, OC$H_3$) 3.70 (1H, dd, 16.8, 9.2 Hz, C(=O)C$H_A$$CH_B$CHOH) 3.34-3.24 (3H, m, C(=O)$CH_A$C$H_B$CHOH, SC$H_A$$CH_B$CHBn, CHC$H_A$$CH_B$Ph) 3.01 (1H, dd, 13.2, 11.0 Hz, $CHCH_A$C$H_B$Ph) 2.88 (1H, d, 11.4 Hz, $SCH_A$C$H_B$CHBn) 1.38 (3H, d, 6.4 Hz, CH(C$H_3$)OPMB) 0.87 (9H, s, SiC(C$H_3$)$_3$) 0.10 (3H, s, SiC$H_3$) 0.05 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 201.68, 171.86, 159.02, 151.05, 136.65, 130.55,

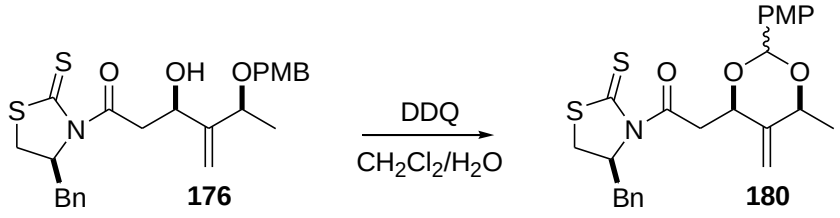
129.40, 129.05, 128.89, 127.14, 113.72, 113.65, 75.41, 69.82, 69.32, 68.81, 55.23, 47.03, 36.40, 32.24, 25.77, 20.45, 18.05, -4.31, -5.11.

**1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2-(2-methyl-butyryl)-4-methylene-hexan-1-one (179)**




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 $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) 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.

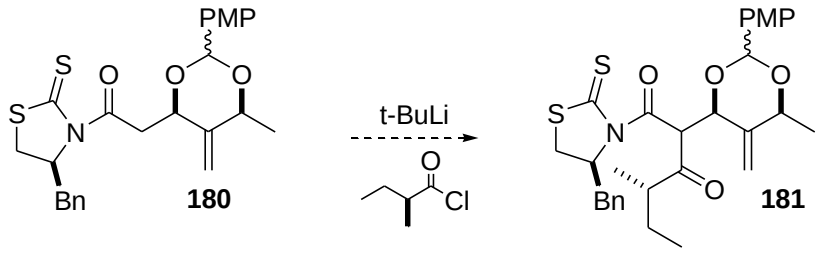
**1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-2-[2-(4-methoxy-phenyl)-6-methyl-5-methylene-[1,3]dioxan-4-yl]-ethanone (180)**




To a solution of aldol adduct **176** (200 mg; 0.44 mmol) in $CH_2Cl_2$ (23 mL) and $H_2O$ (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 $NaHCO_3$ solution (100 mL). The

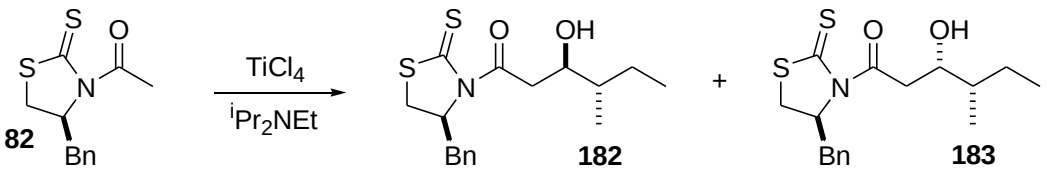
aqueous layer was extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% $Et_2OCH_2Cl_2$) gave the PMP-acetal **180** (176 mg; 85%) as a yellow oil. $R_F$ = 0.71, $^1$H NMR (600MHz; $CDCl_3$) δ 7.43 (2H, m, Ar*H*) 7.35 (2H, m, Ar*H*) 7.29 (3H, m, Ar*H*) 6.86 (2H, m, Ar*H*) 5.83 (1H, s, C*H*PMP) 5.30 (1H, m, NC*H*$CH_2$Ph) 5.12 (1H, s, C=C$H_A$$CH_B$) 5.05 (1H, s, C=$CH_A$C$H_B$) 5.00 (1H, dd, 8.1, 4.0 Hz, C(=O)$CH_2$C*H*O-) 4.50 (1H, q, 6.2 Hz, C*H*($CH_3$)O-) 3.78 (2H, m, C(=O)C$H_2$CHO-) 3.77 (3H, s, OC$H_3$) 3.33 (1H, dd, 11.5, 7.1 Hz, SC$H_A$$CH_B$CHBn) 3.24 (1H, dd, 13.1, 3.6 Hz, CHC$H_A$$CH_B$Ph) 3.05 (1H, dd, 13.1, 10.6 Hz, $CHCH_A$C$H_B$Ph) 2.86 (1H, d, 11.5 Hz, $SCH_A$C$H_B$CHBn) 1.50 (3H, d, 6.2 Hz, CH(C$H_3$)) 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)**



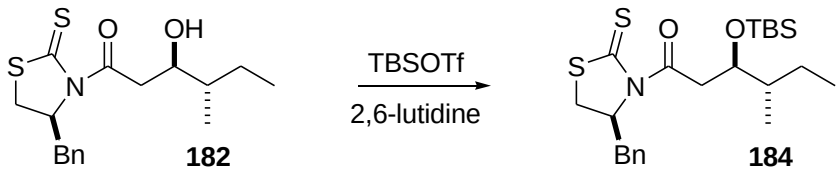

To a solution of PMP-acetal **180** (185 mg; 0.40 mmol) in THF (5 mL) at -78°C was added *t*-BuLi (0.23 mL of a 1.7 M solution in hexanes; 0.40 mmol). The mixture was stirred at -78°C for 15 minutes, then (*S*)-2-methyl butyryl chloride (**120**) (62 µL; 0.50 mmol) in THF (0.5 mL) was added *via* cannula. 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 $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) 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.

**(*S*,*S*,*S*)-1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-hydroxy-4-methyl-hexan-1-one (182) and (*S*,*S*,*R*)- 1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-hydroxy-4-methyl-hexan-1-one (183)**



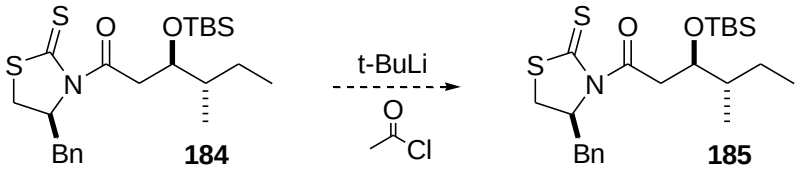

To a solution of *N*-acetyl-(4*S*)-benzylthiazolidinethione (**82**) (650 mg; 2.60 mmol) in $CH_2Cl_2$ (15 mL) at -40°C was added dropwise $TiCl_4$ solution (2.68 mL; 1 M solution in $CH_2Cl_2$; 2.68 mmol). The solution was stirred for 30 minutes. $^{i}Pr_2NEt$ (0.60 mL; 2.80 mmol) was then added and stirring continued for an additional hour. The mixture was then cooled to -78°C and (*S*)-2-methyl-aldehyde (**162**) (0.28 mL; 2.65 mmol) was added via cannula (5 mL; $CH_2Cl_2$) and stirring continued at -78°C for a further two hours. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) then quenched by the addition of saturated $NH_4Cl$ solution (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) 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:** $R_F$ = 0.15, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.27 (5H, m, Ar*H*) 5.39 (1H, td, 10.5, 7.2, 4.0 Hz, NC*H*$CH_2$Ph) 4.04 (1H, dd, 10.1, 5.8 Hz, C*H*OH) 3.57 (1H, dd, 17.7, 1.9 Hz, C(=O)C$H_A$$CH_B$CHOH) 3.39 (1H, dd, 11.5, 7.2 Hz, SC$H_A$$CH_B$CHBn) 3.22 (1H, dd, 13.2, 4.0 Hz, CHC$H_A$$CH_B$Ph) 3.17 (1H, dd, 17.7, 10.1 Hz, C(=O)$CH_A$C$H_B$CHOH) 3.04 (1H, dd, 13.2, 10.5 Hz, $CHCH_A$C$H_B$Ph)) 2.88 (1H, d, 11.5 Hz, $SCH_A$C$H_B$CHBn) 2.16 (1H, brs, CHO*H*) 1.60-1.52 (2H, m, C$H_2CH_3$) 1.23-1.18 (1H, m, C*H*($CH_3$)$CH_2CH_3$) 0.93 (3H, d, 7.3 Hz, CH(C$H_3$)$CH_2CH_3$) 0.91 (3H, d, 6.9 Hz, $CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 201.29, 173.64, 136.26, 129.27, 128.75, 127.09, 71.04, 68.24, 42.50, 39.64, 36.62, 31.89, 24.92, 14.44, 11.42; **Minor diastereomer:** $R_F$ = 0.19, $^1$H NMR (400MHz; $CDCl_3$) δ 7.37-7.27 (5H, m, Ar*H*) 5.42 (1H, td, 10.5, 7.2, 4.0 Hz, NC*H*$CH_2$Ph) 4.03-4.01 (1H, m, C*H*OH) 3.54 (1H, dd, 17.7, 1.9 Hz, C(=O)C$H_A$$CH_B$CHOH) 3.40 (1H, dd, 11.5, 7.2 Hz, SC$H_A$$CH_B$CHBn) 3.29 (1H, dd, 13.2, 4.0 Hz, CHC$H_A$$CH_B$Ph) 3.23 (1H, dd, 17.7, 10.1 Hz, C(=O)$CH_A$C$H_B$CHOH) 3.05 (1H, dd, 13.2, 10.5 Hz, $CHCH_A$C$H_B$Ph)) 3.00 (1H, brs, CHO*H*) 2.91 (1H, d, 11.5 Hz, $SCH_A$C$H_B$CHBn) 1.62-1.46 (2H, m, C$H_A$$CH_B$$CH_3$, C*H*($CH_3$)$CH_2CH_3$) 1.26-1.15 (1H, m, $CH_A$C$H_B$$CH_3$) 0.95 (3H, d, 7.3 Hz, CH(C$H_3$)$CH_2CH_3$) 0.92 (3H, d, 6.9 Hz, $CH_2$C$H_3$) $^{13}$C NMR (100MHz; $CDCl_3$) 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.

**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 $CH_2Cl_2$ (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 $CH_2Cl_2$ (20 mL) and warmed to ambient temperature. The mixture was quenched with $NaHCO_3$ (30 mL) and extracted with $CH_2Cl_2$ (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification of column chromatography ($CH_2Cl_2$) gave the TBS-protected aldol product **184** (348 mg; 93%) as yellow oil. $R_F$ = 0.52, $^1$H NMR (400MHz; $CDCl_3$) δ 7.38-7.27 (5H, m, ArH) 5.35 (1H, td, $NCHCH_2Ph$) 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, $SCH_ACH_BCHBn$) 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, $SCH_ACH_BCHBn$) 1.64-1.54 (1H, m, $CH_ACH_BCH_3$) 1.53-1.44 (1H, m, $CH(CH_3)CH_2CH_3$) 1.17-1.06 (1H, m, $CH_ACH_BCH_3$) 0.90-0.85 (15H, m, $SiC(CH_3)_3$, $CH_2CH_3$, $CH(CH_3)CH_2CH_3$) 0.10 (3H, s, $SiCH_3$) 0.08 (3H, s, $SiCH_3$) $^{13}$C NMR (100MHz; $CDCl_3$) 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.

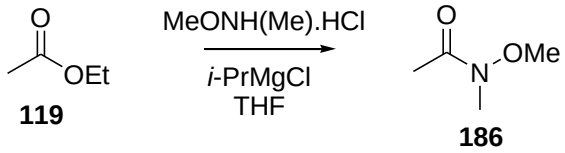
**1-(4-Benzyl-2-thioxo-thiazolidin-3-yl)-3-(tert-butyl-dimethyl-silanyloxy)-4-methyl-hexan-1-one (185)**




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 $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Analysis of the crude $^1$H NMR spectrum

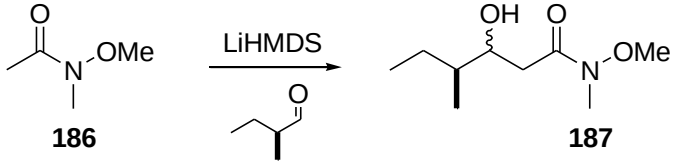
indicated that no acylation had occurred and that amide **184** was recovered following purification by column chromatography.

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




To a solution of ethyl acetate (**119**) (0.5 g; 5.68 mmol) in THF (5 mL) and $Et_2O$ (5 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.36 g; 14 mmol). The mixture was cooled to -20°C and $^{i}$PrMgCl (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 $NH_4Cl$ (50 mL) was added cautiously. The mixture was extracted with $Et_2O$ (3*20 mL) and $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (50% $Et_2O/CH_2Cl_2$) to give the amide **186** (503 mg; 86%) as a colourless oil. $R_F$ = 0.35, $^1$H NMR (600MHz; $CDCl_3$) δ 3.67 (3H, s, NOC*H*$_3$) 3.16 (3H, s, NC*H*$_3$) 2.11 (3H, s, C(=O)C*H*$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 175.43, 61.16, 32.28, 25.15.

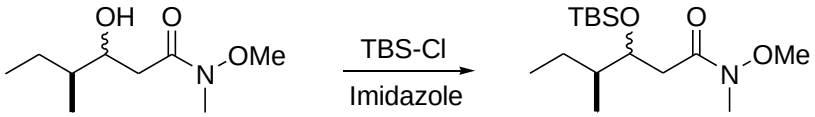
**3-Hydroxy-4-methyl-hexanoic acid methoxy-methyl-amide (187)**




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 $NH_4Cl$ (30 mL), extracted $Et_2O$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% EtOAc/hexanes) gave the acetate-aldol product **187** (632 mg; 76%) as a clear oil. $R_F$ = 0.57, $^1$H NMR (600MHz; $CDCl_3$) δ 3.72 (1H, ddd, 8.1, 5.4, 2.7 Hz, C*H*OH) 3.67

(3H, s, NOC$H_3$) 3.15 (3H, s, NC$H_3$) 2.32 (1H, dd, 14.5, 5.4 Hz, C$H_A$CH$_B$C(=O)) 2.17 (1H, dd, 14.5, 2.7 Hz, CH$_A$C$H_B$C(=O)) 1.45-1.39 (1H, m, C$H$CH$_3$) 1.43-1.37 (1H, m, C$H_A$CH$_B$CH$_3$) 1.11-1.02 (1H, m, CH$_A$C$H_B$CH$_3$) 0.93 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 0.90 (3H, d, 6.9 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 178.33, 73.07, 61.44, 38.15, 31.88, 26.73, 17.92, 13.90, 12.24

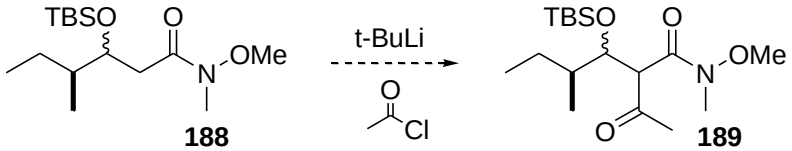
**3-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-hexanoic acid methoxy-methyl-amide (188)**




**187** **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 NaHCO$_3$ solution (150 mL). The aqueous layer was extracted with Et$_2$O (3*50 mL) and 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 TBS-protected adduct **188** (8.8 g; 94%) as a clear oil. R$_F$ = 0.47, $^1$H NMR (600MHz; CDCl$_3$) δ 4.23 (1H, dt, 12.8, 4.4, 3.3 Hz, C$H$OTBS) 3.69 (3H, s, NOC$H_3$) 3.16 (3H, brs, NC$H_3$) 2.30 (1H, dd, 14.6, 4.4 Hz, C$H_A$CH$_B$C(=O)) 2.18 (1H, dd, 14.6, 3.3 Hz, CH$_A$C$H_B$C(=O)) 1.46-1.41 (1H, m, C$H$CH$_3$) 1.40-1.33 (1H, m, C$H_A$CH$_B$CH$_3$) 1.13-1.03 (1H, m, CH$_A$C$H_B$CH$_3$) 0.90 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 0.89 (3H, d, 6.9 Hz, CHC$H_3$) 0.85 (9H, s, SiC(C$H_3$)$_3$) 0.05 (3H, s, SiC$H_3$) 0.00 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 172.85, 72.47, 61.16, 40.78, 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)**

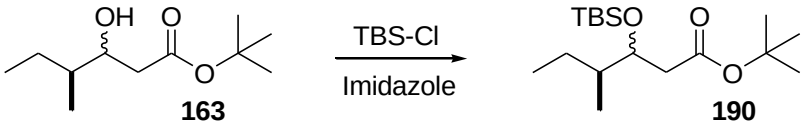



**188** **189**

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

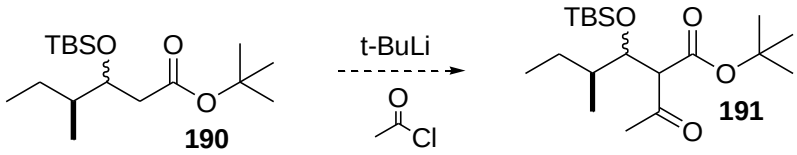
for an additional 2 hours at -78°C then warmed to 0°C over 30 minutes and quenched by the addition of saturated ammonium chloride solution (5 mL), extracted with $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Analysis of the crude $^1$H NMR spectrum indicated that no acylation had 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 $NaHCO_3$ (200 mL), extracted with $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (80% $CH_2Cl_2$/hexanes) gave the TBS protected adduct **190** (2.79 g; 88%) as a clear oil. $R_F$ = 0.85, $^1$H NMR (600MHz; $CDCl_3$) δ 4.08-4.04 (1H, m, C*H*OTBS) 2.31 (1H, dd, 7.6, 5.8 Hz, CHOTBSC$H_A$CH$_B$C(=O)) 2.25 (1H, dd, 6.6, 5.8 Hz, CHOTBSCH$_A$C$H_B$C(=O)) 1.56-1.48 (1H, m, C$H_A$CH$_B$CH$_3$) 1.43 (9H, s, OC(C$H_3$)$_3$) 1.39-1.31 (1H, m, C*H*(CH$_3$)CH$_2$CH$_3$) 1.10-1.00 (1H, m, CH$_A$C$H_B$CH$_3$) 0.89 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 0.85 (9H, s, SiC(C$H_3$)$_3$) 0.82 (3H, d, 6.9 Hz, CH(C$H_3$)CH2CH$_3$) 0.05 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) $^{13}$C 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

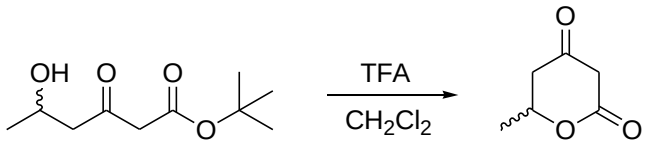
**3-(tert-Butyl-dimethyl-silanyloxy)-2-butyryl-4-methyl-hexanoic acid tert-butyl ester (191)**




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

saturated ammonium chloride solution (5 mL), extracted with $Et_2O$ (3*5 mL), dried ($Na_2SO_4$) 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.

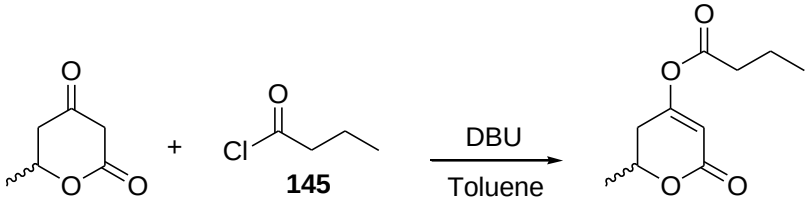
**6-Methyl-dihydro-pyran-2,4-dione (192)**




**143** **192**

To a solution of β-hydroxy-diketone **143** (300 mg; 1.48 mmol) in $CH_2Cl_2$ (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% $Et_2O/CH_2Cl_2$) to give the β-keto-lactone product **192** (153 mg; 81%) as clear oil. $R_F$ = 0.45, $^1H$ NMR (600MHz; $CDCl_3$) δ 4.79 (1H, dqd, 11.3, 6.3, 2.9 Hz, OC*H*$CH_3$) 3.56 (1H, d, 18.7 Hz, C(=O)C$H_A$$CH_B$C(=O)) 3.42 (1H, d, 18.7 Hz, C(=O)$CH_A$C$H_B$C(=O)) 2.71 (1H, dd, 18.3, 2.9 Hz, C(=O)C$H_A$$CH_B$$CHCH_3$) 2.46 (1H, dd, 18.3, 11.3 Hz, C(=O)$CH_A$C$H_B$$CHCH_3$) 1.51 (3H, d, 6.3 Hz, OCHC$H_3$) $^{13}C$ NMR (150MHz; $CDCl_3$) 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)**

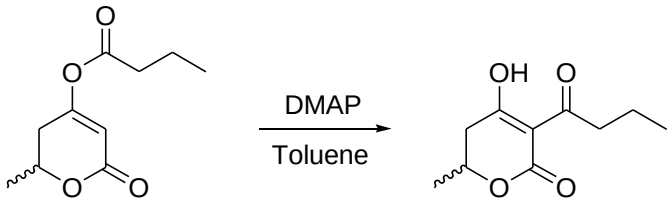



**192** **145** **197**

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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography

($CH_2Cl_2$) gave the *O*-acylated diester product **197** (110 mg; 72%) as clear colourless oil. $R_F$ = 0.25, $^1$H NMR (600MHz; $CDCl_3$) δ 5.90 (1H, d, 1.9 Hz, C=C*H*C(=O)) 4.61 (1H, m, OC*H*$CH_3$) 2.63 (1H, td, 17.5, 11.5, 1.9 Hz, C$H_A$$CH_B$$CHCH_3$) 2.45 (1H, m, $CH_A$C$H_B$$CHCH_3$) 2.44 (2H, t, 7.3 Hz, C(=O)C$H_2$$CH_2CH_3$) 1.70 (2H, dq, 7.4, 7.3 Hz, C(=O)$CH_2$C$H_2$$CH_3$) 1.44 (3H, d, 6.3 Hz, OCHC$H_3$) 0.97 (3H, t, 7.4 Hz, C(=O)$CH_2CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 169.87, 165.59, 163.93 106.50, 72.87, 36.08, 33.99, 20.39, 17.98, 13.41.

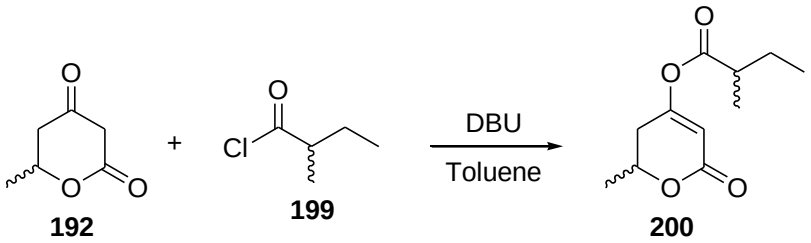
**3-Butyryl-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one (198)**




**197** **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 ($CH_2Cl_2$) gave the racemic acyl pyranone product **198** (45 mg; 66%) as clear oil. $R_F$ = 0.21, $^1$H NMR (600MHz; $CDCl_3$) 17.92 (1H, s, C=C(O*H*)) 4.51 (1H, m, OC*H*$CH_3$) 3.04 (1H, m, C(=O)C$H_A$$CH_B$$CH_2CH_3$) 2.96 (1H, m, C(=O)$CH_A$C$H_B$$CH_2CH_3$) 2.61 (2H, m, $CH_2CHCH_3$) 1.67 (2H, m, C(=O)$CH_2$C$H_2$$CH_3$) 1.44 (3H, d, 6.3 Hz, OCHC$H_3$) 0.97 (3H, t, 7.4 Hz, C(=O)$CH_2CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 204.43, 194.90, 164.25, 102.96, 70.23, 40.33, 39.32, 20.56, 18.29, 13.77.

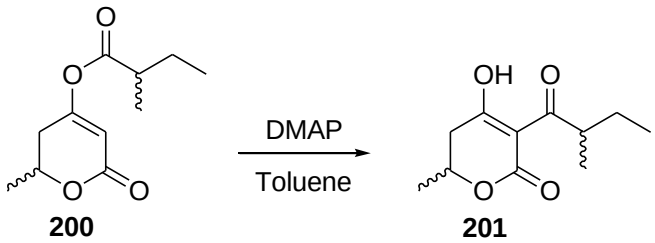
**2-Methyl-butyric acid 2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (200)**




**192** **199** **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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the *O*-acylated diester product **200** (140 mg; 84%) as clear colourless oil. $R_F$ = 0.26, $^1$H NMR (600MHz; $CDCl_3$) δ 5.88 (1H, d, 2.1 Hz, C=C*H*C(=O)) 4.62 (1H, m, OC*H*$CH_3$) 2.64 (1H, dtd, 17.5, 11.5, 2.1 Hz, C$H_A$$CH_B$$CHCH_3$) 2.51 (1H, dq, 7.0, 6.9 Hz, C(=O)C*H*$CH_3$) 2.63 (1H, td, 17.5, 11.5, 1.9 Hz, C$H_A$$CH_B$$CHCH_3$) 2.43 (1H, td, 17.5, 3.7, 2.6 Hz, $CH_A$C$H_B$$CHCH_3$) 1.73 (1H, m, C$H_A$$CH_B$$CH_3$) 1.55 (1H, m, $CH_A$C$H_B$$CH_3$) 1.45 (3H, d, 6.2 Hz, OCHC$H_3$) 1.20 (3H, d, 7.0 Hz, C(=O)CHC$H_3$) 0.94 (3H, t, 7.4 Hz, $CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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-butyryl)-5,6-dihydro-pyran-2-one (201)**

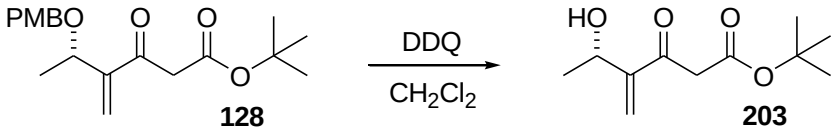



**200** **201**

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 ($CH_2Cl_2$) gave the racemic acyl pyranone product **201** (70 mg; 70%) as clear oil. $R_F$ = 0.21, **Isomer 1**: $^1$H NMR (600MHz; $CDCl_3$) δ 18.14 (1H, s, C=C(O*H*)) 4.52 (1H, m, OC*H*$CH_3$) 3.81 (1H, dq, 6.7 Hz, C(=O)C*H*$CH_3$) 2.64 (1H, dd, 10.0, 1.00 Hz, C$H_A$$CH_B$$CHCH_3$) 2.62 (1H, dd, 10.0 Hz, 3.6 Hz, $CH_A$C$H_B$$CHCH_3$) 1.75 (2H, m,

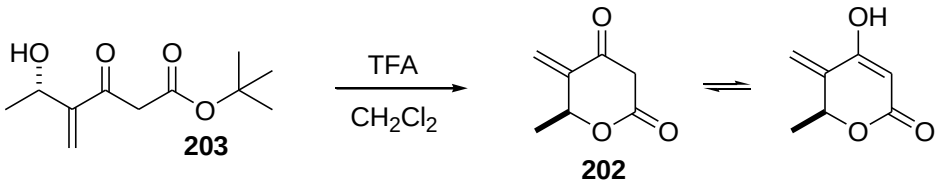
C*H*$_2$CH$_3$) 1.45 (3H, d, 6.3 Hz, OCHC*H*$_3$) 1.17 (3H, d, 6.7 Hz, C(=O)CHC*H*$_3$) 0.93 (3H, t, 7.5 Hz, CH$_2$C*H*$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 208.12, 195.80, 164.18, 102.74, 70.21, 41.39, 39.72, 26.79, 20.56, 16.69, 11.79. **Isomer 2**: $^{1}$H NMR (600MHz; CDCl$_3$) δ 18.12 (1H, s, C=C(O*H*)) 4.51 (1H, m, OC*H*CH$_3$) 3.77 (1H, dq, 6.7 Hz, C(=O)C*H*CH$_3$) 2.64 (1H, dd, 10.0, 1.00 Hz, C*H*$_A$CH$_B$CHCH$_3$) 2.62 (1H, dd, 10.0 Hz, 3.6 Hz, CH$_A$C*H*$_B$CHCH$_3$) 1.70 (2H, m, C*H*$_2$CH$_3$) 1.44 (3H, d, 6.3 Hz, OCHC*H*$_3$) 1.12 (3H, d, 6.7 Hz, C(=O)CHC*H*$_3$) 0.86 (3H, t, 7.5 Hz, CH$_2$C*H*$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) 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 CH$_2$Cl$_2$ (20 mL) and H$_2$O (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 NaHCO$_3$ solution (20 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3*20 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-diketone **203** (145 mg; 91%) as a clear oil. R$_F$ = 0.15, $^{1}$H NMR (600MHz; CDCl$_3$) δ 6.10 (1H, s, C=C*H*$_A$CH$_B$) 6.04 (1H, s, C=CH$_A$C*H*$_B$) 4.65 (1H, q, 6.4 Hz, C*H*OH) 3.63 (1H, d, 15.4 Hz, C(=O)C*H*$_A$CH$_B$C(=O)) 3.59 (1H, d, 15.4 Hz, C(=O)CH$_A$C*H*$_B$C(=O)) 2.77 (1H, brs, CHO*H*) 1.41 (9H, s, OC(C*H*$_3$)$_3$) 1.31 (3H, d, 6.4 Hz, HOCHC*H*$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) δ 194.98, 166.49, 150.98, 125.26, 82.05, 66.25, 47.03, 27.80, 22.19.

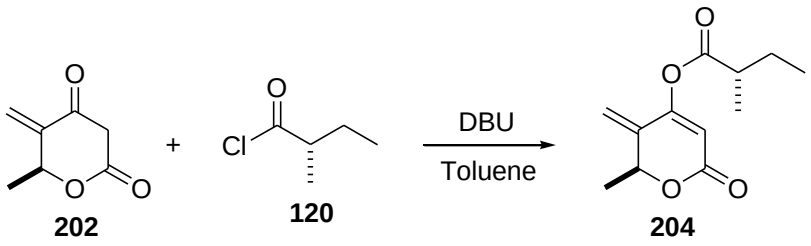
**6-Methyl-5-methylene-dihydro-pyran-2,4-dione (202)**




To a solution of β-hydroxy-diketone **203** (0.5 g; 2.33 mmol) in CH$_2$Cl$_2$ (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% $Et_2O/CH_2Cl_2$) to give the unsaturated-β-keto-lactone product **202** (280 mg; 86%) as clear oil. $R_F$ = 0.22, $^1$H NMR (600MHz; $CDCl_3$) **Ketone** δ 6.42 (1H, d, 1.2 Hz, C=C$H_A$CH$_B$) 5.66 (1H, d, 1.2 Hz, C=CH$_A$C$H_B$) 5.28 (1H, q, 6.6 Hz, C$H$CH$_3$) 3.75 (1H, d, 17.8 Hz, C(=O)C$H_A$CH$_B$C(=O)) 3.56 (1H, d, 17.8 Hz, C(=O)CH$_A$C$H_B$C(=O)) 1.65 (3H, d, 6.6 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 189.05, 167.10, 140.09, 136.80, 74.17, 47.10, 17.55. **Enol** δ 15.43 (1H, s, CO$H$) 5.94 (1H, s, C=C$H_A$CH$_B$) 5.42 (1H, s, C=CH$_A$C$H_B$) 5.38 (1H, s, C(OH)C=C$H$C(=O)) 5.12 (1H, q, 6.5 Hz, C$H$CH$_3$) 1.56 (3H, d, 6.5 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 169.00, 164.96, 123.96, 116.39, 92.65, 75.53, 20.59.

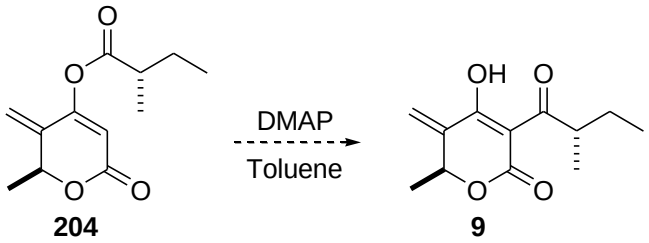
**2-Methyl-butyric acid 2-methyl-3-methylene-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (204)**




**202** **120** **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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the *O*-acylated product **204** (123 mg; 77%) as a clear colourless oil. $R_F$ = 0.27, $^1$H NMR (600MHz; $CDCl_3$) δ 5.90 (1H, d, 2.1 Hz, C=C$H$C(=O)) 4.63 (1H, m, OC$H$CH$_3$) 2.62 (1H, dtd, 17.5, 11.5, 2.1 Hz, C$H_A$CH$_B$CHCH$_3$) 2.50 (1H, dq, 7.0, 6.9 Hz, C(=O)C$H$CH$_3$) 2.45 (1H, td, 17.5, 3.7, 2.6 Hz, CH$_A$C$H_B$CHCH$_3$) 1.71 (1H, m, C$H_A$CH$_B$CH$_3$) 1.55 (1H, m, CH$_A$C$H_B$CH$_3$) 1.46 (3H, d, 6.2 Hz, OCHC$H_3$) 1.22 (3H, d, 7.0 Hz, C(=O)CHC$H_3$) 0.93 (3H, t, 7.4 Hz, CH$_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 172.94, 165.55, 164.15, 106.45, 72.87, 41.01, 33.92, 26.35, 20.34, 16.10, 11.34.

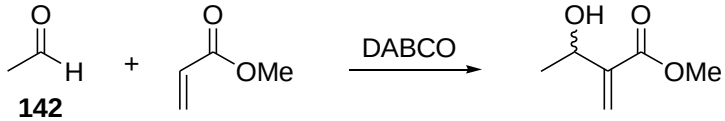
**4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)**




**204** **9**

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.

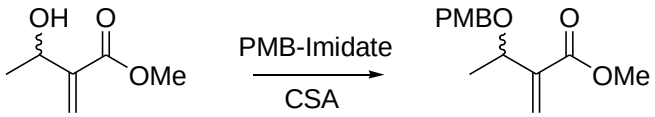
**3-Hydroxy-2-methylene-butyric acid methyl ester (210)**




**142** **209** **210**

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 $Et_2O$ (5*100 mL). The organic extracts were washed with $H_2O$ (2*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the unsaturated hydroxyl ester **210** (10 g; 70%) as clear oil. $R_F$ = 0.20, $^1$H NMR (600MHz; $CDCl_3$) δ 6.19 (1H, s, C=C$H_A$CH$_B$) 5.81 (1H, s, C=CH$_A$C$H_B$) 4.60 (1H, q, 6.4 Hz, C*H*OH) 3.76 (3H, s, OC$H_3$) 2.87 (1H, brs, CHO*H*) 1.35 (3H, d, 6.4 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 167.04, 143.35, 124.19, 66.98, 51.87, 21.99.

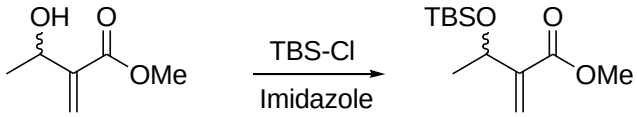
**3-(4-Methoxy-benzyloxy)-2-methylene-butyric acid methyl ester (211)**




**210** **211**

To a solution of methyl ester **210** (2.0 g; 15.4 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ (100mL) and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 80 mL). Organic extracts were combined and concentrated in vacuo. The slurry produced was triturated (25% $CH_2Cl_2$/Hexanes), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the PMB-hydroxy-ester **211** (2.50 g; 65%) as a colourless oil. $R_F$ = 0.35, $^1$H NMR (600MHz; $CDCl_3$) δ 7.25 (2H, d, 8.7 Hz, Ar*H*) 6.87 (2H, d, 8.7 Hz, Ar*H*) 6.31 (1H, d, 1.3 Hz, C=C$H_A$CH$_B$) 5.95 (1H, t, 1.3 Hz, C=CH$_A$C$H_B$) 4.46 (1H, d, 11.3 Hz, OC$H_A$CH$_B$PMP) 4.41 (1H, qd, 6.3, 0.8 Hz, C*H*OPMB) 4.33 (1H, d, 11.3 Hz, OCH$_A$C$H_B$PMP) 3.79 (3H, s, PhOC$H_3$) 3.77 (3H, s, C(=O)OC$H_3$) 1.32 (3H, d, 6.3 Hz, CHC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**




**210** **216**

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 $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with $Et_2O$ (3*50 mL) and $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the TBS-protected adduct **216** (8.8 g; 94%) as a clear oil. $R_F$ = 0.45, $^1$H NMR (600MHz; $CDCl_3$) δ 6.18 (1H, s, C=C$H_A$CH$_B$) 5.95 (1H, s, C=CH$_A$C$H_B$) 4.68 (1H, dq, 6.2, 1.1 Hz, C*H*OTBS) 3.74 (3H, s, OC$H_3$) 1.25 (3H, d, 6.2 Hz, CHC$H_3$) 0.88 (9H, s,

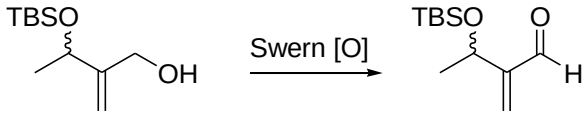
SiC($CH_3$)$_3$) 0.08 (3H, s, SiC$H_3$) 0.05 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 166.75, 145.13, 123.54, 66.76, 51.65, 25.77, 25.62, 18.16, -3.61, -5.02.

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


**216** **217**

To a solution of unsaturated TBS-protected methyl ester **216** (3.0 g; 12.27 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the primary alcohol **217** (2.0 g; 75%) as clear oil. $R_F$ = 0.35, $^1$H NMR (600MHZ; $CDCl_3$) δ 5.01 (1H, s, C=C$H_A$CH$_B$) 5.00 (1H, s, C=CH$_A$C$H_B$) 4.45 (1H, q, 6.6 Hz, C*H*OTBS) 4.30 (1H, dd, 13.2, 4.7 Hz, C$H_A$CH$_B$OH) 4.13 (1H, dd, 13.2, 6.9 Hz, CH$_A$C$H_B$OH) 1.30 (3H, d, 6.6 Hz, CHC$H_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.08 (3H, s, SiC$H_3$) 0.07 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 151.16, 110.31, 71.64, 63.63, 25.72, 25.61, 23.64, 18.05, -4.89, -5.04.

**3-(tert-Butyl-dimethyl-silanyloxy)-2-methylene-butyraldehyde (218)**

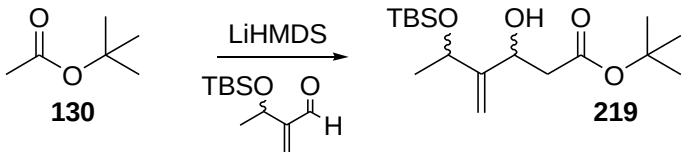



**217** **218**

To a solution of DMSO (1.72 mL; 24.3 mmol) in $CH_2Cl_2$ (50 mL) at -78°C was added oxalyl chloride (6 mL of a 2 M solution in $CH_2Cl_2$; 12.1 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **217** (1.75 g; 8.1 mmol) in $CH_2Cl_2$ (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 $NH_4Cl$ (80 mL) then extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and carefully concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the desired aldehyde **218** (1.56 g; 90%) as a colourless oil. $R_F$ =

0.43, $^{1}$H NMR (600MHz; $CDCl_3$) δ 9.57 (1H, s, C*H*O) 6.57 (1H, s, C=C$H_A$CH$_B$) 6.03 (1H, s, C=CH$_A$C$H_B$) 4.68 (1H, q, 6.2 Hz, C*H*OTBS) 1.25 (3H, d, 6.2 Hz, CHC$H_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.05 (3H, s, SiC$H_3$) 0.01 (3H, s, SiC$H_3$) $^{13}$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)**

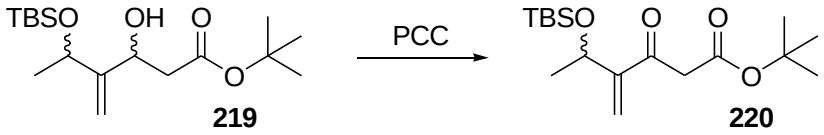



**130** **219**

To a solution of LiHMDS (7.6 mL; of a 1 M solution in THF; 7.6 mmol) at -78°C *t*-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 $NH_4Cl$ (100 mL), extracted $Et_2O$ (3*100 mL), dried ($Na_2SO_4$) 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$H_A$CH$_B$) 5.07 (1H, s, C=CH$_A$C$H_B$) 4.61-4.58 (1H, m, C*H*OH) 4.45 (1H, q, 6.6 Hz, C*H*OTBS) 3.40 (1H, s, CHO*H*) 2.66 (1H, dd, 16.5, 3.6 Hz, CH(OH)C$H_A$CH$_B$C(=O)) 2.51 (1H, dd, 16.5, 8.8 Hz, CH(OH)CH$_A$C$H_B$C(=O)) 1.45 (9H, s, OC(C$H_3$)$_3$) 1.30 (3H, d, 6.6 Hz, CHC$H_3$) 0.88 (9H, s, SiC(C$H_3$)$_3$) 0.06 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) $^{13}$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=C$H_A$CH$_B$) 5.08 (1H, s, C=CH$_A$C$H_B$) 4.63-4.60 (1H, m, C*H*OH) 4.41 (1H, q, 6.6 Hz, C*H*OTBS) 3.53 (1H, s, CHO*H*) 2.59 (1H, dd, 16.5, 3.6 Hz, CH(OH)C$H_A$CH$_B$C(=O)) 2.51 (1H, dd, 16.5, 8.8 Hz, CH(OH)CH$_A$C$H_B$C(=O)) 1.46 (9H, s, OC(C$H_3$)$_3$) 1.31 (3H, d, 6.6 Hz, CHC$H_3$) 0.88 (9H, s, SiC(C$H_3$)$_3$) 0.07 (3H, s, SiC$H_3$) 0.06 (3H, s, SiC$H_3$) $^{13}$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.

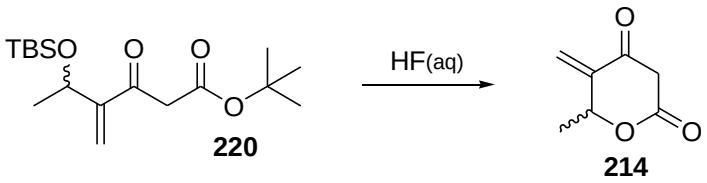
**5-(tert-Butyl-dimethyl-silanyloxy)-4-methylene-3-oxo-hexanoic acid tert-butyl ester (220)**




**219** **220**

To a stirring solution of β-hydroxy esters **219** (1.55 g; 4.65 mmol) in $CH_2Cl_2$ (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 ($CH_2Cl_2$) produced the β-keto ester **220** (1.34 g; 88%) as clear oil. RF = 0.56, $^1$H NMR (600MHz; $CDCl_3$) δ 6.24 (1H, s, C=C$H_A$CH$_B$) 6.06 (1H, s, C=CH$_A$C$H_B$) 4.75 (1H, q, 6.2 Hz, C*H*OTBS) 3.65 (1H, d, 15.0 Hz, C(=O)C$H_A$CH$_B$C(=O)) 3.58 (1H, d, 15.0 Hz, C(=O)CH$_A$C$H_B$C(=O)) 1.43 (9H, s, OC(C$H_3$)$_3$) 1.20 (3H, d, 6.2 Hz, CHC$H_3$) 0.88 (9H, s, SiC(C$H_3$)$_3$) 0.04 (3H, s, SiC$H_3$) 0.01 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

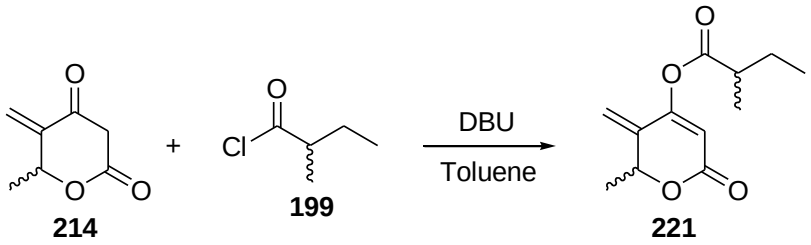
**6-Methyl-5-methylene-dihydro-pyran-2,4-dione (214)**




**220** **214**

To a solution of β-keto ester **220** (600 mg; 1.83 mmol) in $CH_2Cl_2$ (40 mL) and $CH_3CN$ (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 $NaHCO_3$ solution (50 mL), extracted with $Et_2O$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% $Et_2O/CH_2Cl_2$) gave the unsaturated β-keto lactone **214** (210 mg; 82%) as clear oil. Data in agreement with that described above.

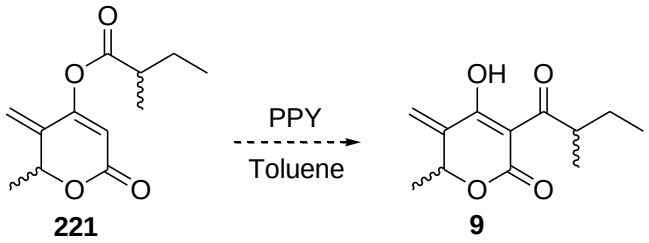
**2-Methyl-butyric acid 2-methyl-3-methylene-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (221)**




**214** **221**

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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the *O*-acylated diester product **221** (271 mg; 85%) as a clear colourless oil. Data in agreement with that described above for **204**.

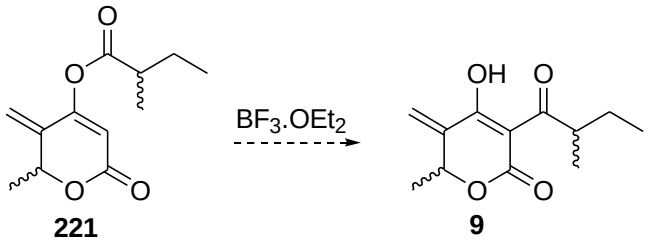
**4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)**




**221** **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**.

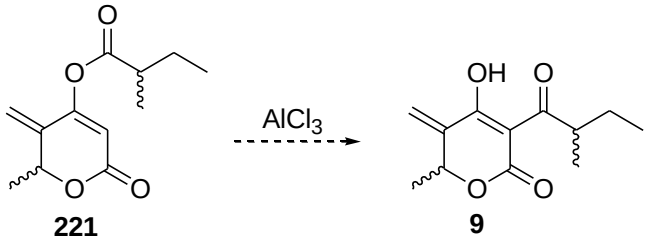
**4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)**




**221** **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 ($Na_2SO_4$) and concentrated *in vacuo*. Analysis of the crude $^1H$ 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.

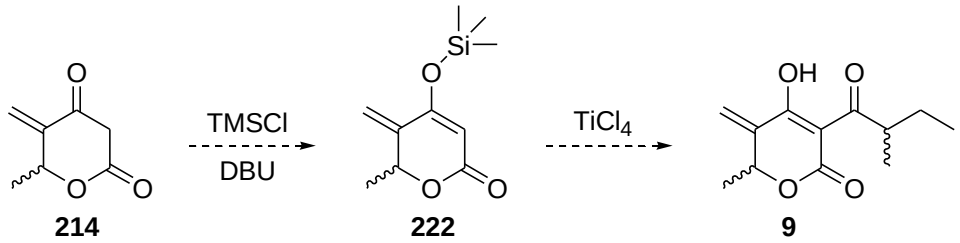
**4-Hydroxy-6-methyl-3-(2-methyl-butyryl)-5-methylene-5,6-dihydro-pyran-2-one, CR377 (9)**




**221** **9**

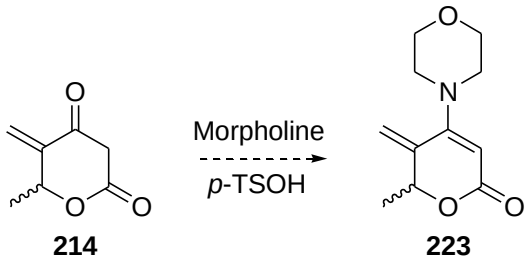
To a solution of diester **221** (100 mg; 0.45 mmol) in methylene chloride (10 mL) was added $AlCl_3$ (133 mg; 1.0mmol) at room temperature. The mixture was heated to reflux (40°C) and stirring continued for six hours at that temperature. The reaction was quenched by the addition of a 2 M HCl (5 mL) solution and extracted with $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Analysis of the crude $^1H$ 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 $CH_2Cl_2$ (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 $TiCl_4$ (150 µL of a 1 M solution in $CH_2Cl_2$; 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 $CH_2Cl_2$ (3*3 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Analysis of $^1$H 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.

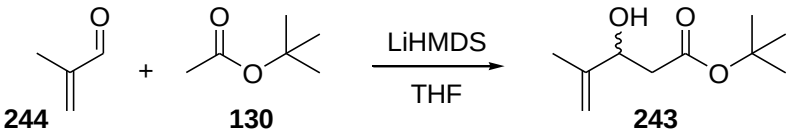
**6-Methyl-4-morpholin-4-yl-5,6-dihydro-pyran-2-one (223)**




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 $^1$H NMR indicated no enamine formation and that the model pyranone **214** had decomposed under the above conditions.

## 5.3 Experimental Procedures for Chapter Three

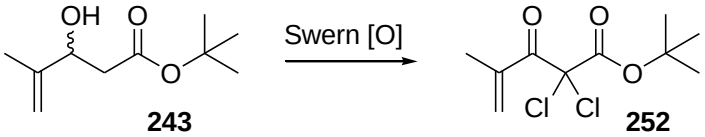
**3-Hydroxy-4-methyl-pent-4-enoic acid tert-butyl ester (243)**




**244** **130** **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 $NH_4Cl$ (20 mL), extracted with diethyl ether (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the β-hydroxy ester **243** in (0.70 g; 88%) as a clear yellow oil. $R_f$ = 0.2, $^1$H NMR (600MHz; $CDCl_3$) δ 4.98 (1H, d, 0.7 Hz, C=C$H_A$CH$_B$) 4.83 (1H, d, 0.7 Hz, C=CH$_A$C$H_B$) 4.39 (1H, m, C*H*(OH)) 3.28 (1H, d, 4.0 Hz, CH(O*H*) 2.45 (2H, m, CH(OH)C$H_2$C(=O)) 1.71 (3H, s, $H_2$C=C(C$H_3$)) 1.43 (9H, s, C(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

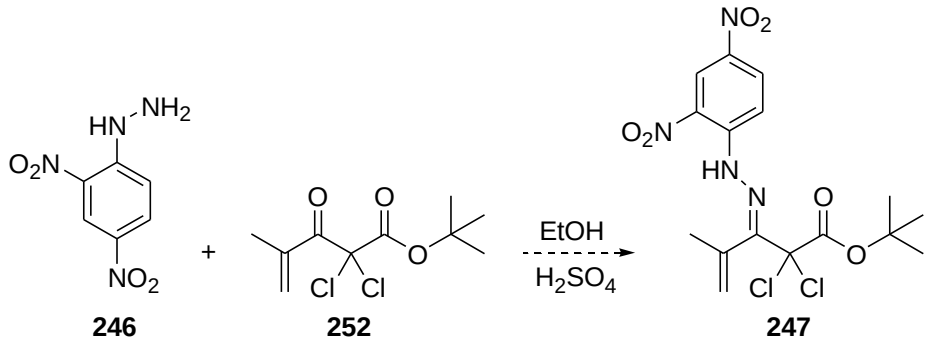



**243** **252**

To a solution of DMSO (0.34mL; 4.8x10$^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (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 $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the α,α-dichlorinated product **252** (0.33 g; 82%) as a clear oil. $R_f$ = 0.80, $^1$H NMR (600MHz; $CDCl_3$) δ 6.05 (1H, brs, C=C$H_A$CH$_B$) 5.92 (1H, d, 1.4, C=CH$_A$C$H_B$) 1.98 (3H, s,

$_2$HC=C(C$H_3$)) 1.47 (9H, s, C(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 184.38, 162.49, 138.36, 127.90, 86.29, 82.59, 27.31, 19.44

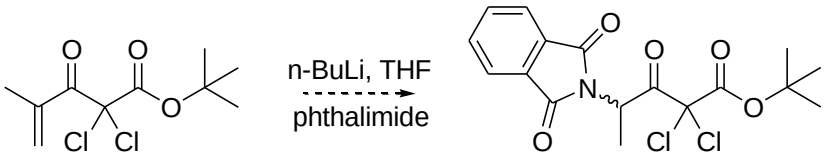
**3-[(2,4-Dinitro-phenyl)-hydrazono]-4-methyl-pent-4-enoic acid tert-butyl ester (247)**




**246** **252** **247**

To a premade solution of dinitrophenylhydrazine (**246**) (79 mg; 0.4 mmol), ethanol (4 mL) and $H_2SO_4$ (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)**

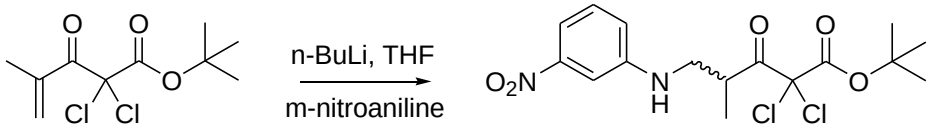



**252** **250**

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 $NH_4Cl$ (4 mL), extracted with diethyl ether (2*5 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. NMR analysis showed the presence of both the unknown

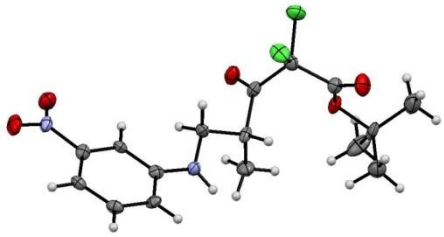
oxidation product **252** and phthalimide (**248**) reagents indicating no desired conjugate addition product had formed.

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




**252** **253**

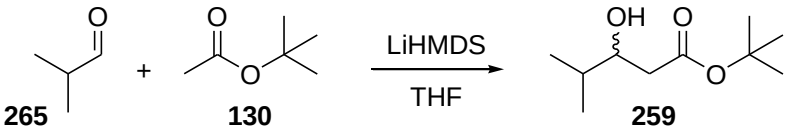
To a solution of *m*-nitroaniline (**249**) (0.28 g; 2 mmol) in THF (5 mL) at -78°C was added *n*-butyl lithium (1.33 mL; 2 mmol; 1.5 M in ether) dropwise. This mixture was stirred for 15 minutes and the unknown oxidation product **252** (0.5 g; 1.98 mmol) was added *via* cannula (THF). The mixture was further stirred at -78°C for one hour then warmed to 0°C and quenched $NH_4Cl$ (20 mL), extracted with diethyl ether (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the *m*-nitroaniline unknown oxidation product solid derivative **253** (0.46 g; 60%) as orange crystals. $R_f$ = 0.25, $^1$H NMR (600MHz; $CDCl_3$) δ 7.52 (1H, dd, 8.1, 1.9 Hz, Ar*H*) 7.40 (1H, t, 2.2 Hz, Ar*H*) 7.27 (1H, t, 8.10 Hz, Ar*H*) 6.86 (1H, dd, 8.0, 2.2 Hz, Ar*H*) 4.46 (1H, t, 6.2 Hz, N*H*) 3.59 (2H, m, C$H_2$NH) 3.32 (1H, m, C*H*($CH_3$) 1.52 (9H, s, C(C$H_3$)$_3$) 1.37 (3H, d, 6.6 Hz, CH(C$H_3$)) $^{13}$C NMR (150MHz; $CDCl_3$) 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 $C_{16}H_{20}Cl_2N_2O_5^+$ $[M+H]^+$ : 390.0749; found 390.0725



Crystal data and Structure Refinement for **253**

| Parameter | 253 |
|---|---|
| **Empirical Formula** | $C_{16}\ H_{20}\ Cl_2\ N_2\ O_5$ |
| **Formula Weight** | 391.24 |
| **Temperature (K)** | 150 |
| **Wavelength (Å)** | 0.71 |
| **Space Group** | P-1 |
| **Unit Cell Dimensions** | a= 16.9439, b= 8.4927, c= 13.2696 |
| **Theta Max** | 29.13 |
| **Reflections Used** | 5989 |
| **$R_1$** | 0.0455 |
| **$wR_2$** | 0.1142 |
| **Data Completeness** | 1.216 |

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

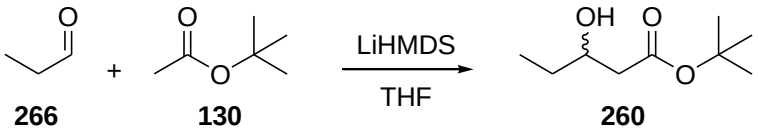



**265** **130** **259**

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 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 $NH_4Cl$ (20 mL), extracted with diethyl ether (3x50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the β-hydroxy ester **259** in (0.75 g; 93%) as a clear yellow oil. $R_f$ = 0.25, $^1$H NMR (600MHz; $CDCl_3$) δ 3.68 (1H, m, C*H*(OH)) 3.14 (1H, d, 3.8 Hz, CH(O*H*)) 2.37 (1H, dq, 5.7, 16.2 Hz, CH(OH)C$H_A$$H_B$C(=O)) 2.29 (1H, dq, 5.7, 16.2 Hz,

$CH(OH)CH_AH_BC(=O)$) 1.65 (1H, m, $(CH_3)_2CH$) 1.42 (9H, s, $OC(CH_3)_3$) 0.90 (3H, d, 6.8 Hz, $(CH_3)_2CH$) 0.87 (3H, d, 6.8 Hz, $(CH_3)_2CH$) $^{13}C$ NMR (150MHz; $CDCl_3$) δ 172.90, 81.07, 72.70, 39.34, 33.04, 28.00, 18.25, 17.73

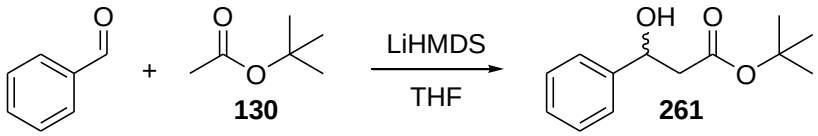
**3-Hydroxy-pentanoic acid tert-butyl ester (260)**




**266** **130** **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 $NH_4Cl$ (20 mL), extracted with diethyl ether (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the β-hydroxy ester **260** in (0.71 g; 95%) as a clear yellow oil. $R_f$ = 0.30, $^1H$ NMR (600MHz; $CDCl_3$) δ 3.87 (1H, m, $(CH)OH$) 3.13 (1H, brs, $CH(OH)$) 2.41 (1H, dq, 6.3, 16.4 Hz, $CH(OH)CH_AH_BC(=O)$) 2.30 (1H, dq, 6.3, 16.4 Hz, $CH(OH)CH_AH_BC(=O)$) 1.52 (2H, m, $CH_2CH_3$) 1.45 (9H, s, $OC(CH_3)_3$) 0.94 (3H, t, 7.4 Hz, $CH_2CH_3$) $^{13}C$ NMR (150MHz; $CDCl_3$) 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)**

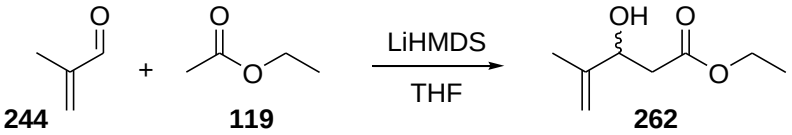



**267** **130** **261**

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 $NH_4Cl$ (20 mL), extracted with diethyl ether (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the β-hydroxy

ester **261** in (0.86 g; 90%) as a clear yellow oil. $R_f$ = 0.30, $^1$H NMR (600MHz; $CDCl_3$) δ 7.36-7.24 (5H, m, Ar*H*) 5.06 (1H, dt, 8.8, 3.7 Hz, (C*H*)OH) 3.60 (1H, d, 3.7 Hz, CH(O*H*)) 2.64 (1H, dq, 16.1, 8.8 Hz, CH(OH)C$H_A$H$_B$C(=O)) 2.62 (1H, dq, 16.1, 8.8 Hz, CH(OH)CH$_A$C$H_B$C(=O)) 1.44 (9H, s, OC(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 171.70, 142.60, 128.31, 127.50, 125.62, 81.31, 70.27, 44.23, 27.93

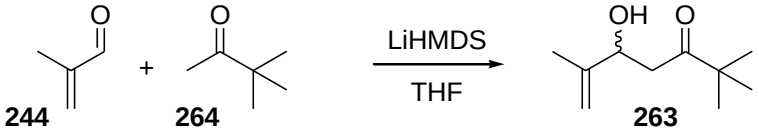
**3-Hydroxy-4-methyl-pent-4-enoic acid ethyl ester (262)**




**244** **119** **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 30mins 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 $NH_4Cl$ (20 mL), extracted with diethyl ether (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) 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$H_A$H$_B$) 4.83 (1H, brs, C=CH$_A$$H_B$) 4.44 (1H, q, 4.0 Hz, (C*H*)OH) 4.14 (2H, q, 7.2 Hz, OC$H_2$CH$_3$) 3.11 (1H, brs, CH(O*H*)) 2.52 (1H, q, 15.8, 4.0 Hz CH(OH)C$H_A$H$_B$C(=O)) 2.50 (1H, q, 15.8, 0.7 Hz, CH(OH)CH$_A$C$H_B$C(=O)) 1.72 (3H, s, (C$H_3$)C=CH$_A$CH$_B$) 1.23 (3H, t, 7.2 Hz, OCH$_2$C$H_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)**

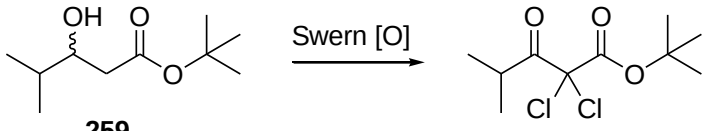



**244** **264** **263**

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 30mins 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

quenched with $NH_4Cl$ (20 mL), extracted with diethyl ether (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the β-hydroxy ketone **263** in (0.59 g; 81%) as a clear yellow oil. $R_f$ = 0.24, $^1$H NMR (600MHz; $CDCl_3$) δ 4.99 (1H, brs, C=C$H_A$H$_B$) 4.83 (1H, brs, C=CH$_A$$H_B$) 4.44 (1H, d, 8.8 Hz, C*H*(OH)) 3.29 (1H, d, 2.9 Hz, CH(O*H*)) 2.69 (1H, q, 17.6, 8.8 Hz, CH(OH)C$H_A$CH$_B$C(=O)) 2.67 (1H, q, 17.6, 3.30 Hz, CH(OH)CH$_A$$H_B$C(=O)) 1.73 (3H, s, (C$H_3$)C=CH$_A$H$_B$) 1.12 (9H, s, C(C$H_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 217.04, 145.79, 110.99, 71.07, 44.38, 41.71, 26.14, 18.40

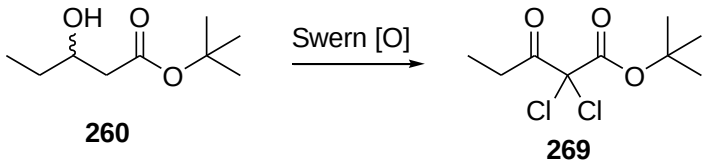
**2,2-Dichloro-4-methyl-3-oxo-pentanoic acid tert-butyl ester (268)**




**259** **268**

To a solution of DMSO (0.34 mL; 4.8x10$^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (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 $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the α,α-dichlorinated product **268** (0.29 g; 70%) as a clear oil. $R_f$ = 0.90, $^1$H NMR (600MHz; $CDCl_3$) δ 3.15 (1H, septet, 6.7 Hz, $(CH_3)_2$C*H*) 1.47 (9H, s, OC(C$H_3$)$_3$) 1.22 (6H, d, 6.7 Hz, (C$H_3$)$_2$CH) $^{13}$C NMR (150MHz; $CDCl_3$) δ 198.42, 161.93, 86.29, 82.92, 35.93, 27.45, 20.90*2

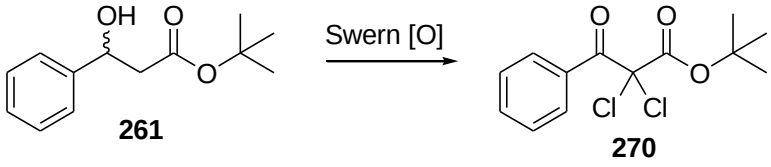
**2,2-Dichloro-3-oxo-pentanoic acid tert-butyl ester (269)**




**260** **269**

To a solution of DMSO (0.37 mL; $5.1x10^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (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 $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the α,α-dichlorinated product **269** (0.32 g; 78%) as a clear oil. $R_f$ = 0.92, $^1$H NMR (600MHz; $CDCl_3$) δ 2.78 (1H, q, 7.2 Hz, $CH_2CH_3$) 1.48 (9H, s, $OC(CH_3)_3$) 1.16 (3H, t, 7.2 Hz, $(CH_3)CH_2$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

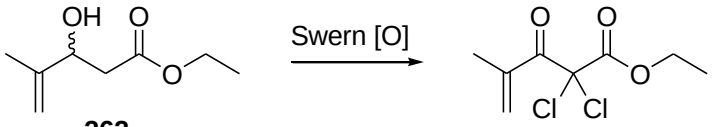



**261** **270**

To a solution of DMSO (0.29 mL; $4.0x10^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (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 $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the α,α-dichlorinated product **270** (0.32 g;

85%) as a clear oil. $R_f$ = 0.85, $^1$H NMR (600MHz; $CDCl_3$) δ 7.99 (2H, d, 8.4 Hz, Ar*H*) 7.58 (1H, t, 7.7 Hz, Ar*H*) 7.44 (2H, t, 7.7 Hz, Ar*H*) 1.33 (9H, s, OC($CH_3$)$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 183.08, 162.44, 133.97, 131.22, 129.82, 128.53, 86.39, 82.78, 27.15

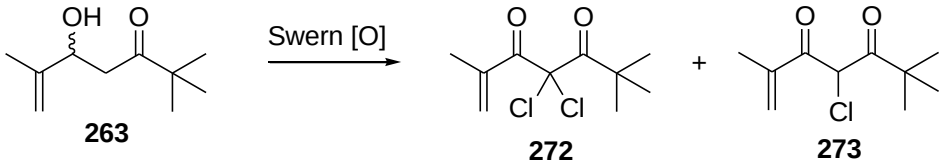
**2,2-Dichloro-4-methyl-3-oxo-pent-4-enoic acid ethyl ester (271)**




**262** **271**

To a solution of DMSO (0.40 mL; 5.7x10$^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (1.43 mL; 2.9x10$^{-3}$ mol) dropwise and allowed to stir for 20 minutes at this temperature. A solution of β-hydroxyester **262** (0.3 g; 1.9x10$^{-3}$ mol) in $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the α,α-dichlorinated product **271** (0.38 g; 89%) as a clear oil. $R_f$ = 0.87, $^1$H NMR (600MHz; $CDCl_3$) δ 6.07 (1H, s, $CH_3C=CH_AH_B$) 5.93 (1H, q, 1.5 Hz, $CH_3C=CH_AH_B$) 4.33 (2H, q, 7.0 Hz, $OCH_2CH_3$) 1.97 (3H, s, $CH_3C=CH_ACH_B$) 1.29 (3H, t, 7.0 Hz, $OCH_2CH_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 184.37, 164.02, 138.06, 128.44, 81.68, 64.57, 19.41, 13.63

**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)**



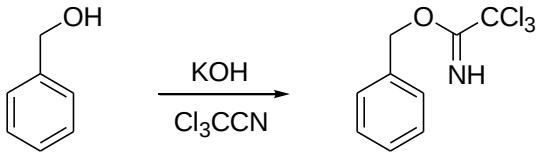

**263** **272** **273**

To a solution of DMSO (0.38 mL; 5.3x10$^{-3}$ mol) in $CH_2Cl_2$ (10 mL) at -78°C was added a 2 M oxalyl chloride solution in $CH_2Cl_2$ (1.35 mL; 2.7x10$^{-3}$ mol) dropwise and allowed to stir for 20 minutes at this

temperature. A solution of β-hydroxyketone **263** (0.3 g; $1.8x10^{-3}$ mol) in $CH_2Cl_2$ 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 $NH_4Cl$ (20 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% Hexanes/$CH_2Cl_2$) 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, $^1$H NMR (600MHz; $CDCl_3$) δ 6.17 (1H, brs, $CH_3C=C\mathit{H}_A H_B$) 6.00 (1H, s, $CH_3C=CH_A\mathit{H}_B$) 1.52 (3H, s, $C\mathit{H}_3C=CH_AH_B$) 1.17 (9H, s, $C(C\mathit{H}_3)_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 199.65, 199.63, 136.47, 109.07, 77.98, 38.91, 27.35, 18.21 **Minor 273:** $R_f$ = 0.5, $^1$H NMR (600MHz; $CDCl_3$) δ (1H, d, 0.78 Hz, $CH_3C=C\mathit{H}_ACH_B$), 5.97 (1H, m, $CH_3C=CH_AC\mathit{H}_B$), 5.82 (1H, s, C(=O)C*H*ClC(=O)), 1.94 (3H, brs, $C\mathit{H}_3C=CH_ACH_B$), 1.20 (9H, s, $C(C\mathit{H}_3)_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 204.02, 191.05, 142.00, 127.46, 58.44, 44.72, 26.90, 18.05

## 5.4 Experimental Procedures for Chapter Four

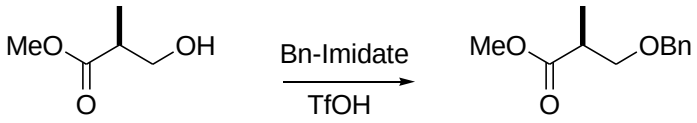
**2,2,2-Trichloro-acetimidic acid benzyl ester (339)**




**340** **339**

To a solution of benzyl alcohol (**340**) (18 mL; 0.16 mol) in $CH_2Cl_2$ (100 mL) was added 50% (w/w) KOH solution (50 g in 100 mL $H_2O$) 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 $H_2O$ (150 mL) and extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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, N*H*) 7.48 (2H, d, Ar*H*) 7.43 (2H, t, Ar*H*) 7.38 (1H, t, Ar*H*) 5.39 (2H, s, C$H_2$Ph) $^{13}$C NMR (150MHz; $CDCl_3$) δ 207.30, 162.46, 135.37, 128.46, 128.21, 127.63, 70.64.

**3-Benzyloxy-2(*S*)-methyl-propionic acid methyl ester (338)**

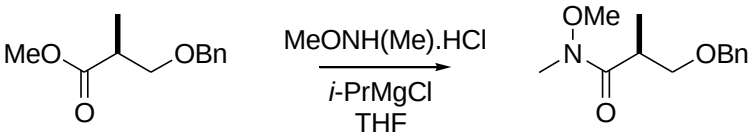



**337** **338**

To a solution of (*S*)-methyl-3-hydroxy-2-methylpropionate (**337**) (5 g; 42 mmol) in cyclohexane (100 mL) and $CH_2Cl_2$ (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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatrography ($CH_2Cl_2$) 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, Ar*H*) 4.53 (1H, d, 12.1 Hz, C$H_A$CH$_B$Ph) 4.52 (1H, d, 12.1 Hz, CH$_A$C$H_B$Ph) 3.70 (3H, s, OC*H3*) 3.66 (1H, dd, 9.1, 7.4 Hz, C*HA*CHBOBn) 3.50 (1H, dd,

9.0, 5.9 Hz, $CH_ACH_BOBn$) 2.79 (1H, dq, 7.1, 6.0 Hz, $CH(CH_3)CH_2OBn$) 1.18 (3H, d, 7.1 Hz, $CH(CH_3)CH_2OBn$) $^{13}C$ NMR (150MHz; $CDCl_3$) δ 175.30, 138.13, 128.33, 127.58, 127.56, 73.07, 71.92, 51.71, 40.15, 13.96.

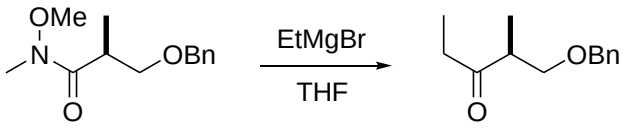
**3-Benzyloxy-N-methoxy-2,N-dimethyl-propionamide (341)**




**338** **341**

To a solution of benzyl ester **338** (5 g; 24 mmol) in THF (60 mL) and $Et_2O$ (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 $NH_4Cl$ (200 mL) was added cautiously. The mixture was extracted with $Et_2O$ (3*100 mL) and $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) 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. $R_F$ = 0.1, $^1H$ NMR (600MHz; $CDCl_3$) δ 7.30-7.23 (5H, m, Ar*H*) 4.54 (1H, d, 12.1 Hz, $CH_ACH_BPh$) 4.46 (1H, d, 12.1 Hz, $CH_ACH_BPh$) 3.70 (1H, t, 8.6 Hz, $CH_ACH_BOBn$) 3.68 (3H, s, $NOCH_3$) 3.42 (1H, dd, 8.6, 5.8 Hz, $CH_ACH_BOBn$) 3.28 (1H, m, $CH(CH_3)CH_2OBn$) 3.19 (3H, brs, $NCH_3$) 1.10 (3H, d, 7.0 Hz, $CH(CH_3)CH_2OBn$) $^{13}C$ NMR (150MHz; $CDCl_3$) δ 175.77, 138.25, 128.16, 127.39, 127.34, 73.06, 72.44, 61.40, 35.65, 31.91, 14.08.

**1-Benzyloxy-2(*S*)-methyl-pentan-3-one (332)**

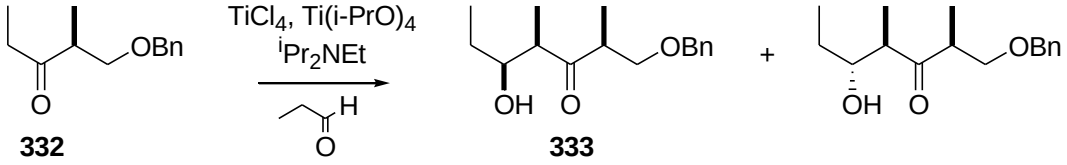



**341** **332**

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 $NH_4Cl$ (100 mL) was carefully added. The mixture was extracted with $Et_2O$ (3*100 mL) and $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column

chromatography ($CH_2Cl_2$) 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, Ar*H*) 4.49 (1H, d, 12.0 Hz, OC*H*$_A$CH$_B$Ph) 4.46 (1H, d, 12.0 Hz, OCH$_A$C*H*$_B$Ph) 3.63 (1H, dd, 9.1, 8.0 Hz, C*H*$_A$CH$_B$OBn) 3.46 (1H, dd, 9.1, 5.4 Hz, CH$_A$C*H*$_B$OBn) 2.88 (1H, m, C*H*(CH$_3$)CH$_2$OBn) 2.50 (2H, dq, 7.3, 1.2 Hz, C*H*$_2$CH$_3$) 1.07 (3H, d, 7.1 Hz, CH(C*H*$_3$)CH$_2$OBn) 1.04 (3H, t, 7.3 Hz, CH$_2$C*H*$_3$) $^{13}$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-Benzyloxy-5(*S*)-hydroxy-2(*S*),4(*R*)-dimethyl-heptan-3-one (333)**

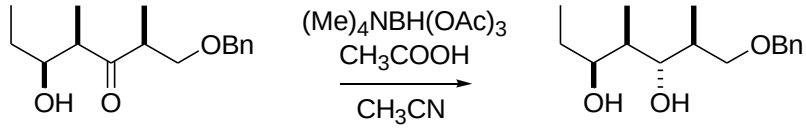



**332** **333**

To a solution of benzyl ketone **332** (5 g; 22.5 mmol) in $CH_2Cl_2$ (120 mL) was added a mixture of $TiCl_4$ (20.5 mL; 1 M of a solution in $CH_2Cl_2$; 20.5 mmol) and Ti($^i$PrO)$_4$ (2 mL; 6.8 mmol) at -78°C *via* cannula. The mixture was stirred for 20 minutes then $^i$Pr$_2$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 $NH_4Cl$ (100 mL), extracted with $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) 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, Ar*H*) 4.44 (1H, d, 11.8 Hz, C*H*$_A$CH$_B$Ph) 4.41 (1H, d, 11.8 Hz, CH$_A$C*H*$_B$Ph) 3.89-3.87 (1H, m, C*H*OH) 3.64 (1H, t, 9.0 Hz, C*H*$_A$CH$_B$OBn) 3.46 (1H, dd, 9.0, 5.0 Hz, CH$_A$C*H*$_B$OBn) 3.18-3.12 (1H, m, C(=O)C*H*(CH$_3$)CHOH) 2.96 (1H, d, 3.3 Hz, CHO*H*) 2.74 (1H, dq, 7.1, 3.0 Hz, C*H*(CH$_3$)CH$_2$OBn) 1.50-1.43 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.38-1.32 (1H, m, CH$_A$C*H*$_B$CH$_3$) 1.07 (3H, d, 7.1 Hz, C(=O)CH(C*H*$_3$)CHOH) 1.02 (3H, d, 7.1 Hz, CH(C*H*$_3$)CH$_2$OBn) 0.89 (3H, t, 7.6 Hz, CH$_A$CH$_B$C*H*$_3$) $^{13}$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, Ar*H*) 4.49 (1H, d, 11.8 Hz, C*H*$_A$CH$_B$Ph) 4.45 (1H, d, 11.8 Hz, CH$_A$C*H*$_B$Ph) 3.80-3.77 (1H, m, C*H*OH) 3.66 (1H, t, 9.0 Hz, C*H*$_A$CH$_B$OBn) 3.43 (1H, dd, 9.0, 5.0 Hz, CH$_A$C*H*$_B$OBn) 3.13-3.07 (1H, m, C(=O)C*H*(CH$_3$)CHOH) 2.92 (1H, brs, CHO*H*) 2.70 (1H, dq, 7.1, 2.8 Hz, C*H*(CH$_3$)CH$_2$OBn) 1.55-1.47 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.40-1.33 (1H, m, CH$_A$C*H*$_B$CH$_3$) 1.12 (3H, d, 7.1 Hz, C(=O)CH(C*H*$_3$)CHOH) 1.05 (3H, d, 7.1 Hz, CH(C*H*$_3$)CH$_2$OBn) 0.92 (3H, t, 7.4

Hz, $CH_2CH_3$) $^{13}C$ 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.

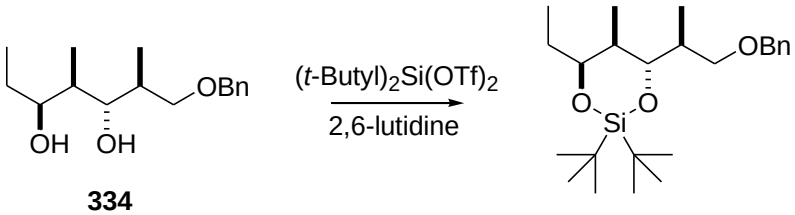
**1-Benzyloxy-2(*S*),4(*R*)-dimethyl-heptane-3(*S*),5(*S*)-diol (334)**




**333** **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 them 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 $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) 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, Ar*H*) 4.53 (2H, s, C$H_2$OBn) 3.90 (1H, t, 7.3 Hz, C*H*(OH)$CH_2CH_3$) 3.84 (1H, brs, CH(O*H*)) 3.68 (1H, dd, 9.0, 4.0 Hz, C$H_A$$CH_B$OBn) 3.66 (1H, m, CH(O*H*)) 3.59 (1H, dd, 8.3, 1.7 Hz, CH($CH_3$)C*H*(OH)CH($CH_3$) 3.48 (1H, t, 9.0 Hz, $CH_ACH_B$OBn) 2.16-2.13 (1H, m, C*H*($CH_3$)$CH_2$OBn) 1.74-1.70 (1H, qdd, 7.0, 3.7, 1.5 Hz, CH(OH)C*H*($CH_3$)CH(OH)) 1.63-1.55 (1H, m, C$H_A$$CH_B$$CH_3$) 1.42-1.35 (1H, m, $CH_A$C$H_B$$CH_3$) 0.97 (3H, d, 7.2 Hz, CH(C$H_3$)$CH_2$OBn) 0.92 (3H, t, 7.4 Hz, $CH_2CH_3$) 0.84 (3H, d, 7.0 Hz, CH(OH)CH(C$H_3$)CH(OH)) $^{13}C$ 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.

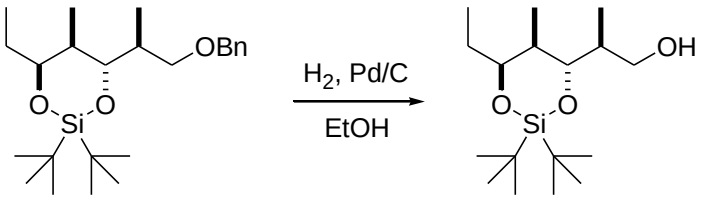
**4-(2-Benzyloxy-1-methyl-ethyl)-2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinane (355)**




**334** **335**

To a solution of diol **334** (1.60 g; 6 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ (100 mL), extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the silyl protected ether **335** (2.20 g; 90%) as a clear oil. $R_F$ = 0.80, $^1$H NMR (600MHz; $CDCl_3$) δ 7.34-7.26 (5H, m, Ar*H*) 4.52 (1H, d, 11.8 Hz, C$H_A$CH$_B$Ph) 4.47 (1H, d, 11.8 Hz, CH$_A$C$H_B$Ph) 3.85-3.82 (1H, m, $CH_3CH_2CH$(OSi)) 3.80 (1H, dd, 11.2, 1.6 Hz, CH($CH_3$)C*H*(OSi)) 3.70 (1H, dd, 9.0, 5.4 Hz, C$H_A$CH$_B$OBn) 3.33 (1H, t, 9.0 Hz, CH$_A$C$H_B$OBn) 2.33-2.27 (1H, m, CH(OSi)C*H*($CH_3$)CH(OSi)) 2.04-2.01 (1H, m, C*H*($CH_3$)$CH_2$OBn) 1.52-1.42 (2H, m, C$H_2$CH$_3$) 1.09 (3H, d, 6.8 Hz, CH(C$H_3$)$CH_2$OBn) 1.05 (3H, t, 7.3 Hz, $CH_2CH_3$) 1.00 (9H, s, SiC(C$H_3$)$_3$) 0.99 (9H, s, SiC(C$H_3$)$_3$) 0.78 (3H, d, 7.2 Hz, CH(OSi)CH(C$H_3$)CH(OSi)) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

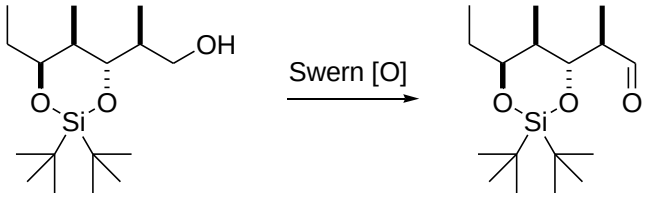



**335** **336**

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 $H_2$ 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% $Et_2O/CH_2Cl_2$) gave the primary alcohol **336** (500 mg; 86%) as a clear oil. $R_F$ = 0.32, $^1$H NMR (600MHz; $CDCl_3$) δ 3.92-

3.87 (3H, m, 2* C*H*(OSi), C$H_A$CH$_B$OH) 3.61 (1H, dd, 10.9, 4.3 Hz, CH$_A$C$H_B$OH) 2.36-2.30 (1H, m, CH(OSi)C*H*(CH$_3$)CH(OSi)) 1.80-1.74 (1H, m, C*H*(CH$_3$)CH$_2$OH) 1.48-1.44 (2H, m, C$H_2$CH$_3$) 1.14 (3H, d, 7.0 Hz, CH(OSi)CH(C$H_3$)CH(OSi)) 1.03 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 1.00 (9H, s, SiC(C$H_3$)$_3$) 0.99 (9H, s, SiC(C$H_3$)$_3$) 0.76 (3H, d, 7.2 Hz, CH(C$H_3$)CH$_2$OH) $^{13}$C NMR (150MHz; CDCl$_3$) 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.

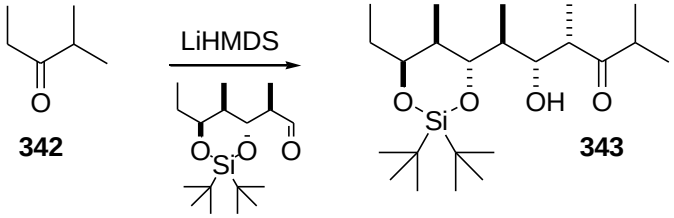
**2-(2,2-Di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-propionaldehyde (330)**




**336** **330**

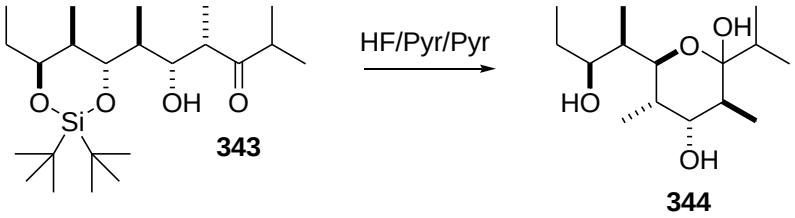
To a solution of DMSO (300 µL; 4.26 mmol) in CH$_2$Cl$_2$ (20 mL) at -78°C was added oxalyl chloride (1.06 mL of a 2 M solution in CH$_2$Cl$_2$; 2.13 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **336** (450 mg; 1.42 mmol) in CH$_2$Cl$_2$ (5 mL) was added *via* cannula. This mixture was stirred for a further 30 minutes then NEt$_3$ (1.2 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 NH$_4$Cl (70 mL) then extracted with CH$_2$Cl$_2$ (3*20 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by column chromatography (CH$_2$Cl$_2$) gave the desired aldehyde **330** (406 mg; 91%) as a colourless oil. $R_F$ = 0.78, $^1$H NMR (600MHz; CDCl$_3$) δ 9.81 (1H, d, 3.1 Hz, C*H*(=O)) 4.01 (1H, dd, 9.7, 2.5 Hz, C*H*(OSi)CH(CH$_3$)CH(=O)) 3.87 (1H, dt, 9.6, 4.9 Hz, CH$_3$CH$_2$C*H*(OSi)) 2.49-2.42 (1H, m, C*H*(CH$_3$)CH(=O)) 2.33-2.29 (1H, m, CH(OSi)C*H*(CH$_3$)CH(OSi)) 1.48-1.44 (2H, m, C$H_2$CH$_3$) 1.25 (3H, d, 7.0 Hz, CH(C$H_3$)CH(=O)) 1.04 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 1.00 (9H, s, SiC(C$H_3$)$_3$) 0.97 (9H, s, SIC(C$H_3$)$_3$) 0.82 (3H, d, 7.2 Hz, CH(OSi)CH(C$H_3$)CH(OSi)) $^{13}$C NMR (150MHz; CDCl$_3$) 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 $NH_4Cl$ (30 mL), extracted with $Et_2O$ (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) 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:** $R_F$ = 0.4, $^1$H NMR (600MHz; $CDCl_3$) δ 3.89-3.84 (3H, m, $CH_3CH_2CH$(OSi), C*H*(OSi)CH($CH_3$)CH(OH), CH(O*H*)) 3.74-3.71 (1H, m, C*H*(OH)) 3.08 (1H, dq, 7.3, 3.1 Hz, C(=O)C*H*($CH_3$)) 2.78 (1H, sept, 6.9 Hz, C(=O)C*H*($CH_3$)$_2$) 2.44-2.41 (1H, m, CH(OSi)C*H*($CH_3$)CH(OSi)) 1.86-1.82 (1H, m, C*H*($CH_3$)CH(OH)) 1.50-1.38 (2H, m, C*H*$_2$$CH_3$) 1.27 (3H, d, 7.3 Hz, C(=O)CH(C*H*$_3$)) 1.10 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$)$_2$) 1.08 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$)$_2$) 1.02 (9H, s, SiC(C*H*$_3$)$_3$) 1.00-0.98 (3H, m, $CH_2$C*H*$_3$) 0.98 (9H, s, SiC(C*H*$_3$)$_3$) 0.93 (3H, d, 7.0 Hz, CH(C*H*$_3$)CH(OH)) 0.82 (3H, d, 7.1 Hz, CH(OSi)CH(C*H*$_3$)CH(OSi)) $^{13}$C NMR (150MHz; $CDCl_3$) δ 222.13, 78.84, 77.84, 76.37, 71.01, 45.65, 40.78, 39.97, 27.60, 27.47, 23.97, 21.64, 20.97, 18.35, 18.21, 16.13, 15.66, 13.96, 10.93. **Minor Isomer:** $R_f$ = 0.45, $^1$H NMR (600MHz; $CDCl_3$) δ 4.13 (1H, d, 9.8 Hz, C*H*(OH)) 3.92-3.90 (2H, m, $CH_3CH_2CH$(OSi), C*H*(OSi)CH($CH_3$)CH(OH)) 3.89 (1H, s, CH(O*H*)) 2.93 (1H, dq, 9.8, 6.9 Hz, C(=O)C*H*($CH_3$)) 2.70 (1H, sept, 6.9 Hz, C(=O)C*H*($CH_3$)$_2$) 2.51-2.47 (1H, m, CH(OSi)C*H*($CH_3$)CH(OSi)) 1.51-1.38 (3H, m, C*H*$_2$$CH_3$, C*H*($CH_3$)CH(OH)) 1.21 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$) 1.11-1.08 (9H, m, 2*CH(C*H*$_3$)$_2$, $CH_2$C*H*$_3$)) 1.06 (3H, d, 7.0 Hz, CH(C*H*$_3$)CH(OH)) 1.02 (9H, s, SiC(C*H*$_3$)$_3$) 0.98 (9H, s, SiC(C*H*$_3$)$_3$) 0.72 (3H, d, 7.1 Hz, CH(OSi)CH(C*H*$_3$)CH(OSi)) $^{13}$C NMR (150MHz; $CDCl_3$) δ 217.76, 79.85, 78.59, 71.17, 48.14, 41.94, 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.

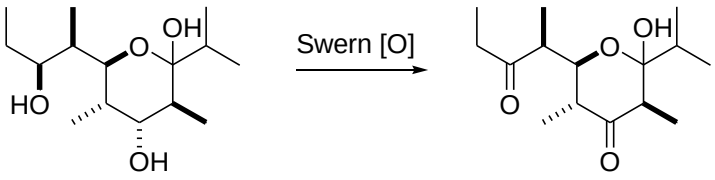
**6-(2-Hydroxy-1-methyl-butyl)-2-isopropyl-3,5-dimethyl-tetrahydro-pyran-2,4-diol (344)**




**343** **344**

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 $Et_2O$ (10 mL) and quenched with $NaHCO_3$ (20 mL) followed by $CuSO_4$ (10 mL). The aqueous layers were re-extracted with $Et_2O$ (2*10 mL) dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% $Et_2O/CH_2Cl_2$) yielded model hemiacetal **344** (105 mg; 80%) as a clear oil. $R_F$ = 0.35, $^1$H NMR (600MHz; $CDCl_3$) δ 4.71 (1H, brs, C*H*(-O-)C(OH)) 3.90-3.85 (2H, m, CH(-O-)C(O*H*), $CH_3CH_2CH$(OH)) 3.73-3.68 (2H, m, $CH(CH_3)CH$(OH)$CH(CH_3)$, CH(O*H*)) 3.41 (1H, d, 5.9 Hz, CH(O*H*)) 1.96 (1H, sept, 6.8 Hz, C*H*$(CH_3)_2$) 1.89-1.84 (2H, m, $CH_2CH_3$) 1.78-1.73 (1H, m, C*H*$(CH_3)$CH(OH)) 1.63-1.56 (1H, m, C*H*$(CH_3)$CH(OH)$CH(CH_3)$) 1.40-1.33 (1H, m, C*H*$(CH_3)$CH(OH)$CH_2CH_3$) 1.06 (3H, d, 7.1 Hz, CH(C*H*$_3$)CH(OH)) 1.03 (3H, d, 7.0 Hz, CH(C*H*$_3$)CH(OH)$CH_2CH_3$) 0.95 (3H, d, 6.8 Hz, CH(C*H*$_3$)$_2$ ) 0.93-0.86 (6H, m, CH(C*H*$_3$)$_2$, $CH_2$C*H*$_3$ ) 0.84 (3H, d, 7.0 Hz, CH(C*H*$_3$)CH(OH)$CH_2CH_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

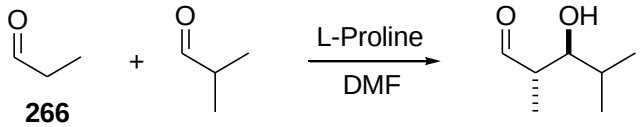



**344** **345**

To a solution of DMSO (165 µL; 2.22 mmol) in $CH_2Cl_2$ (10 mL) at -78°C was added oxalyl chloride (0.55 mL of a 2 M solution in $CH_2Cl_2$; 1.11 mmol) dropwise. The mixture was stirred for 20 minutes then hemiacetal **344** (100 mg; 0.37 mmol) in $CH_2Cl_2$ (5 mL) was added *via* cannula. This mixture was stirred for a further 30 minutes then $NEt_3$ (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 $NH_4Cl$ (20 mL) then extracted with $CH_2Cl_2$ (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the diketone **345** (75 mg; 75%) as a colourless oil. $R_F$ = 0.70, $^1$H NMR (600MHz; $CDCl_3$) δ 3.83 (1H, dd, 10.3, 3.2 Hz, C*H*(-O-)C(OH)CH($CH_3$)$_2$) 2.76 (1H, dq, 7.1, 3.4 Hz, C*H*($CH_3$)C(=O)CH($CH_3$)C(OH)) 2.64 (1H, q, 6.5 Hz, C(=O)C*H*($CH_3$)C(OH)) 2.60 (1H, m, C$H_A$C$H_B$C$H_3$) 2.53 (1H, m, C$H_A$C$H_B$C$H_3$) 2.46 (1H, dq, 9.90, 6.6 Hz, C*H*($CH_3$)C(=O)C$H_2$C$H_3$) 1.98 (1H, sept, 6.8 Hz, C*H*($CH_3$)$_2$) 1.28 (3H, d, 7.1 Hz, CH(C*H*$_3$)C(=O)CH($CH_3$)C(OH)) 1.04-0.98 (15H, m, 2*CH(C*H*$_3$)$_2$, C$H_2$C*H*$_3$, C(=O)CH(C*H*$_3$)C(OH), CH(C*H*$_3$)C(=O)C$H_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

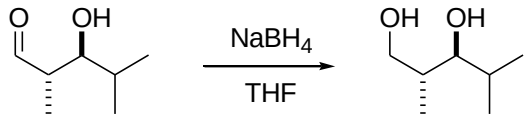
**3-Hydroxy-2,4-dimethyl-pentanal (346)**




**266** **265** **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 $Et_2O$ (150 mL) and washed with water (300 mL) and brine (100 mL). The aqueous layers are combined and re-extracted with $Et_2O$ (3*50 mL) then dried ($Na_2SO_4$) and concentrated *in vacuo*. Due to stability of the final product **346** it was used in the following step without further purification. $^1$H NMR (600MHz; $CDCl_3$) δ 9.77 (1H, d, 3.1 Hz, C*H*(=O)) 3.54 (1H, dd, 10.9, 6.8 Hz, C*H*(OH)) 2.54 (1H, dq, 10.9, 3.1 Hz C*H*($CH_3$)CH(OH)) 1.81-1.74 (1H, m, C*H*($CH_3$)$_2$) 1.14-0.91 (9H, m, 2*CH(C*H*$_3$)$_2$, CH(C*H*$_3$)CH(OH))

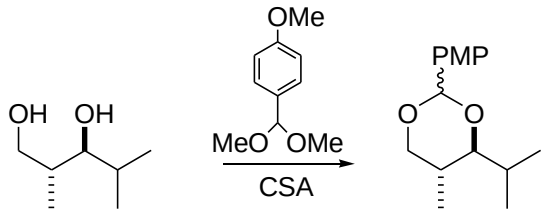
**2,4-Dimethyl-pentane-1,3-diol (348)**




**346** **348**

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 $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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, $^1$H NMR (600MHz; $CDCl_3$) δ 3.69 (1H, dd, 10.9, 3.6 Hz, C$H_A$CH$_B$(OH)) 3.63 (1H, brs, CH(O*H*)) 3.55 (1H, dd, 10.9, 7.3 Hz, CH$_A$C$H_B$(OH)) 3.45 (1H, brs, CH(O*H*)) 3.27 (1H, dd, 8.0, 3.8 Hz, C*H*(OH)) 1.90-1.84 (1H, m, C*H*(CH$_3$)$_2$) 1.78-1.73 (1H, m, C*H*(CH$_3$)) 0.88 (3H, d, 6.6 Hz, CH(C$H_3$)) 0.84 (3H, d, 6.8 Hz, CH(C$H_3$)$_2$) 0.80 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 81.58, 67.72, 36.88, 30.20, 19.60, 16.55, 14.98.

**4-Isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (350)**

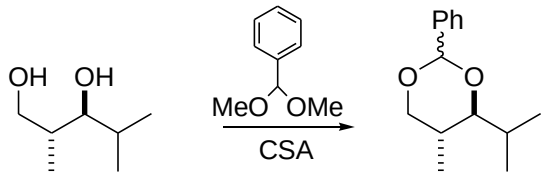



**348** **350**

To a solution of diol **348** (5 g; 38 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) yielded the protected acetal **350** (6.50 g; 68%) and as clear oil. $R_F$ = 0.6, $^1$H NMR (600MHz; $CDCl_3$) δ 7.41 (2H, d, 8.6 Hz, Ar*H*) 6.88 (2H, d, 8.6 Hz, Ar*H*) 5.41 (1H, s, C*H*PMP) 4.08 (1H, dd, 11.1, 4.7 Hz, C$H_A$CH$_B$O) 3.80 (3H, s, OC$H_3$) 3.47 (1H, t, 11.0 Hz, C*H*O) 3.29 (1H, dd, 9.9, 1.9 Hz, CH$_A$C$H_B$O) 1.95 (2H, m, C*H*(CH$_3$), C*H*(CH$_3$)$_2$) 1.05 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 0.96 (3H, d, 6.9 Hz, CH(C$H_3$)$_2$)

0.75 (3H, d, 6.7 Hz, CH(C*H*$_3$)) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

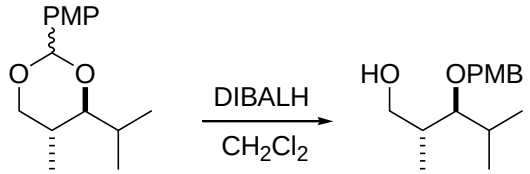
**4-Isopropyl-5-methyl-2-phenyl-[1,3]dioxane (349)**




**348** **349**

To a solution of diol **348** (3 g; 22.7 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ (80 mL). The mixture was separated and extracted with $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) yielded the protected acetal **349** (4.0 g; 80%) and as clear oil. $R_F$ = 0.63, $^1$H NMR (600MHz; $CDCl_3$) δ 7.36 (2H, d, 6.0 Hz, Ar*H*) 7.34-7.31 (3H, m, Ar*H*) 5.49 (1H, s, C*H*Ph) 4.11 (1H, dd, 11.4, 4.8 Hz, C$H_A$CH$_B$CH(CH$_3$)) 3.50 (1H, t, 10.8 Hz, CH$_A$C$H_B$CH(CH$_3$)) 3.31 (1H, d, 9.6, 1.8 Hz, C*H*O) 2.05-1.95 (2H, m, C*H*(CH$_3$), C*H*(CH$_3$)$_2$) 1.08 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 0.99 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 0.77 (3H, d, 6.6 Hz, CH(C$H_3$)) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

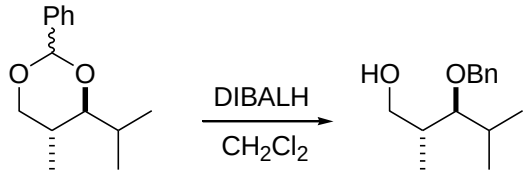



**350** **352**

To a stirred solution of acetal **350** (2 g; 8 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ and 2 M HCl (200 mL; 1:1). The mixture was further diluted with $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the primary alcohol **352** (1.92 g; 95%) as a clear oil. $R_F$ = 0.3, $^1$H NMR (600MHz; $CDCl_3$) δ 7.27 (2H, d, 8.7 Hz, Ar*H*) 6.86 (2H, d, 8.7 Hz, Ar*H*) 4.57 (1H, d, 10.5 Hz, OC$H_A$$CH_B$PMP) 4.50 (1H, d, 10.5 Hz, $OCH_ACH_B$PMP) 3.79 (3H, s, $OCH_3$) 3.69 (1H, dd, 10.9, 3.1 Hz, C$H_A$$CH_B$OH) 3.58 (1H, dd, 10.9, 5.6 Hz, $CH_ACH_B$OH) 3.14 ( 1H, dd, 5.8, 5.2 Hz, C*H*OPMB) 2.86 (1H, brs, $CH_2OH$) 1.96-1.85 (1H, m, C*H*$(CH3)_2$, C*H*$(CH_3)$) 1.01-0.96 (9H, m, CH(C$H_3$), CH(C$H_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

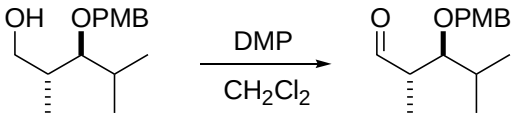
**3-Benzyloxy-2,4-dimethyl-pentan-1-ol (351)**




**349** **351**

To a stirred solution of acetal **349** (0.5 g; 2.27 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ and 2 M HCl (200 mL; 1:1). The mixture was further diluted with $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the primary alcohol **351** (0.47 g; 93%) as a clear oil. $R_F$ = 0.35, $^1$H NMR (600MHz; $CDCl_3$) δ 7.35-7.26 (5H, m, ArH) 4.62 (1H, d, 10.8 Hz, OC$H_A$$CH_B$Ph) 4.59 (1H, d, 10.8 Hz, $OCH_ACH_B$Ph) 3.73 (1H, dd, 10.9, 3.7 Hz, C$H_A$$CH_B$OH) 3.61 (1H, dd, 10.9, 5.5 Hz, $CH_ACH_B$OH) 3.17 (1H, t, 6.2 Hz, C*H*OBn) 2.73-2.69 (1H, m, $CH_ACH_B$(O*H*)) 1.98-1.90 (2H, m, C*H*$(CH_3)_2$, C*H*$(CH_3)$) 1.02-0.99 (9H, m, 2*CH(C$H_3$)$_2$, CH(C$H_3$)) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

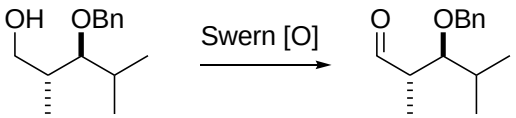
**3-(4-Methoxy-benzyloxy)-2,4-dimethyl-pentanal (353)**




**352** **353**

To a solution of alcohol **352** (130 mg; 0.52 mmol) in $CH_2Cl_2$ (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 $Na_2S_2O_3$ in $NaHCO_3$ (20 mL; 1.2 g per 100 mL). The mixture was extracted with $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) 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, C*H*(=O)) 7.25 (2H, d, 8.7 Hz, Ar*H*) 6.87 (2H, d, 8.7 Hz, Ar*H*) 4.52 (1H, d, 10.8 Hz, OC$H_A$CH$_B$PMP) 4.48 (1H, d, 10.8 Hz, OCH$_A$C$H_B$PMP) 3.80 (3H, s, OC$H_3$) 3.39 (1H, t, 5.6 Hz, C*H*OPMB) 2.67 (1H, dqn, 5.6, 2.3 Hz, C*H*($CH_3$)CH(=O)) 1.97-1.91 (1H, m C*H*($CH_3$)$_2$) 1.11 (3H, d, 7.0 Hz, CH(C$H_3$)CH(=O)) 0.99 (3H, d, 6.8 Hz, CH(C$H_3$)$_2$) 0.96 (3H, d, 6.8 Hz, CH(C$H_3$)$_2$) $^{13}$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)**

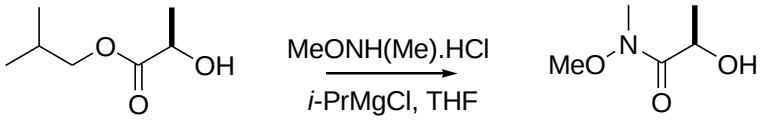



**351** **347**

To a solution of DMSO (0.38 mL; 5.4 mmol) in $CH_2Cl_2$ (25 mL) at -78°C was added oxalyl chloride (1.35 mL of a 2 M solution in $CH_2Cl_2$; 2.7 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **351** (0.41 g; 1.85 mmol) in $CH_2Cl_2$ (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 $NH_4Cl$ (50 mL), then extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) 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, C*H*(=O)) 7.36-7.26 (5H, m, Ar*H*) 4.61 (1H, d, 11.3 Hz, OC$H_A$CH$_B$Ph) 4.56 (1H, d, 11.3 Hz, OCH$_A$C$H_B$Ph) 3.42 (1H, t, 5.6 Hz, C*H*OBn) 2.74-2.69 (1H, m, C*H*($CH_3$)) 1.96 (1H, dsept, 6.8, 1.2 Hz, C*H*($CH_3$)$_2$) 1.13 (3H, d, 7.0 Hz, CH(C$H_3$)) 1.01 (3H, d, 6.8 Hz, CH(C$H_3$)$_2$) 0.98

(3H, d, 6.8 Hz, CH(C*H*$_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 204.75, 138.25, 128.32, 127.60, 127.54, 85.94, 74.13, 48.87, 30.83, 19.46. 17.78, 11.36

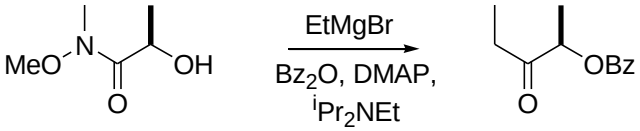
**2-(*R*)-Hydroxy-*N*-methoxy-*N*-methylpropionamide (354)**




**138** **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 $Et_2O$ (60 mL) at -20°C was added $^{i}$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 $NH_4Cl$ (300 mL) was added cautiously. The mixture was extracted with $Et_2O$ (4*100 mL) and $CH_2Cl_2$ (4*100 mL) dried ($Na_2SO_4$) 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. $^1$H NMR (600MHz; $CDCl_3$) δ 4.42 (1H, q, 6.4 Hz, C*H*($CH_3$)) 3.65 (3H, s, OC*H*$_3$) 3.42 (1H, brs, CH(O*H*)) 3.19 (3H, s, NC*H*$_3$) 1.29 (3H, d, 6.4 Hz, CH(C*H*$_3$)). $^{13}$C NMR (150 MHz; $CDCl_3$) δ 175.49, 64.75, 61.15, 32.20, 20.77.

**2-(*R*)-Benzoyloxypentan-3-one (82)**

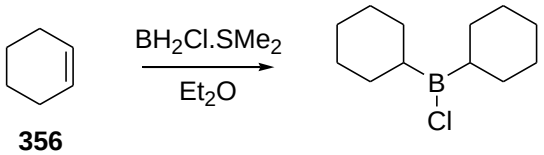



**354** **82**

To a solution of the amide **354** (4.1 g; 31 mmol) in THF (120 mL) at 0°C was added 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 $NH_4Cl$ (180 mL) was added with caution and the mixture was extracted with $Et_2O$ (2*80 mL) and $CH_2Cl_2$ (2*80 mL). The combined organic extracts were dried ($Na_2SO_4$) 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 $^{i}Pr_2NEt$ (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

ethylenediamine (2.3 mL; 34 mmol). $H_2O$ (200 mL) was added and the mixture was extracted with $Et_2O$ (4*80 mL), then the combined organic extracts were dried ($Na_2SO_4$) 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. $R_F$ = 0.40, $^1$H NMR (600MHz; $CDCl_3$) δ 8.08 (2H, d, 6.9, Hz, Ar*H*) 7.59 (1H, t, 6.9 Hz, Ar*H*) 7.46 (2H, t, 6.9Hz, Ar*H*) 5.35 (1H, q, 7.0 Hz, BzOC*H*($CH_3$)) 2.66 (1H, dq, 18.3, 7.2 Hz, C$H_A$$CH_B$$CH_3$) 2.52 (1H, dq, 18.3, 7.2 Hz, $CH_A$C$H_B$$CH_3$) 1.53 (3H, d, 7.0 Hz, BzOCH(C$H_3$)) 1.09 (3H, t, 7.2 Hz, $CH_2$C$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 208.53, 165.88, 133.34, 129.74, 129.47, 128.46, 75.10, 31.43, 16.46, 7.18.

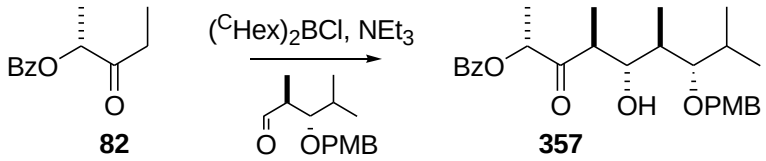
**Dicyclohexylboron chloride (355)**




**356** **355**

To a solution of freshly distilled cyclohexene (**356**) (20 mL; 207 mmol) in $Et_2O$ (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. $^{13}$C NMR (150MHz; $CDCl_3$) δ 36.28, 27.65, 27.14, 26.59.

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

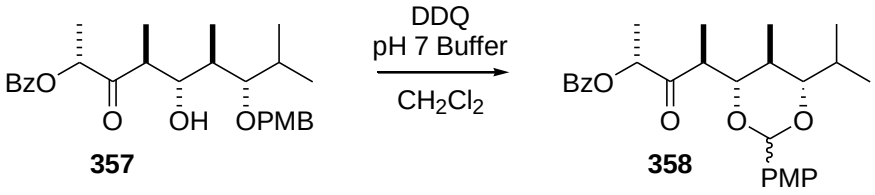



**82** **357**

To a solution of dicyclohexylboron chloride (**355**) (0.5 mL; 2.3 mmol) in $Et_2O$ (5 mL) at -78°C was added $NEt_3$ (380 µL; 2.8 mmol) followed by ketone **82** (100 mg; 0.5 mmol) in $Et_2O$ (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. The

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% $H_2O_2$ solution (1 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between $H_2O$ (30 mL) and extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/hexanes) gave the *anti*-aldol product **357** (101 mg; 55%) as a clear oil. $R_F$ = 0.25, $^1$H NMR (600MHz; $CDCl_3$) δ 8.06 (2H, d, 8.2 Hz, Bz-Ar*H*) 7.56 (1H, t, 7.4 Hz, Bz-Ar*H*) 7.44 (2H, t, 8.0 Hz, Bz-Ar*H*) 7.23 (2H, d, 8.6 Hz, PMB-Ar*H*) 6.83 (2H, d, 8.6 Hz, PMB-Ar*H*) 5.36 (1H, q, 7.0 Hz, BzOC*H*($CH_3$)) 4.53 (1H, d, 11.0 Hz, OC$H_A$$CH_B$PMP) 4.52(1H, d, 11.0 Hz, OC$H_A$C$H_B$PMP) 3.79 (3H, s, OC$H_3$) 3.75 (1H, q, 6.5 Hz, C*H*(OH)) 3.37 (1H, d, 6.7 Hz, CH(O*H*)) 3.31 (1H, dd, 6.2, 4.7 Hz, C*H*OPMB) 3.19 (1H, qn, 7.1 Hz, C*H*($CH_3$)CHOH) 2.05-1.93 (2H, m, C*H*($CH_3$)CHOPMB, C*H*($CH_3$)$_2$) 1.40 (3H, d, 7.0 Hz, BzOCH(C$H_3$)) 1.27 (3H, d, 7.1 Hz, CH(C$H_3$)CHOH) 0.99 (3H, d, 6.9 Hz, CH(C$H_3$)CHOPMB) 0.96 (3H, d, 7.1 Hz, CH(C$H_3$)$_2$) 0.95 (1H, d, 7.1 Hz, CH(C$H_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

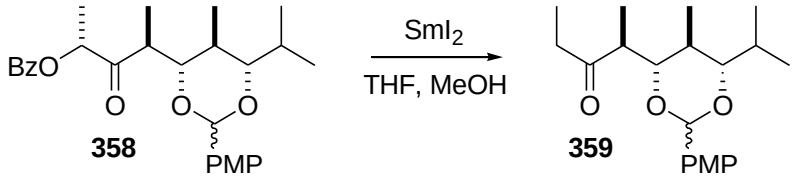
**Benzoic acid 3-[6-isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-1-methyl-2-oxo-butyl ester (358)**




To a solution of aldol product **357** (100 mg; 0.22 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ solution (15 mL). The mixture was extracted with $CH_2Cl_2$ (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the desired PMP-acetal adduct **358** (86 mg; 86%) as a clear oil. $R_F$ = 0.7, $^1$H NMR (600MHz; $CDCl_3$) δ 8.08 (2H, d, 8.2 Hz, Bz-Ar*H*) 7.56 (1H, t, 7.4 Hz, Bz-Ar*H*) 7.43 (2H, t, 8.1 Hz, Bz-Ar*H*) 7.26 (2H, d, 8.8 Hz, PMB-Ar*H*) 6.83 (2H, d, 8.8 Hz, PMB-Ar*H*) 5.56 (1H, q, 6.8 Hz, BzOC*H*($CH_3$)) 5.34 (1H, s, C*H*PMP) 3.79 (3H, s, OC$H_3$) 3.73 (1H, dd, 10.0, 4.1 Hz, C*H*OCHPMP) 3.29 (1H, m, C(=O)C*H*($CH_3$)) 3.25 (1H, dd, 9.8, 2.0 Hz, C*H*OCHPMP) 1.95 (1H, dsept, 6.9, 2.0 Hz, C*H*($CH_3$)$_2$) 1.92-1.85 (1H, m, C*H*($CH_3$)) 1.48 (3H, d, 6.9 Hz, BzOCH(C$H_3$)) 1.32 (3H, d, 7.1 Hz, C(=O)CH(C$H_3$)) 1.02 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 0.90 (3H, d, 7.0 Hz,

CH(C*H*$_3$)$_2$)) 0.78 (3H, d, 6.6 Hz, CH(C*H*$_3$)) $^{13}$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.

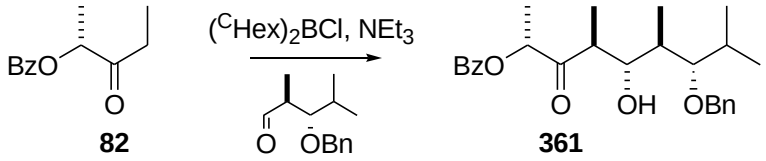
**2-[6-Isopropyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-pentan-3-one (359)**




**358** **359**

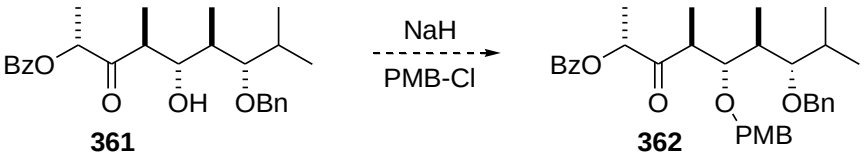
To a solution of PMP acetal adduct **358** (85 mg; 0.19 mmol) in THF (2.5 mL) and MeOH (1.5 mL) at 0°C was added $SmI_2$ (7.4 mL of a 0.1 M solution in THF, 0.74 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0°C with the addition of saturated $K_2CO_3$ (15 mL) and allowed to warm to room temperature. The aqueous layer was extracted with $Et_2O$ (3*20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% $CH_2Cl_2$/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, Ar*H*) 6.88 (2H, d, 8.8 Hz, Ar*H*) 5.44 (1H, s, C*H*PMP) 3.80 (3H, s, OC*H*$_3$) 3.58 (1H, dd, 10.0, 3.3 Hz, C*H*O) 3.27 (1H, dd, 9.8, 2.0 Hz, C*H*O) 2.86 (1H, dq, 7.2, 3.4 Hz, C(=O)C*H*($CH_3$)) 2.61 (1H, dq, 18.4, 7.1 Hz, C*H*$_A$CH$_B$CH$_3$) 2.50 (1H, dq, 18.4, 7.1 Hz, CH$_A$C*H*$_B$CH$_3$) 1.97 (1H, dsept, 6.9, 1.9 Hz, C*H*($CH_3$)$_2$) 1.70-1.65 (1H, m, C*H*($CH_3$)) 1.29 (3H, d, 7.2 Hz, C(=O)CH(C*H*$_3$)) 1.04 (3H, d, 6.9 Hz, CH(C*H*$_3$)$_2$) 1.00 (3H, t, 7.1 Hz, C(=O)CH$_2$C*H*$_3$) 0.88 (3H, d, 6.9 Hz, CH(C*H*$_3$)$_2$) 0.80 (3H, d, CH(C*H*$_3$)) $^{13}$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.

**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 $Et_2O$ (15 mL) at -78°C was added $NEt_3$ (750 µL; 5.38 mmol) followed by ketone **82** (605 mg; 2.93 mmol) in $Et_2O$ (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% $H_2O_2$ solution (10 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between $H_2O$ (80 mL) and extracted with $Et_2O$ (3*50 mL) and $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the anti aldol product **361** (515 mg; 62%) as a clear oil. $R_F$ = 0.20 , $^1$H NMR (600MHz; $CDCl_3$) δ 8.05 (2H, d, 9.5 Hz, Bz-Ar*H*) 7.55 (1H, t, 7.4 Hz, Bz-Ar*H*) 7.43 (2H, t, 7.9 Hz, Bz-Ar*H*) 7.33-7.24 (5H, m, Bn-Ar*H*) 5.32 (1H, q, 7.0 Hz, BzOC*H*($CH_3$)) 4.61 (2H, s, OC$H_2$Ph) 3.78 (1H, q, 6.6 Hz, C*H*(OH)) 3.36 (1H, dd, 6.6, 4.2 Hz, C*H*OBn) 3.31 (1H, d, 6.6 Hz, CH(O*H*)) 3.19 (1H, qn, 7.1 Hz, C(=O)C*H*($CH_3$)) 2.06-1.94 (2H, m, C*H*($CH_3$)$_2$, C*H*($CH_3$)CHOBn) 1.36 (3H, d, 7.0 Hz, BZOCH(C$H_3$)) 1.28 (3H, d, 7.1 Hz, C(=O)CH(C$H_3$)) 1.01 (3H, d, 6.9 Hz, CH(C$H_3$)CHOBn) 0.99-0.96 (6H, m, 2* CH(C$H_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

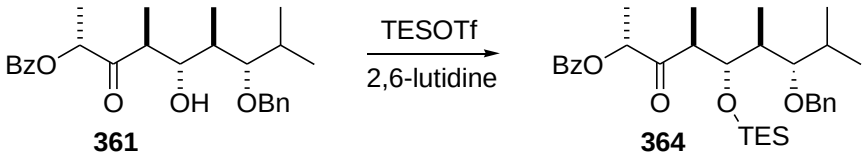
**Benzoic acid 6-benzyloxy-4-(4-methoxy-benzyloxy)-1,3,5,7-tetramethyl-2-oxo-octyl ester (362)**




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 $NH_4Cl$ solution (5 mL), extracted with ether (3*5 mL), dried ($Na_2SO_4$) and concentrated *in*

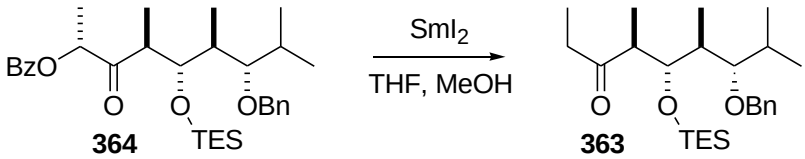
*vacuo*. Analysis of the crude $^{1}$H NMR spectrum indicated the alcohol **361** had decomposed to the enone through β-elimination under the above reaction conditions.

**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 $CH_2Cl_2$ (10 mL) at -78°C was added 2,6-lutidine (265 µL; 2.28 mmol) and TESOTf (420 µL; 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 $CH_2Cl_2$ (3*40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification of column chromatrography (50% $CH_2Cl_2$/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-Ar*H*) 7.55 (1H, t, 7.2 Hz, Bz-Ar*H*) 7.42 (2H, t, 7.8 Hz, Bz-Ar*H*) 7.35 (2H, d, 7.8 Hz Bn-Ar*H*) 7.30 (2H, t, 7.2 Hz, Bn-Ar*H*) 7.23 (1H, t, 7.8 Hz, Bn-Ar*H*) 5.27 (1H, q, 7.2 Hz, BzOC*H*($CH_3$)) 4.79 (1H, d, 12.0 Hz, OC$H_A$$CH_B$Ph) 4.65 (1H, d, 12.0 Hz, OC$H_A$C$H_B$Ph) 4.28 (1H, dd, 9.6, 1.2 Hz, C*H*OTES) 3.35 (1H, dd, 9.6, 1.8 Hz, C*H*OBn) 3.23 (1H, dq, 9.6, 7.2 Hz, C(=O)C*H*($CH_3$)) 2.02-1.98 (1H, m, C*H*($CH_3$)CHOBn) 1.92-1.88 (1H, m, C*H*($CH_3$)$_2$) 1.34 (3H, d, 7.2 Hz, BzOCH(C$H_3$)) 1.20 (3H, d, 7.2 Hz, C(=O)CH(C$H_3$)) 1.06 (3H, d, 7.2 Hz, CH(C$H_3$)$_2$) 0.97 (3H, d, 7.2 Hz, CH(C$H_3$)$_2$)) 0.96-0.93 (12H, m, CH(C$H_3$)CHOBn, 3*OSiCH$_2$C$H_3$) 0.60 (6H, q, 8.4 Hz, 3*OSiC$H_2$CH$_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.

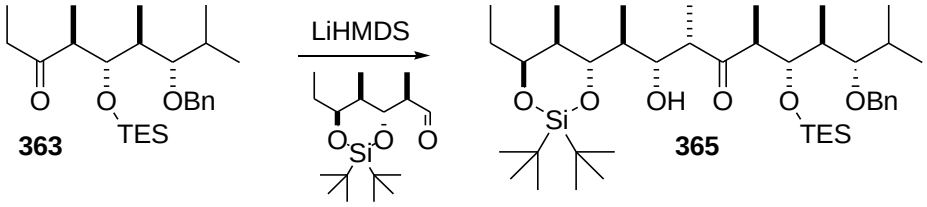
**7-Benzyloxy-4,6,8-trimethyl-5-triethylsilanyloxy-nonan-3-one (363)**




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 $SmI_2$ (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 $K_2CO_3$ (80 mL) and allowed to warm to room temperature. The aqueous layer was extracted with $Et_2O$ (3*70 mL), dried ($Na_2SO_4$) and concentrated in vacuo. Purification by column chromatography (50% $CH_2Cl_2$/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, Ar*H*) 4.74 (1H, d, 11.6 Hz, OC$H_A$CH$_B$Ph) 4.62 (1H, d, 11.6 Hz, OCH$_A$C$H_B$Ph) 4.09 (1H, dd, 8.3, 1.9 Hz, C*H*OTES) 3.33 (1H, dd, 9.7, 2.2 Hz, C*H*OBn) 2.96 (1H, qn, 7.1 Hz, C(=O)C*H*(CH$_3$)) 2.36 (1H, dq, 18.5, 7.3 Hz, C$H_A$CH$_B$CH$_3$) 2.27 (1H, dq, 18.5, 7.3 Hz, CH$_A$C$H_B$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(C$H_3$)$_2$) 0.96-0.89 (21H, m, CH$_2$C$H_3$, C(=O)CH(C$H_3$), CH(C$H_3$)CHOBn, CH(C$H_3$)$_2$, 3*OSiCH$_2$C$H_3$) 0.56 (6H, q, 8.0 Hz, 3*OSiC$H_2$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.

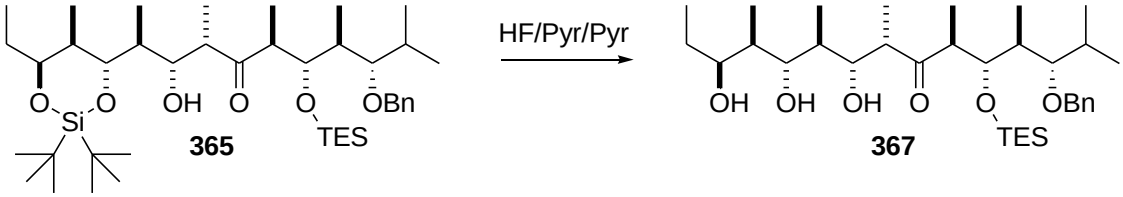
**9-Benzyloxy-2-(2,2-di-tert-butyl-6-ethyl-5-methyl-[1,3,2]dioxasilinan-4-yl)-3-hydroxy-4,6,8,10-tetramethyl-7-triethylsilanyloxy-undecan-5-one (365)**




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 $Et_2O$ (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 $Et_2O$ (3*15 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% $Et_2O$/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, Ar*H*) 4.82 (1H, d, 12 Hz, OC$H_A$CH$_B$Ph) 4.63 (1H, d, 12 Hz, OCH$_A$C$H_B$Ph) 4.14 (1H, dd, 9.2, 1.3 Hz, C*H*OTES) 4.01 (1H, dd, 9.3, 1.3 Hz, C*H*(OH)) 3.89-3.86 (1H, m, CH$_3$CH$_2$CH(OSi)) 3.77 (1H, dd, 7.9, 4.0 Hz, CH(CH$_3$)C*H*(OSi)CH(CH$_3$)) 3.55 (1H, brs, CH(O*H*)) 3.33 (1H, dd, 10.0, 2.0 Hz, C*H*OBn) 3.16 (1H, dq, 9.0, 7.1 Hz, C(=O)C*H*(CH$_3$)CHOTES) 2.48 (1H, dq, 7.0, 1.3 Hz, CH(OH)C*H*(CH$_3$)C(=O)) 2.37-2.31 (1H, m,

CH(OSi)C*H*($CH_3$)CH(OSi)) 2.00-1.94 (1H, m, C*H*($CH_3$)CH(OBn)) 1.90-1.85 (1H, m, C*H*($CH_3$)$_2$) 1.73-1.68 (1H, m, C*H*($CH_3$)CH(OH)) 1.54-1.47 (1H, m, C$H_A$C$H_B$$CH_3$) 1.47-1.38 (1H, m, $CH_A$C$H_B$$CH_3$) 1.04 (3H, d, 7.0 Hz, CH(C$H_3$)CH(OBn)) 1.02-0.99 (21H, m, 2* SiC(C$H_3$)$_3$, $CH_2$C$H_3$) 0.95-0.85 (24H, m, 3*OSi$CH_2$C$H_3$, 2*C(C$H_3$)$_2$, C(=O)CH(C$H_3$), CH(OSi)CH(C$H_3$)CH(OSi), CH(OH)CH(C$H_3$)C(=O)) 0.70 (3H, d, 6.9 Hz, CH(C$H_3$)CH(OH)) 0.57 (6H, q, 7.9 Hz, 3*OSIC$H_2$$CH_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

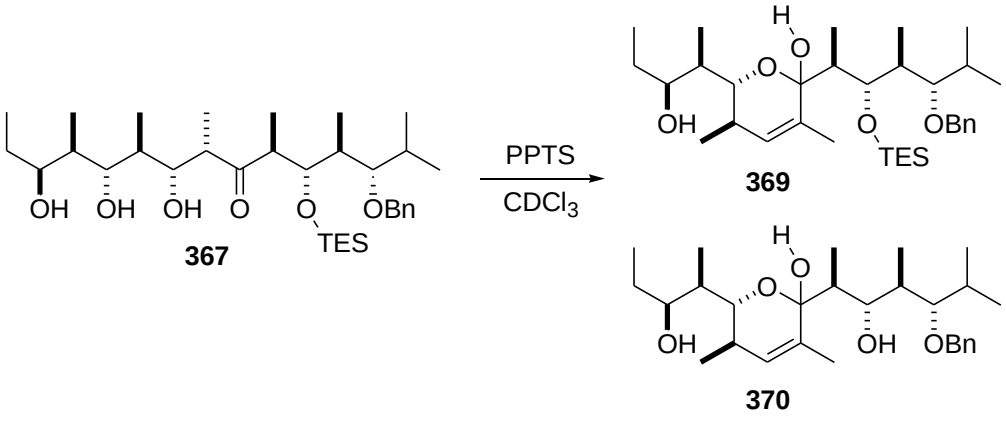
**3-Benzyloxy-9,11,13-trihydroxy-2,4,6,8,10,12-hexamethyl-5-triethylsilanyloxy-pentadecan-7-one (367)**




To a solution of aldol product **365** (20 mg; 0.03 mmol) in THF (1.5 mL) and $H_2O$ (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 $Et_2O$ (3 mL) and quenched with $NaHCO_3$ (2 mL) followed by $CuSO_4$ (2 mL). The aqueous layers were re-extracted with $Et_2O$ (2*5 mL) dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% $Et_2O$/hexanes) yielded triol **367** (13mg; 90%) as a clear oil. $R_F$ = 0.15, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.25 (5H, m, Ar*H*) 5.46 (1H, brs, CH(O*H*)) 4.75 (1H, d, 12 Hz, OC$H_A$C$H_B$Ph) 4.68 (1H, d, 12 Hz, OC$H_A$C$H_B$Ph) 4.66 (1H, brs, CH(O*H*)) 4.16 (1H, d, 8.6 Hz, C*H*OTES) 4.05 (1H, brs, CH(O*H*)) 3.86 (1H, t, 7.3 Hz, $CH_3CH_2$C*H*(OH)) 3.80 (1H, dd, 9.5, 1.3 Hz, C*H*(OH)CH($CH_3$)C(=O)) 3.57 (1H, dd, 9.1, 1.9 Hz, $CH_3CH_2$CH(OH)CH($CH_3$)C*H*(OH)) 3.33 (1H, dd, 10.1, 2 Hz, C*H*OBn) 3.16 (1H, dq, 9.3, 7.2 Hz, C(=O)C*H*($CH_3$)CHOTES) 2.52 (1H, q, 6.0, 1.2 Hz, CH(OH)C*H*($CH_3$)C(=O)) 1.97-1.94 (1H, m, C*H*($CH_3$)CH(OBn)) 1.93-1.79 (2H, m, C*H*($CH_3$)$_2$, C*H*($CH_3$)CH(OH)CH($CH_3$)C(=O)) 1.70 (1H, q, 7.1, 7.1 Hz, $CH_3CH_2$CH(OH)C*H*($CH_3$)) 1.61-1.56 (1H, m, C$H_A$C$H_B$$CH_3$) 1.39-1.34 (1H, m, $CH_A$C$H_B$$CH_3$) 1.07 (3H, d, 7.1 Hz $CH_3CH_2$CH(OH)CH(C$H_3$)) 1.06 (3H, d, 6.9 Hz, CH(C$H_3$)CH(OH)CH($CH_3$)C(=O)), 1.00 (3H, d, 7.1 Hz, CH(C$H_3$)CH(OBn)) 0.96-0.91 (21H, m, 3* OSi$CH_2$C$H_3$, 2* CH(C$H_3$)$_2$, CH(OH)CH(C$H_3$)C(=O), C(=O)CH(C$H_3$)CHOTES) 0.60-0.55 (9H, m, 3*OSiC$H_2$$CH_3$, $CH_3CH_2$CH(OH)CH(C$H_3$)) $^{13}$C NMR (150MHz;

$CDCl_3$) 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.

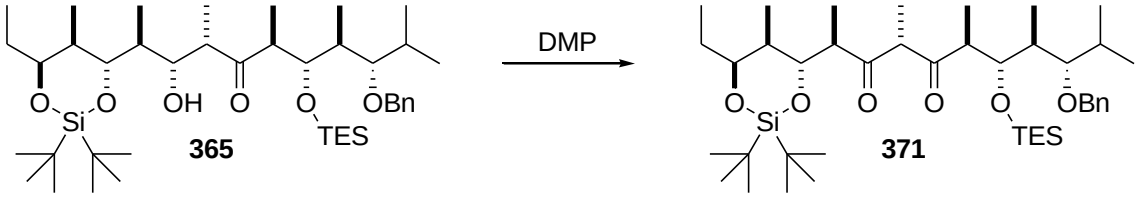
**2-(4-Benzyloxy-1,3,5-trimethyl-2-triethylsilanyloxy-hexyl)-6-(2-hydroxy-1-methyl-butyl)-3,5-dimethyl-5,6-dihydro-2H-pyran-2-ol (369), 2-(4-Benzyloxy-2-hydroxy-1,3,5-trimethyl-hexyl)-6-(2-hydroxy-1-methyl-butyl)-3,5-dimethyl-5,6-dihydro-2H-pyran-2-ol (370)**




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**. Hemiacetal **369**, $R_F$ = 0.40, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37 (2H, d, 7.3 Hz, Ar*H*) 7.30 (2H, t, 7.3 Hz, Ar*H*) 7.22 (1H, t, 7.3 Hz, Ar*H*) 5.74 (1H, d, 5.2 Hz, C*H*=$CCH_3$) 4.72 (1H, d, 12.0 Hz, $OCH_ACH_BPh$) 4.42 (1H, t, 3.3 Hz, C*H*-O-COH) 4.37 (1H, d, 12.0 Hz, $OCH_ACH_BPh$) 4.05 (1H, t, 6.7 Hz, C*H*OTES) 3.86 (1H, m, C*H*OH) 3.63 (1H, dd, 4.1, 2.1 Hz, C*H*OBn) 3.53 (1H, s, CHO*H*) 2.71 (1H, m, C*H*($CH_3$)CHOBn) 2.19 (1H, dq, 6.9, 2.2 Hz, C*H*($CH_3$)$_2$) 2.09 (1H, dq, 7.3, 3.3 Hz, C*H*($CH_3$)CH-O-) 1.92 (1H, m, C*H*($CH_3$)CH=$CCH_3$) 1.64-148 (2H, m, $CH_ACH_BCH_3$, C*H*($CH_3$)CHOTES) 1.53 (3H, s, CH=CC$H_3$) 1.38-1.30 (1H, m, $CH_ACH_BCH_3$) 1.09 (3H, d, 6.9 Hz, CH(C$H_3$)CHOBn) 1.07 (3H, d, 6.9 Hz, CH(C$H_3$)CH=$CCH_3$) 1.05 (3H, d, 7.3 Hz, CH(C$H_3$)CHOTES) 0.98-0.95 (15H, m, 3*OSi$CH_2$C$H_3$, CH(C$H_3$)$CH_3$, CH(C$H_3$)CH-O-) 0.91 (3H, d, 6.9 Hz, CH(C$H_3$)$CH_3$) 0.86 (3H, t, 7.2 Hz, $CH_2$C$H_3$) 0.62 (6H, dq, 7.7, 3.3 Hz, 3*OSiC$H_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. Hemiacetal **370**, $R_F$ = 0.20, $^1$H NMR (600MHz; $CDCl_3$) δ 7.33 (2H, d, 7.3 Hz, Ar*H*) 7.27 (2H, t, 7.3 Hz, Ar*H*) 7.18 (1H, t, 7.3 Hz, Ar*H*) 5.61 (1H, d, 5.1 Hz, C*H*=$CCH_3$) 5.00 (1H, s, C-O*H*) 4.90 (1H, d, 12.1 Hz,

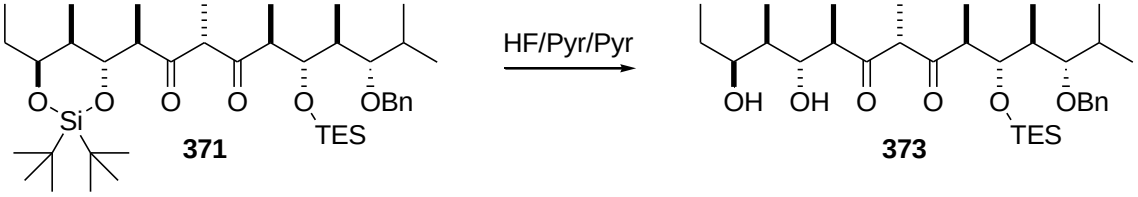
OC*H*$_A$CH$_B$Ph) 4.63 (1H, d, 12.1 Hz, OCH$_A$C*H*$_B$Ph) 4.05 (1H, d, 8.8 Hz, C*H*OH) 3.86 (1H, td, 8.3, 5.2, 2.9 Hz, CH$_3$CH$_2$C*H*OH) 3.61 (1H, s, CH(CH$_3$)C*H*-O-COH) 3.54 (1H, dd, 9.5, 2.1 Hz, C*H*OBn) 2.19 (1H, dq, 8.8, 7.0 Hz, C*H*(CH$_3$)CHOH) 2.06 (1H, m, C*H*(CH$_3$)CHOBn) 1.91 (1H, m, C*H*(CH$_3$)$_2$) 1.57 (3H, brs, CH=CC*H*$_3$) 1.54 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.35-1.26 (3H, m, CH$_A$C*H*$_B$CH$_3$, C*H*(CH$_3$)CH-O-COH, C*H*(CH$_3$)CH=C(CH$_3$)) 1.13 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH-O-COH) 1.05-1.02 (6H, m, CH(C*H*$_3$)CH$_3$, CH(C*H*$_3$)CHOBn) 0.96 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH$_3$) 0.89-0.82 (6H, m, CH$_2$C*H*$_3$, CH(C*H*$_3$)CH=C(CH$_3$)) 0.77 (3H, d, 7.0 Hz, CH(C*H*$_3$)CHOH) $^{13}$C NMR (150MHz; CDCl$_3$) δ 140.19, 130.27, 130.07, 127.91, 128.53, 126.46, 101.53, 84.00, 79.63, 77.36, 73.42, 71.68, 40.68, 36.44, 34.42, 31.58, 30.63, 25.46, 22.62, 20.35, 17.76, 17.33, 15.39, 14.12, 13.13, 9.84.

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



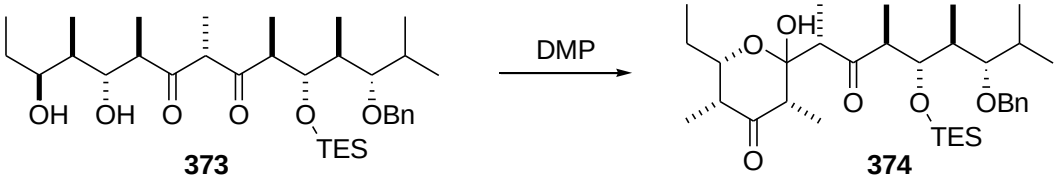

To a solution of aldol product **365** (40 mg; 0.05 mmol) in CH$_2$Cl$_2$ (1 mL) at room temperature was added NaHCO$_3$ (45 mg) and DMP (50 mg; 0.12 mmol). The reaction mixture was stirred for 2 hours at ambient temperature. The mixture was loaded directly onto silica and purified by column chromatography (50% CH$_2$Cl$_2$/hexanes) to give diketone **371** (33 mg; 88%) as a clear oil. $R_F$ = 0.25, $^1$H NMR (600MHz; CDCl$_3$) δ 7.36-7.22 (5H, m, Ar*H*) 4.78 (1H, d, 11.8 Hz, OC*H*$_A$CH$_B$Ph) 4.61 (1H, d, 11.8 Hz, OCH$_A$C*H*$_B$Ph) 4.16 (1H, dd, 9.4, 1.1 Hz, C*H*OTES) 3.93-3.88 (3H, m, C(=O)C*H*(CH$_3$)C(=O), CH$_3$CH$_2$C*H*OSi, CH(CH$_3$)C*H*(OSi)CH(CH$_3$)) 3.31 (1H, dd, 10.1, 2.0 Hz, C*H*OBn) 3.03 (1H, dq, 9.4, 7.0 Hz, C(=O)C*H*(CH$_3$)CHOTES) 2.72 (1H, qn, 7.3, 6.8 Hz, C*H*(CH$_3$)C(=O)CH(CH$_3$)C(=O)) 1.98-1.93 (2H, m, C*H*(CH$_3$)CHOBn, CH(OSi)C*H*(CH$_3$)CH(OSi)) 1.91-1.86 (1H, dqn, 6.8, 1.9 Hz, C*H*(CH$_3$)$_2$) 1.54-1.46 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.41-1.34 (1H, m, CH$_A$C*H*$_B$CH$_3$) 1.09-1.07 (6H, m, C(=O)CH(C*H*$_3$)CHOTES, CH(C*H*$_3$)C(=O)CH(CH$_3$)C(=O)) 1.04 (3H, d, 7.0 Hz, C(=O)CH(C*H*$_3$)C(=O), 1.01-0.89 (39H, m, 6*SiC(C*H*$_3$)$_3$, 3*OSiCH$_2$C*H*$_3$, 2*CH(C*H*$_3$)$_2$, CH$_2$C*H*$_3$, CH(C*H*$_3$)CHOBn ) 0.83 (3H, d, 7.2 Hz, CH(OSi)CH(C*H*$_3$)CH(OSi)) 0.55 (6H, q 7.9 Hz, 3*OSiC*H*$_2$CH$_3$) $^{13}$C NMR (150MHz; CDCl$_3$) 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-Benzyloxy-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 $H_2O$ (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 $Et_2O$ (5 mL) and quenched with $NaHCO_3$ (4 mL) followed by $CuSO_4$ (4 mL). The aqueous layers were re-extracted with $Et_2O$ (2*10 mL) dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/hexanes) yielded diol **373** (16 mg; 85%) as a clear oil. **Crude Compound**: $^1$H NMR (600MHz; $CDCl_3$) δ 7.35-7.24 (5H, m, Ar*H*) 4.72 (1H, d, 11.6 Hz, OC*H*$_A$CH$_B$Ph) 4.63 (1H, d, 11.6 Hz, OCH$_A$C*H*$_B$Ph) 4.12 (1H, dd, 9.4, 1.0 Hz, C*H*OTES) 3.88 (1H, q, 7.1 Hz, C(=O)C*H*($CH_3$)C(=O)) 3.83 (1H, t, 6.7 Hz, $CH_3CH_2$C*H*(OH)) 3.69 (1H, brs, CH(O*H*)) 3.44 (1H, brs, CH(O*H*)) 3.28 (1H, dd, 8.0, 2.0 Hz, C*H*OBn) 2.99-2.94 (3H, m, C*H*($CH_3$)C(=O)CH($CH_3$)C(=O), C*H*(OH)CH($CH_3$)C(=O), C(=O)C*H*($CH_3$)CHOTES) 1.95-1.87 (2H, m, C*H*($CH_3$)$_2$, C*H*($CH_3$)CHOBn) 1.65-1.60 (1H, m, CH(OH)C*H*($CH_3$)CH(OH)) 1.59-1.53 (1H, m, C*H*$_A$CH$_B$$CH_3$) 1.40-1.35 (1H, m, CH$_A$C*H*$_B$$CH_3$) 1.15 (3H, d, 7.1 Hz, C(=O)CH(C*H*$_3$)C(=O)) 1.07-1.03 (9H, m, CH(C*H*$_3$)$_2$, C(=O)CH(C*H*$_3$)CHOTES, CH(C*H*$_3$)C(=O)CH($CH_3$)C(=O), 0.98 (3H, d, 7.0 Hz, CH(C*H*$_3$)$_2$) 0.94-0.88 (18H, m, 3*OSiCH$_2$C*H*$_3$, CH$_2$C*H*$_3$, CH(C*H*$_3$)CHOBn, CH(OH)CH(C*H*$_3$)CH(OH)) 0.54 (6H, q, 8.0 Hz, 3*OSiC*H*$_2$$CH_3$) **Purified Compound**: $R_F$ = 0.3, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.24 (5H, m, Ar*H*) 4.74 (1H, d, 11.8 Hz, OC*H*$_A$CH$_B$Ph) 4.66 (1H, d, 11.8 Hz, OCH$_A$C*H*$_B$Ph) 4.20 (1H, d, 9.0 Hz, C*H*OTES) 4.13 (1H, d, 10.2 Hz, $CH_3CH_2$C*H*(OH)) 3.73-3.69 (1H, m, C*H*(OH)CH($CH_3$)C(=O)) 3.53 (1H, d, 7.3 Hz, CH(O*H*)) 3.33 (1H, dd, 9.6, 1.7 Hz C*H*OBn) 3.18 (1H, brs, CH(O*H*)) 3.09 (1H, qn, 8.9, 7.2 Hz, C(=O)C*H*($CH_3$)CHOTES) 2.99-2.92 (1H, m, C*H*($CH_3$)C(=O)CH($CH_3$)C(=O)) 2.61-2.51 (3H, m, C*H*$_A$CH$_B$$CH_3$, CH$_A$C*H*$_B$$CH_3$, C(=O)C*H*($CH_3$)C(=O)) 2.00-1.86 (2H, m, C*H*($CH_3$)$_2$, C*H*($CH_3$)CHOBn) 1.69-1.67 (1H, m, CH(OH)C*H*($CH_3$)CH(OH)) 1.16-0.88 (30H, m, 3*OSiCH$_2$C*H*$_3$, 2*CH(C*H*$_3$)$_2$, CH$_2$C*H*$_3$, CH(C*H*$_3$)CHOBn, CH(OH)CH(C*H*$_3$)CH(OH), C(=O)CH(C*H*$_3$)CHOTES, CH(C*H*$_3$)C(=O)CH($CH_3$)C(=O)) 0.72 (3H, d, 7.3 Hz, C(=O)CH(C*H*$_3$)C(=O)) 0.58 (6H, q, 7.9 Hz, 3*OSiC*H*$_2$$CH_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

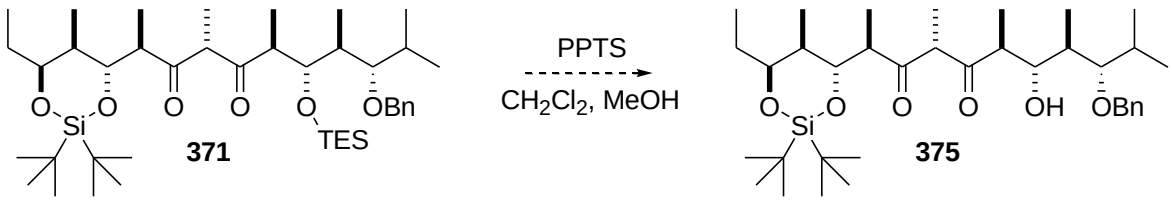
**2-(6-Benzyloxy-1,3,5,7-tetramethyl-2-oxo-4-triethylsilanyloxy-octyl)-6-ethyl-2-hydroxy-3,5-dimethyl-tetrahydro-pyran-4-one (374)**




**373** **374**

To a solution of diol **373** (7 mg; 0.015 mmol) in $CH_2Cl_2$ (1 mL) at room temperature was added $NaHCO_3$ (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 ($CH_2Cl_2$) to give hemiacetal **374** (5.9 mg; 84%) as a clear oil. $R_F$ = 0.7, $^1$H NMR (600MHz; $CDCl_3$) δ 7.36-7.24 (5H, m, Ar*H*) 4.76 (1H, d, 11.9 Hz, OC*H*$_A$CH$_B$Ph) 4.67 (1H, d, 11.9 Hz, OCH$_A$C*H*$_B$Ph) 4.34 (1H, dd, 10.4, 2.6 Hz, $CH_3CH_2CH$-O-) 4.13 (1H, dd, 9.0, 1.4 Hz, C*H*OTES) 3.35 (1H, dd, 9.5, 2.1 Hz, C*H*OBn) 3.01 (1H, dq, 9.0, 7.2 Hz, C(=O)C*H*(CH$_3$)CHOTES) 2.65 (1H, q, 6.7 Hz, C(=O)C*H*CH$_3$C-OH) 2.50 (1H, m, HO-CC*H*(CH$_3$)C(=O)) 2.37 (1H, dq, 7.0, 2.6 Hz, C(=O)C*H*(CH$_3$)C-O-) 2.27 (1H, d, 1.4 Hz, C-O*H*) 1.99 (1H, m, C*H*(CH$_3$)CHOBn) 1.89 (1H, m, C*H*(CH$_3$)$_2$) 1.71 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.58 (1H, m, CH$_A$C*H*$_B$CH$_3$) 1.05 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH$_3$) 1.02 (3H, d, 6.7 Hz, C(=O)CHC*H*$_3$C-OH) 1.01 (3H, d, 7.0 Hz, C(=O)CH(C*H*$_3$)C-O-) 0.95-0.92 (15H, m, 3*OSiCH$_2$C*H*$_3$, CH(C*H*$_3$)CH$_3$, CH(C*H*$_3$)CHOBn) 0.98 (3H, d, 7.2 Hz, C(=O)CH(C*H*$_3$)CHOTES) 0.88 (3H, t, 7.4 Hz, CH$_2$C*H*$_3$) 0.67 (3H, d, 7.0 Hz, HO-CCH(C*H*$_3$)C(=O)) 0.60 (6H, q, 7.9 Hz, 3*OSiC*H*$_2$CH$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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-Benzyloxy-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)**

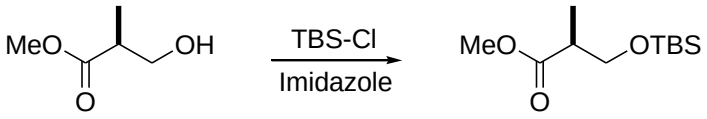



**371** **375**

To a solution of diketone **371** (20 mg; 0.03 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) 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, Ar*H*) 4.59 (1H, d, 11.3 Hz, OC$H_A$CH$_B$Ph) 4.53 (1H, d, 11.3 Hz, OCH$_A$C$H_B$Ph) 4.08 (1H, dd, 11.9, 2.2 Hz, C*H*(OH)) 4.02-3.97 (3H, m, C(=O)C*H*($CH_3$)C(=O), 2*C*H*(OSi)) 3.42 (1H, dd, 9.0, 2.3 Hz, C*H*OBn) 2.99 (1H, qd, 8.1, 6.8 Hz, C*H*($CH_3$)C(=O)CH($CH_3$)C(=O)) 2.60-2.54 (1H, m, C(=O)C*H*($CH_3$)CHOH) 2.25 (1H, qd, 7.1, 2.1 Hz, C*H*($CH_3$)$_2$) 1.99-1.95 (1H, m, C*H*($CH_3$)CHOBn) 1.92-1.87 (1H, m, CH(OSi)C*H*($CH_3$)CH(OSi)) 1.60-1.53 (1H, m, C$H_A$CH$_B$CH$_3$) 1.39-1.34 (1H, m, CH$_A$C$H_B$CH$_3$) 1.16-0.92 (42H, m, 2*SiC(C$H_3$)$_3$, 2*CH(C$H_3$)$_2$, $CH_2CH_3$, CH(OSi)CH(C$H_3$)CH(OSi), CH(C$H_3$)C(=O)CH($CH_3$)C(=O), C(=O)CH(C$H_3$)C(=O), C(=O)CH(C$H_3$)CHOH, CH(C$H_3$)CHOBn)

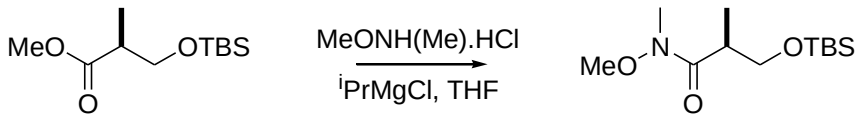
**3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propionic acid methyl ester (379)**




**337** **379**

To a solution of ester **337** (3 g; 25.4 mmol) in $CH_2Cl_2$ (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 ($CH_2Cl_2$) gave TBS-protected roche ester **379** (5.5 g; 93%) as a clear oil. $R_F$ = 0.73, $[\alpha]^{20}_D$ = +18.9 (*c* 1.0, $CHCl_3$), $^1$H NMR (600MHz; $CDCl_3$) δ 3.76 (1H, dd, 9.8, 7.0 Hz, C$H_A$CH$_B$OTBS) 3.67 (3H, s, OC$H_3$) 3.64 (1H, dd, 9.8, 7.0 Hz, CH$_A$C$H_B$OTBS) 2.64 (1H, sex, 6.8 Hz, C(=O)C*H*($CH_3$)) 1.13 (3H, d, 6.8 Hz, CH(C$H_3$)) 0.86 (9H, s, SiC(C$H_3$)$_3$) 0.03 (3H, s, SiC$H_3$) 0.02 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 175.48, 65.21, 51.50, 42.49, 25.74, 18.18, 13.42, -5.53*2.

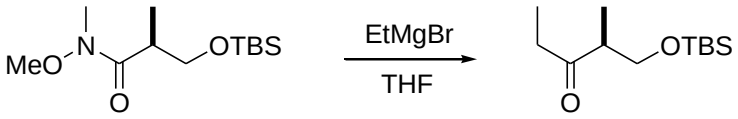
**3-(tert-Butyl-dimethyl-silanyloxy)-*N*-methoxy-*N*-methyl-propionamide (380)**




**379** **380**

To a solution of TBS-protected roche ester **379** (1.0 g; 4.24 mmol) in THF (12 mL) and $Et_2O$ (12 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 g; 10.6 mmol). The mixture was cooled to -20°C and $^{i}$PrMgCl (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 $NH_4Cl$ (80 mL) was added cautiously. The mixture was extracted with $Et_2O$ (3*50 mL) and $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give Weinreb amide **380** (1.10 g; 98%) as a clear oil. $^1$H NMR (600MHz; $CDCl_3$) δ 3.82 (1H, dd, 9.4, 8.3 Hz, C$H_A$CH$_B$OTBS) 3.70 (1H, s, NOC$H_3$) 3.51 (1H, dd, 9.5, 6.1 Hz, CH$_A$C$H_B$OTBS) 3.22-3.16 (4H, m, NC$H_3$, C$H$(CH$_3$)CH$_2$OTBS) 1.06 (3H, d, 7.0 Hz, CH(C$H_3$)CH$_2$OTBS) 0.86 (9H, s, SiC(C$H_3$)$_3$) 0.03 (3H, s, SiC$H_3$) 0.02 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 175.90, 65.49, 61.25, 37.79, 31.72, 25.64, 18.04, 13.54, -5.69, -5.70.

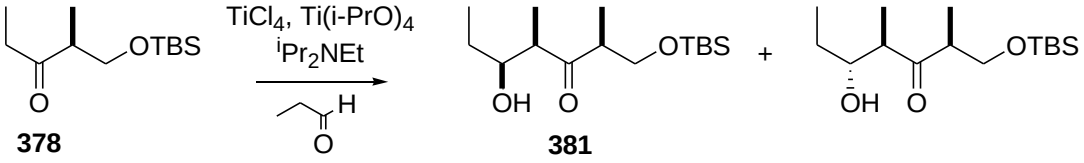
**1-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-pentan-3-one (378)**




**380** **378**

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 $NH_4Cl$ (50 mL) was carefully added. The mixture was extracted with $Et_2O$ (3*50 mL) and $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the ketone **378** (720 mg; 82%) as a clear oil. $R_F$ = 0.65, $[\alpha]^{20}_D$ = +18.9 (*c* 1.0, $CHCl_3$), $^1$H NMR (600MHz; $CDCl_3$) δ 3.71 (1H, dd, 9.8, 5.5 Hz, C$H_A$CH$_B$OTBS) 3.59 (1H, dd, 9.8, 5.5 Hz, CH$_A$C$H_B$OTBS) 2.77 (1H, m, C(=O)C$H$(CH$_3$)) 2.56-2.45 (2H, m, C(=O)C$H_A$H$_B$CH$_3$, C(=O)CH$_A$C$H_B$CH$_3$) 1.04 (3H, t, 7.2 Hz, C(=O)C$H_2$CH$_3$) 1.01 (3H, d, 7.0 Hz, C(=O)CH(C$H_3$)) 0.86 (9H, s, SiC(C$H_3$)$_3$) 0.02 (3H, s, SiC$H_3$) 0.01 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 214.49, 65.71, 48.26, 35.97, 25.77, 18.16, 13.07, 7.44, -5.59, -5.60.

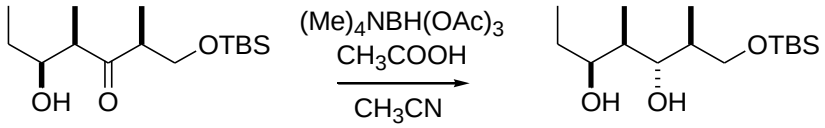
**1-(tert-Butyl-dimethyl-silanyloxy)-5-hydroxy-2,4-dimethyl-heptan-3-one (381)**




**378** **381**

To a solution of TBS-protected ketone **378** (500 mg; 2.14 mmol) in $CH_2Cl_2$ (15 mL) was added a mixture of $TiCl_4$ (2 mL; 1 M of a solution in $CH_2Cl_2$; 2 mmol) and $Ti(^iPrO)_4$ (0.2 mL; 0.65 mmol) at -78°C *via* cannula. The mixture was stirred for 20 minutes then $^iPr_2NEt$ (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 $NH_4Cl$ (50 mL), extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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; $CDCl_3$) δ 3.93-3.89 (1H, m, C*H*(OH)) 3.75 (1H, t, 9.2 Hz, C$H_A$CH$_B$OTBS) 3.58 (1H, dd, 9.5, 4.8 Hz, CH$_A$C$H_B$OTBS) 3.08-3.02 (1H, m, C*H*(CH$_3$)CH$_2$OTBS) 2.99 (1H, d, 3.2 Hz, CH(O*H*)) 2.74 (1H, dq, 7.2, 2.6 Hz, C(=O)C*H*(CH$_3$)CH(OH)) 1.56-1.49 (1H, m, C$H_A$CH$_B$CH$_3$) 1.40-1.33 (1H, m, CH$_A$C$H_B$CH$_3$) 1.08 (3H, d, 7.2 Hz, , C(=O)CH(C$H_3$)CH(OH)) 0.97 (3H, d, 6.9 Hz, CH(C$H_3$)CH$_2$OTBS) 0.94 (3H, t, 7.4 Hz, CH$_2$C$H_3$) 0.86 (9H, s, SiC(CH$_3$)$_3$) 0.04 (3H, s, SiCH$_3$) 0.02 (3H, s, SiCH$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 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** $R_F$ = 0.30, $^1$H NMR (600MHz; $CDCl_3$) δ 3.81-3.78 (2H, m, C*H*(OH), C$H_A$CH$_B$OTBS) 3.55 (1H, dd, 9.6, 5.0 Hz, CH$_A$C$H_B$OTBS) 3.04-2.98 (1H, m, C*H*(CH$_3$)CH$_2$OTBS) 2.95 (1H, d, 2.6 Hz, CH(O*H*)) 2.68 (1H, dq, 7.2, 2.8 Hz, , C(=O)C*H*(CH$_3$)CH(OH)) 1.57-1.50 (1H, m, C$H_A$CH$_B$CH$_3$) 1.41-1.34 (1H, m, CH$_A$C$H_B$CH$_3$) 1.11 (3H, d, 7.2 Hz, C(=O)CH(C$H_3$)CH(OH)) 1.00 (3H, d, 7.0 Hz, CH(C$H_3$)CH$_2$OTBS) 0.95 (3H, t, 7.5 Hz, CH$_2$C$H_3$) 0.86 (9H, s, SiC(C$H_3$)$_3$) 0.04 (3H, s, SiC$H_3$) 0.02 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 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.

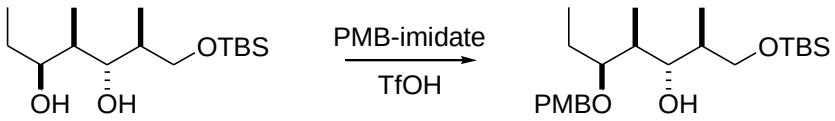
**1-(tert-Butyl-dimethyl-silanyloxy)-2,4-dimethyl-heptane-3,5-diol (382)**




**381** **382**

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 them temperature then placed in the freezer for a further 48 hours. The reaction was quenched at 0°C with careful addition of $NaHCO_3$ (50 mL), warmed to room temperature and extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% EtOAc/hexanes) gave the diol **382** (2.1 g; 83%) as a clear oil. $R_F$ = 0.45, $^1$H NMR (600MHz; $CDCl_3$) δ 4.90 (1H, brs, CH(O*H*)) 4.02 (1H, brs, CH(O*H*)) 3.87 (1H, t, 6.7 Hz, C*H*(OH)$CH_2CH_3$) 3.83 (1H, dd, 10.0, 3.8 Hz, C$H_A$C$H_B$OTBS) 3.62-3.57 (2H, m, C$H_A$C$H_B$OTBS, C*H*(OH)CH($CH_3$)$CH_2$OTBS) 2.06-2.00 (1H, m, C*H*($CH_3$)CH(OH)$CH_2CH_3$) 1.72-1.68 (1H, m, C*H*($CH_3$)$CH_2$OTBS) 1.65-1.55 (1H, m, C$H_A$C$H_B$$CH_3$) 1.43-1.34 (1H, m, C$H_A$C$H_B$$CH_3$) 1.03 (3H, d, 7.1 Hz, CH(C$H_3$)CH(OH)$CH_2CH_3$) 0.93 (3H, t, 7.6 Hz, $CH_2$C$H_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.77 (3H, d, 6.9 Hz, CH(OH)CH(C$H_3$)$CH_2$OTBS) 0.09 (6H, s, 2*SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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-silanyloxy)-5-(4-methoxy-benzyloxy)-2,4-dimethyl-heptan-3-ol (383)**

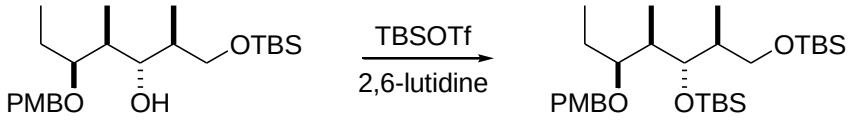



**382** **383**

To a solution of the alcohol **382** (70 mg; 0.22 mmol) in $Et_2O$ (5 mL) at 0°C was added *via* cannula PMB-imidate **147** (95 mg; 0.33 mmol) in $Et_2O$ (3 mL). The solution was then treated with trifluoromethanesulfonic acid (10 µL; 0.1 M of a solution in $Et_2O$) and the resulting yellow solution was warmed to room temperature and stirred for one hour. The reaction was quenched with the addition of $NaHCO_3$ solution (20 mL) and the mixture was extracted with $Et_2O$ (3*20 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography

($CH_2Cl_2$) gave the PMB-protected ether **383** (20 mg; 21%) as a clear oil. $R_F$ = 0.60, $^1$H NMR (600MHz; $CDCl_3$) δ 7.25 (2H, d, 8.6 Hz, Ar*H*) 6.86 (2H, d, 8.6 Hz, Ar*H*) 4.52 (1H, d, 11.0 Hz, OC$H_A$$CH_B$PMP) 4.49 (1H, d, 11.0 Hz, $OCH_ACH_B$PMP) 3.80 (3H, s, OC$H_3$) 3.79-3.76 (1H, m, C$H_A$$CH_B$OTBS) 3.73-3.66 (3H, m, $CH_ACH_B$OTBS, CH(O*H*), C*H*OPMB) 3.42 (1H, q, 7.2, 5.3 Hz, C*H*(OH)) 1.96-1.91 (1H, m, C*H*($CH_3$)CHOPMB) 1.80-1.72 (2H, m, C*H*($CH_3$)$CH_2$OTBS, C$H_A$$CH_B$$CH_3$) 1.52-1.46 (1H, m, $CH_ACH_B$$CH_3$) 1.02 (3H, d, 7.0 Hz, CH(C$H_3$)$CH_2$OTBS) 0.92-0.89 (15H, m, SiC(C$H_3$)$_3$, $CH_2CH_3$, CH(C$H_3$)CHOPMB) 0.07 (6H, brs, 2*SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

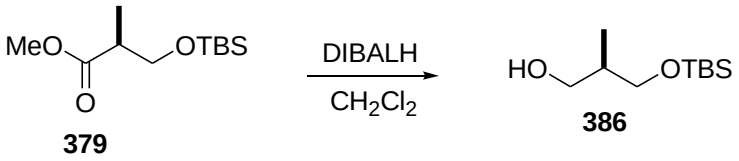
**1-[3,5-Bis-(tert-butyl-dimethyl-silanyloxy)-1-ethyl-2,4-dimethyl-pentyloxymethyl]-4-methoxy-benzene (384)**




**383** **384**

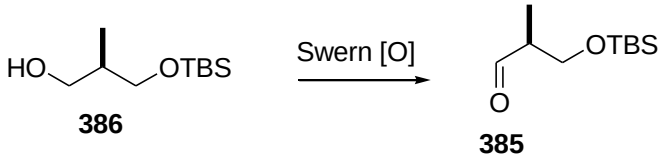
To a solution of alcohol **383** (20 mg; 0.05 mmol) in $CH_2Cl_2$ (3 mL) at -78°C was added 2,6-lutidine (12 µL; 0.10 mmol) followed by TBSOTf (20 µL; 0.08 mmol). The reaction was stirred for 30 minutes at -78°C, warmed to ambient temperature and quenched with $NaHCO_3$ (5 mL). The mixture was extracted with $CH_2Cl_2$ (3*5 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O$/hexanes) gave the protected tri-protected adduct **384** (24 mg; 92%) as a clear oil. $R_F$ = 0.6, $^1$H NMR (600MHz; $CDCl_3$) δ 7.26 (2H, d, 8.5 Hz, Ar*H*) 6.86 (2H, d, 8.5 Hz, Ar*H*) 4.43 (1H, d, 11.0 Hz, OC$H_A$$CH_B$PMP) 4.36 (1H, d, 11.0 Hz, $OCH_ACH_B$PMP) 3.80 (3H, s, OC$H_3$) 3.74-3.69 (2H, m, C$H_A$$CH_B$OTBS, C*H*OTBS) 3.50-3.47 (1H, m, C*H*OPMB) 3.39 (1H, dd, 9.8, 7.9 Hz, $CH_ACH_B$OTBS) 2.07 (1H, C*H*($CH_3$)CHOPMB) 1.93-1.86 (1H, m, C*H*($CH_3$)$CH_2$OTBS) 1.63-1.56 (1H, m, C$H_A$$CH_B$$CH_3$) 1.43-1.37 (1H, $CH_ACH_B$$CH_3$) 0.95-0.86 (18H, m, 2*SiC(C$H_3$)$_3$, $CH_2CH_3$, CH(C$H_3$)CHOPMB, CH(C$H_3$)CH2OTBS) 0.05 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) 0.03 (3H, s, SiC$H_3$) 0.02 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

**3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propan-1-ol (386)**



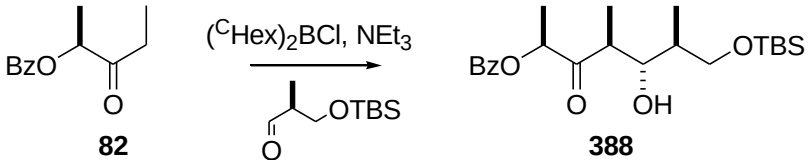

To a solution of TBS-protected roche ester **379** (3.4 g; 14.5 mmol) in $CH_2Cl_2$ (150 mL) was added DIBALH (43 mL; 1.0 M of a solution in $CH_2Cl_2$; 43 mmol) at -78°C. The mixture was stirred for three hours at -78°C then warmed to room temperature for a further hour. The reaction was quenched with $NH_4Cl$ (100 mL), extracted with $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the TBS-protected alcohol **386** (2.86 g; 95%) as a clear oil. $R_F$ = 0.3, $^1$H NMR (600MHz; $CDCl_3$) δ 3.73 (1H, dd, 9.9, 4.4 Hz, C$H_A$CH$_B$OTBS) 3.65-3.58 (2H, m, CH$_A$C$H_B$OTBS, C$H_A$CH$_B$OH) 3.53 (1H, dd, 9.8, 8.0 Hz, CH$_A$C$H_B$OH) 2.90 (1H, brs, CH$_2$O*H*) 1.96-1.91 (1H, m, C*H*CH$_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.83 (3H, d, 7.0 Hz, CHC$H_3$) 0.07 (6H, s, 2*Si(C$H_3$)$_2$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 68.82, 68.37, 36.95, 25.82, 18.14, 13.04, -5.57, -5.64.

**3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propionaldehyde (385)**



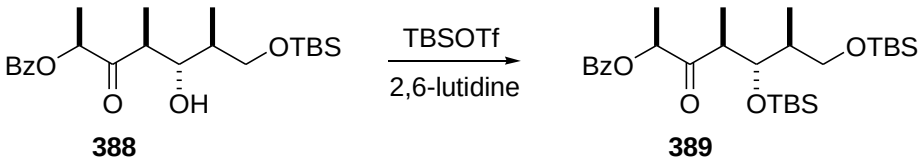

To a solution of DMSO (2.3 mL; 32.3 mmol) in $CH_2Cl_2$ (60 mL) at -78°C was added oxalyl chloride (8.07 mL of a 2 M solution in $CH_2Cl_2$; 16.16 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **386** (2.25 g; 10.77 mmol) in $CH_2Cl_2$ (15 mL) was added *via* cannula. This mixture 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 $NH_4Cl$ (100 mL) then extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the desired aldehyde **385** (2.0 g; 90%) as a colourless oil. $R_F$ = 0.79, $^1$H NMR (600MHz; $CDCl_3$) δ 9.73 (1H, d, 1.5 Hz, C*H*(=O)) 3.85 (1H, dd, 10.2, 5.2 Hz, C$H_A$CH$_B$OTBS) 3.79 (1H, dd, 10.2, 5.2 Hz, CH$_A$C$H_B$OTBS) 2.55-2.49 (1H, m, C*H*CH$_3$) 1.08 (3H, d, 7.0 Hz, CHC$H_3$) 0.87 (9H, s, SiC(C$H_3$)$_3$) 0.04 (6H, s, 2*SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 204.78, 63.40, 48.78, 25.76, 18.20, 10.26, -5.54, -5.57.

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




To a solution of dicyclohexylboron chloride (**355**) (2.5 mL; 11.6 mmol) in $Et_2O$ (30 mL) at -78°C was added $NEt_3$ (1.95 mL; 13.9 mmol) followed by ketone **82** (1.6 g; 7.73 mmol) in $Et_2O$ (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 $Et_2O$ (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% $H_2O_2$ solution (30 mL) and stirring maintained for one hour at ambient temperature. The mixture was extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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, $^1$H NMR (600MHz; $CDCl_3$) δ 8.00 (2H, m, Ar*H*) 7.57 (1H, m, Ar*H*) 7.45 (2H, m, Ar*H*) 5.45 (1H, q, 7.0 Hz, BzOC*H*($CH_3$)) 3.81 (1H, dd, 10.2, 4.0 Hz, C$H_A$$CH_B$OTBS) 3.72 (1H, td, 8.0, 4.0 Hz, C*H*OH) 3.66 (1H, dd, 10.2, 4.0 Hz, $CH_A$C$H_B$OTBS) 3.42 (1H, d, 7.7 Hz, CHO*H*) 3.17 (1H, dqn, 7.1, 1.4 Hz, C*H*($CH_3$)C(OH)) 1.83 (1H, m, C*H*($CH_3$)$CH_2$0TBS) 1.56 (3H, d, 7.0 Hz, BzOCH(C$H_3$)) 1.18 (3H, d, 7.0 Hz, CH(C$H_3$)CHOH) 1.06 (3H, d, 7.1 Hz, CH(C$H_3$)$CH_2$OTBS) 0.88 (9H, s, SiC(C$H_3$)$_3$) 0.05 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

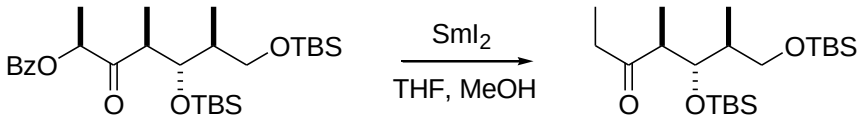
**Benzoic acid 4,6-bis-(tert-butyl-dimethyl-silanyloxy)-1,3,5-trimethyl-2-oxo-hexyl ester (389)**




To a solution of alcohol **388** (1.60 g; 3.88 mmol) in $CH_2Cl_2$ (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 $NaHCO_3$ (70 mL). The mixture was extracted with $CH_2Cl_2$ (3*50 mL), dried ($Na_2SO_4$) 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, $^1$H NMR

(600MHz; $CDCl_3$) δ 8.07 (2H, d, 7.0 Hz, Ar*H*) 7.57 (1H, t, 7.5 Hz, Ar*H*) 7.45 (2H, t, 7.5 Hz, Ar*H*) 5.45 (1H, q, 7.0 Hz, BzOC*H*($CH_3$)) 4.08 (1H, dd, 8.5, 2.5 Hz, C*H*OTBS) 3.69 (1H, dd, 10.0, 7.4 Hz, C$H_A$$CH_B$OTBS) 3.40 (1H, dd, 10.0, 7.4 Hz, $CH_A$C$H_B$OTBS) 3.25 (1H, dqn, 7.0, 1.6 Hz, C*H*($CH_3$)CHOTBS) 1.99-1.92 (1H, m, C*H*($CH_3$)$CH_2$OTBS) 1.52 (3H, d, 7.0 Hz, BzOCH(C$H_3$)) 1.15 (3H, d, 7.0 Hz, CH(C$H_3$)CHOTBS) 0.91 (3H, d, 7.1 Hz, CH(C$H_3$)$CH_2$OTBS) 0.87 (9H, s, SiC($CH_3$)$_3$) 0.85 (9H, s, SiC($CH_3$)$_3$) 0.06 (3H, s, Si$CH_3$) 0.02 (3H, s, Si$CH_3$) 0.01 (3H, s, Si$CH_3$) -0.06 (3H, SiCH3) $^{13}$C NMR (150MHz; $CDCl_3$) δ 208.97, 165.68, 133.18, 129.79, 129.73, 128.39, 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.

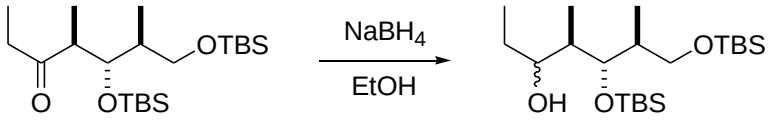
**5,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,6-dimethyl-heptan-3-one (390)**




**389** **390**

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 $K_2CO_3$ (180 mL) and allowed to warm to room temperature. The aqueous layer was extracted with $Et_2O$ (3*100 mL), and the combined organic extracts dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave ketone **390** (1.14 g; 92%) as a clear colourless oil. $R_F$ = 0.87, $^1$H NMR (600MHz; $CDCl_3$) δ 3.99 (1H, dd, 7.1, 3.8 Hz, C*H*OTBS) 3.67 (1H, dd, 9.9, 6.5 Hz, C$H_A$$CH_B$OTBS) 3.41 (1H, dd, 9.9, 6.5 Hz, $CH_A$C$H_B$OTBS) 2.86 (1H, qn, 7.0 Hz, C*H*($CH_3$)CHOTBS) 2.57-2.43 (2H, m, C$H_A$$CH_B$$CH_3$, $CH_A$C$H_B$$CH_3$) 1.91-1.84 (1H, m, C*H*($CH_3$)$CH_2$OTBS) 1.01 (6H, m, CH(C$H_3$)CHOTBS, $CH_2$C$H_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.86 (12H, m, SiC(C$H_3$)$_3$, C*H*($CH_3$)$CH_2$OTBS) 0.06 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) 0.03 (3H, s, SiC$H_3$) -0.04 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) δ 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.

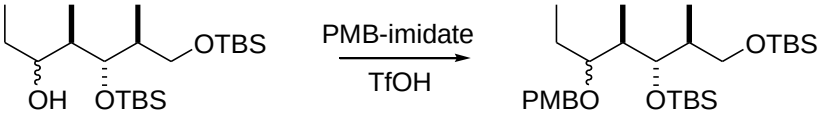
**5,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,6-dimethyl-heptan-3-ol (391/392)**




**390** **391/392**

To a solution of the ketone **390** (800 mg; 1.96 mmol) in EtOH (15 mL) at 0°C was added $NaBH_4$ (150 mg; 3.92 mmol) and the resulting mixture was warmed to room temperature. After six hours $H_2O$ (50 mL) was added and the mixture was extracted with $Et_2O$ (3*100 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (25% $Et_2O$/hexanes) gave the alcohol **391**/**392** (752 mg; 93%) as an inseparable mixture of isomers (4:1). $R_F$ = 0.7, $^1$H NMR (600MHz; $CDCl_3$) δ 3.77 (1H, t, 4.9 Hz, 5.0 Hz, C*H*OTBS) 3.58 (1H, dd, 10.2, 7.3 Hz, C$H_A$CH$_B$OTBS) 3.47 (1H, d, 1.5 Hz, CHO*H*) 3.47-3.44 (1H, m, C*H*OH) 3.40 (1H, dd, 10.2, 6.7 Hz, CH$_A$C$H_B$OTBS) 1.95-1.89 (1H, m, C*H*(CH$_3$)CH$_2$OTBS) 1.76-1.71 (1H, m, C*H*(CH$_3$)CHOTBS) 1.64-1.50 (1H, m, C$H_A$CH$_B$CH$_3$) 1.36-1.25 (1H, m, CH$_A$C$H_B$CH$_3$) 0.96 (3H, t, 7.3 Hz, CH$_2$C$H_3$) 0.91 (9H, s, SiC(C$H_3$)$_3$) 0.89-0.87 (12H, m, SiC(C$H_3$)$_3$, CH(C$H_3$)CH$_2$OTBS) 0.84 (3H, d, 7.0 Hz, CH(C$H_3$)CHOTBS) 0.10 (3H, s, SiC$H_3$) 0.09 (3H, s, SiC$H_3$) 0.04 (3H, s, SiC$H_3$) 0.03 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

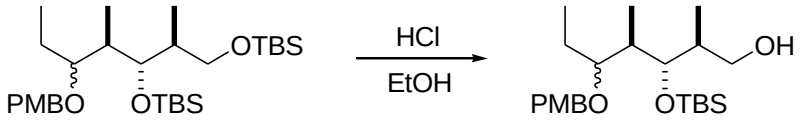
**1-[3,5-Bis-(tert-butyl-dimethyl-silanyloxy)-1-ethyl-2,4-dimethyl-pentyloxymethyl]-4-methoxy-benzene (393)**




**391/392** **393**

To a solution of alcohols **391**/**392** (700 mg; 1.70 mmol) in $Et_2O$ (30 mL) was added PMB-imidate **147** (0.71 mL; 3.4 mmol) and TfOH (40 µL of a 0.9 M solution in $Et_2O$; 3.4 µmol) at 0°C. The mixture was warmed to ambient temperature and stirred for 24 hours. The reaction was quenched with $NaHCO_3$ (50 mL), extracted with $Et_2O$ (3*50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O$/hexanes) gave the protected PMB-ether adduct **393** (520 mg; 58%) as a clear oil. Data in agreement with that described above for **384**.

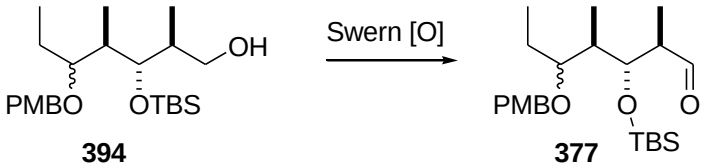
**3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2,4-dimethyl-heptan-1-ol (394)**




**393** **394**

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 $NaHCO_3$ (50 mL), extracted with $Et_2O$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave the primary alcohol **394** (300 mg; 85%) as a clear oil. $R_F$ = 0.55, $^1$H NMR (600MHz; $CDCl_3$) δ 7.24 (2H, d, 8.7 Hz, Ar*H*) 6.87 (2H, d, 8.7 Hz, Ar*H*) 4.44 (1H, d, 11.1 Hz, OC*H*$_A$CH$_B$PMP) 4.31 (1H, d, 11.1 Hz, OCH$_A$C*H*$_B$PMP) 3.96 (1H, dd, 5.3, 3.8 Hz, C*H*OTBS) 3.80 (3H, s, OC*H*$_3$) 3.73 (1H, dd, 10.8, 3.9 Hz, C*H*$_A$CH$_B$OH) 3.57 (1H, dd, 10.8, 5.4 Hz, CH$_A$C*H*$_B$OH) 3.40-3.37 (1H, m, C*H*OPMB) 2.87 (1H, brs, CH$_2$O*H*) 2.08 (1H, qdd, 7.2, 6.0, 5.4 Hz, C*H*(CH$_3$)CHOPMB) 1.93-1.86 (1H, m, C*H*(CH$_3$)CH$_2$OH) 1.73-1.63 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.51-1.44 (1H, m, CH$_A$C*H*$_B$CH$_3$) 0.99 (3H, d, 7.1 Hz, CH(C*H*$_3$)CH$_2$OH) 0.93-0.90 (15H, m, SiC(C*H*$_3$)$_3$, CH$_2$C*H*$_3$, CH(C*H*$_3$)CHOPMB) 0.11 (3H, s, SiC*H*$_3$) 0.07 (3H, s, SiC*H*$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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)**

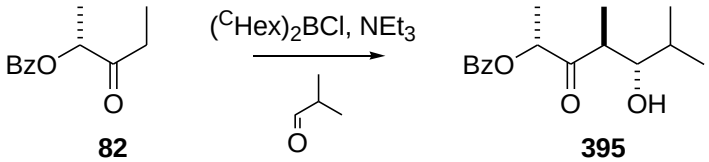



**394** **377**

To a solution of DMSO (155 µL; 2.19 mmol) in $CH_2Cl_2$ (20 mL) at -78°C was added oxalyl chloride (0.55 mL of a 2 M solution in $CH_2Cl_2$; 1.10 mmol) dropwise. The mixture was stirred for 20 minutes then alcohol **394** (300 mg; 0.73 mmol) in $CH_2Cl_2$ (5 mL) was added *via* cannula. This mixture was stirred for a further 30 minutes then $NEt_3$ (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 $NH_4Cl$ (50 mL) then extracted with $CH_2Cl_2$ (3*30 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the desired aldehyde **377** (280 mg; 93%) as a colourless oil. $R_F$ = 0.6, $^1$H

NMR (600MHz; $CDCl_3$) δ 9.77 (1H, d, 2.8 Hz, C*H*(=O)) 7.24 (2H, d, 8.7 Hz, Ar*H*) 6.87 (2H, d, 8.7 Hz, Ar*H*) 4.44 (1H, d, 11.2 Hz, OC$H_A$CH$_B$PMP) 4.32 (1H, d, 11.2 Hz, OCH$_A$C$H_B$PMP) 4.10 (1H, dd, 5.6, 2.6 Hz, C*H*OTBS) 3.80 (3H, s, OC$H_3$) 3.37 (1H, td, 6.4, 3.5 Hz, C*H*OPMB) 2.50-2.46 (1H, m, C*H*(CH$_3$)CH(=O)) 2.06-2.01 (1H, m, C*H*(CH$_3$)CHOTBS) 1.68-1.62 (1H, m, C$H_A$CH$_B$CH$_3$) 1.49-1.42 (1H, m, CH$_A$C$H_B$CH$_3$) 1.07 (3H, d, 7.1 Hz, CH(C$H_3$)CH(=O)) 0.92 (3H, t, 7.4 Hz, CH$_2$C$H_3$) 0.89 (9H, s, SiC(C$H_3$)$_3$) 0.81 (3H, d, 7.2 Hz, CH(C$H_3$)CHOTBS) 0.07 (3H, s, SiC$H_3$) 0.05 (3H, s, SiC$H_3$) $^{13}$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.

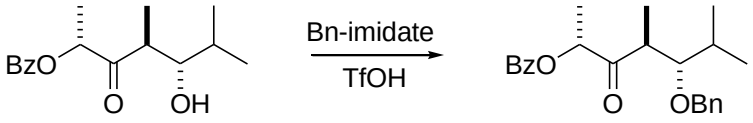
**Benzoic acid 4-hydroxy-1,3,5-trimethyl-2-oxo-hexyl ester (395)**




**82** **395**

To a solution of dicyclohexylboron chloride (**355**) (1.6 mL; 7.4 mmol) in $Et_2O$ (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 $Et_2O$ (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% $H_2O_2$ solution (15 mL). The mixture was stirred for an additional hour at ambient temperature then partitioned between $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (3*100 mL), dried ($Na_2SO_4$) 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, Ar*H*) 7.57 (1H, t, 7.3 Hz, Ar*H*) 7.44 (2H, d, 7.7 Hz, Ar*H*) 5.44 (1H, q, 7.1 Hz, BzOC*H*(CH$_3$)) 3.60-3.56 (1H, m, C*H*(OH)) 3.00 (1H, dq, 7.2 Hz, C(=O)C*H*(CH$_3$)) 2.28 (1H, brs, CH(O*H*)) 1.80-1.75 (1H, m, C*H*(CH$_3$)$_2$) 1.56 (3H, d, 7.1 Hz, BzOCH(C$H_3$)) 1.22 (3H, d, 7.2 Hz, C(=O)CH(C$H_3$)) 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.

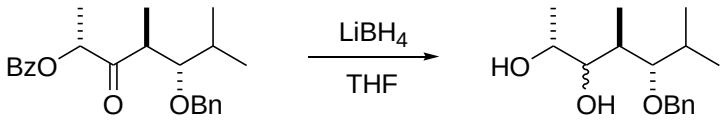
**Benzoic acid 4-benzyloxy-1,3,5-trimethyl-2-oxo-hexyl ester (396)**




**395** **396**

To a solution of the alcohol **395** (1.3 g; 4.7 mmol) in cyclohexane (8 mL) at 0°C was added *via* cannula benzyl-imidate **338** (2.35 g; 9.4 mmol) in $CH_2Cl_2$ (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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% $CH_2Cl_2$/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-Ar*H*) 7.57 (1H, t, 7.5 Hz, Bz-Ar*H*) 7.44 (2H, t, 8.0 Hz, Bz-Ar*H*) 7.32-7.29 (2H, m, Bn-Ar*H*) 7.26-7.23 (3H, m, Bn-Ar*H*) 5.38 (1H, q, 7.1 Hz, BzOC*H*($CH_3$)) 4.52 (1H, d, 11.2 Hz, C$H_A$$CH_B$PMP) 4.43 (1H, d, 11.2 Hz, $CH_A$C$H_B$PMP) 3.69 (1H, dd, 9.8, 2.2 Hz, C*H*OBn) 3.08 (1H, dq, 9.8, 7.0 Hz, C(=O)C*H*($CH_3$)) 1.93-1.88 (1H, m, C*H*($CH_3$)$_2$) 1.42 (3H, d, 7.1 Hz, BzOCH(C$H_3$)) 1.14 (3H, d, 7.0 Hz, C(=O)CH(C$H_3$)) 1.07 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 0.94 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) $^{13}$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-Benzyloxy-4,6-dimethyl-heptane-2,3-diol (397)**

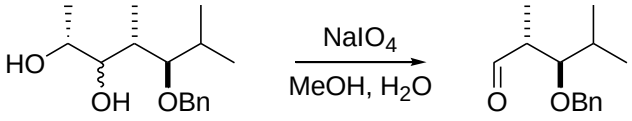



**396** **397**

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 $H_2O$ (50 mL). The mixture was partitioned between $H_2O$ (150 mL) and $Et_2O$ (4*100 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% $Et_2O$/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, Ar*H*) 4.67 (1H, d, 10.9

Hz, $OCH_ACH_BPh$) 4.64 (1H, d, 10.9 Hz, $OCH_ACH_BPh$) 3.80-3.75 (1H, m, $(CH_3)CH(OH)$) 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, $CH(CH_3)_2$) 1.88-1.81 (1H, m, $CH(CH_3)$) 1.16 (3H, d, 6.3 Hz, $(CH_3)CH(OH)$) 1.05 (3H, d, 7.0 Hz, $CH(CH_3)_2$) 0.99 (3H, d, 7.0 Hz, $CH(CH_3)_2$) 0.88 (3H, d, 7.0 Hz, $CH(CH_3)$) $^{13}C$ NMR (150MHz; $CDCl_3$) 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.

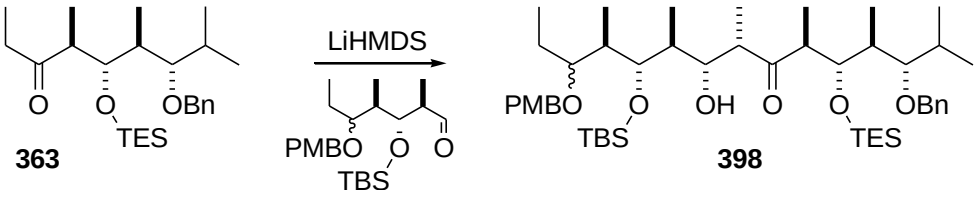
**3-Benzyloxy-2,4-dimethyl-pentanal (347)**




**397** **347**

To a stirred solution of diol **397** (550 mg; 2.07 mmol) in MeOH (25 mL) and $H_2O$ (12.5 mL) was added $NaIO_4$ (2.64 g; 12.4 mmol) at room temperature. The reaction was stirred for 15 minutes, then diluted with $H_2O$ (90 mL) and extracted with $Et_2O$ (3*70 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the aldehyde **347** (430 mg; 96%) as a clear oil. Data in agreement with that described above.

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

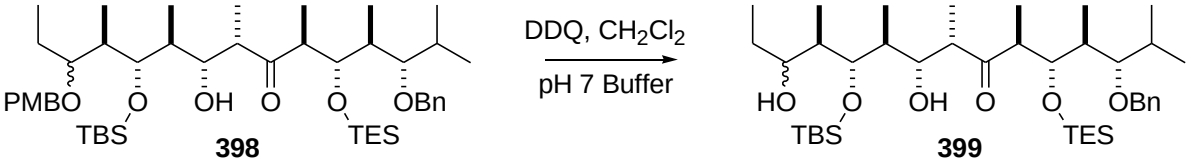



**363** **398**

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 $Et_2O$ (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 $Et_2O$ (3*10 mL),

dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O$/hexanes) gave the aldol product **398** (152 mg; 62%) as a clear oil. $R_F$ = 0.1, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.21 (7H, m, 5*Bn-Ar*H*, 2*PMB-Ar*H*) 4.80 (1H, d, 11.8 Hz, OC*H*$_A$CH$_B$Ph) 4.60 (1H, d, 11.8 Hz, OCH$_A$C*H*$_B$Ph) 4.40 (1H, d, 11.2, OC*H*$_A$CH$_B$PMP) 4.35 (1H, d, 11.2 Hz, OCH$_A$C*H*$_B$PMP) 4.16 (1H, dd, 9.4, 1.4 Hz, C*H*OTES) 3.98 (1H, dd, 6.1, 4.2 Hz, C*H*OTBS) 3.93 (1H, d, 10.3 Hz, C*H*OH) 3.80 (3H, s, OC*H*$_3$) 3.57 (1H, brs, CHO*H*) 3.43 (1H, td, 7.0, 2.9 Hz, C*H*OPMB) 3.31 (1H, dd, 10.0, 1.9 Hz, C*H*OBn) 3.19 (1H, dq, 9.2, 6.9 Hz, C*H*(CH$_3$)CHOTES) 2.55 (1H, qd, 6.9, 1.5 Hz, CH(OH)C*H*(CH$_3$)C(=O)) 2.08-2.03 (1H, m, CH(OPMB)C*H*(CH$_3$)CHOTBS) 1.97-1.80 (3H, m, CH(OTBS)C*H*(CH$_3$)CH(OH), C*H*(CH$_3$)CHOBn, C*H*(CH$_3$)$_2$) 1.66-1.60 (1H, m, C*H*$_A$CH$_B$CH$_3$) 1.46-1.39 (1H, m, CH$_A$C*H*$_B$CH$_3$) 1.04 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTES) 1.04 (3H, d, 6.9 Hz, CH(OH)CH(C*H*$_3$)C(=O)) 0.96-0.86 (33H, m, 3*SiCH$_2$C*H*$_3$, 2*SiC(C*H*$_3$)$_3$, 2*CH(C*H*$_3$)$_2$, CH$_2$C*H*$_3$, CH(C*H*$_3$)CHOTBS, CH(OTBS)CH(C*H*$_3$)CHOH, CH(OTES)CH(C*H*$_3$)CHOBn) 0.73 (3H, d, 7.0 Hz, CH(C*H*$_3$)CHOBn) 0.53 (6H, q, 7.8 Hz, 3*SiC*H*$_2$CH$_3$) 0.08 (3H, s, SiC*H*$_3$) 0.06 (3H, s, SiC*H*$_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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, 25.97, 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.

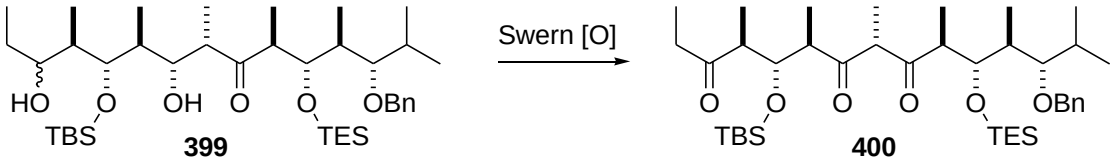
**3-Benzyloxy-11-(tert-butyl-dimethyl-silanyloxy)-9,13-dihydroxy-2,4,6,8,10,12-hexamethyl-5-triethylsilanyloxy-pentadecan-7-one (399)**




To a solution of aldol adduct **398** (80 mg; 0.09 mmol) in $CH_2Cl_2$ (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 $CH_2Cl_2$ (10 mL) and quenched with $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase extracted with $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O$/$CH_2Cl_2$) gave the diol **399** (63 mg; 96%) as a clear oil. $R_F$ = 0.9, $^1$H NMR (600MHz; $CDCl_3$) δ 7.37-7.24 (5H, m, Ar*H*) 4.76 (1H, d, 11.9 Hz, OC*H*$_A$CH$_B$Ph) 4.65 (1H, d, 11.9 Hz, OCH$_A$C*H*$_B$Ph) 4.15 (1H, d, 8.4 Hz, CHOTES) 4.08 (1H, t, 5.0 Hz, C*H*OTBS) 3.71 (1H, d, 9.6 Hz, C*H*(OH)CH(CH$_3$)C(=O)) 3.42 (1H, td, 8.6, 2.8 Hz, CH$_3$CH$_2$C*H*(OH)) 3.33 (1H, dd, 10.1, 1.9 Hz, C*H*OBn) 3.13 (1H, qd, 9.1, 7.1 Hz, C(=O)C*H*(CH$_3$)CHOTES) 2.50 (1H, q, 7.9, 7.0 Hz, CH(OH)C*H*(CH$_3$)C(=O)) 1.95 (1H,

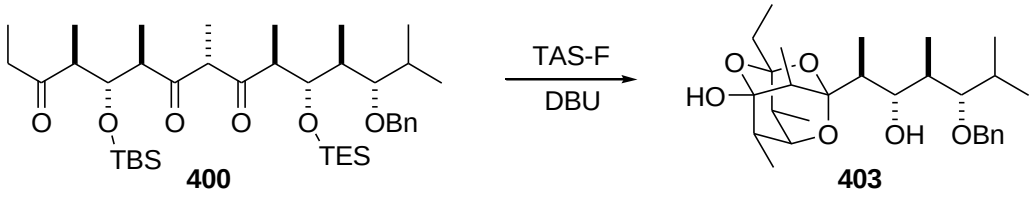
qd, 7.5, 7.3 Hz, C*H*($CH_3$)CHOBn) 1.87 (1H, qdd, 6.8, 5.0, 1.8 Hz, C*H*($CH_3$)$_2$) 1.79-1.73 (1H, m, C*H*($CH_3$)CHOTBS) 1.70-1.59 (2H, m, CH(OTBS)C*H*($CH_3$)CHOH, C$H_A$C$H_B$C$H_3$) 1.35-1.27 (1H, m, C$H_A$C$H_B$C$H_3$) 1.05 (3H, d, 7.0 Hz, CH(C$H_3$)$_2$) 1.00 (3H, d, C(=O)CH(C$H_3$)CHOTES) 0.96-0.89 (30H, m, 3*SiC$H_2$C$H_3$, 2*SiC(C$H_3$)$_3$, CH(C$H_3$)$_2$, $CH_2$C$H_3$, CH(C$H_3$)CHOTBS, CH(OTBS)CH(C$H_3$)CHOH) 0.85 (3H, d, 6.9 Hz, CH(C$H_3$)CHOTBS) 0.72 (3H, d, 7.0 Hz, CH(OH)CH(C$H_3$)C(=O)) $^{13}$C NMR (150MHz; $CDCl_3$) 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-Benzyloxy-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 $CH_2Cl_2$ (1 mL) at -78°C was added oxalyl chloride (131 µL of a 2 M solution in $CH_2Cl_2$, 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 $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3*10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography ($CH_2Cl_2$) gave the trione **400** (41 mg; 68%) as a clear oil. $R_F$ = 0.7, $^1$H NMR (600MHz; $CDCl_3$) δ 7.35-7.23 (5H, m, Ar*H*) 4.74 (1H, d, 11.8 Hz, OC$H_A$C$H_B$Ph) 4.62 (1H, d, 11.8 Hz, OC$H_A$C$H_B$Ph) 4.38 (1H, dd, 8.3, 5.0 Hz, C*H*OTBS) 4.13 (1H, d, 9.4 Hz, C*H*OTES) 3.74 (1H, q, 7.1 Hz, C(=O)C*H*($CH_3$)C(=O)) 3.29 (1H, dd, 12.3, 2.0 Hz, C*H*OBn) 2.95 (1H, dq, 9.3, 7.0 Hz, C(=O)C*H*($CH_3$)CHOTES) 2.76 (1H, qn, 7.3 Hz, CH(OTBS)C*H*($CH_3$)C(=O)) 2.66 (1H, qd, 7.0, 6.9 Hz, C(=O)C*H*($CH_3$)CHOTBS) 2.56 (1H, dq, 18.1, 7.2 Hz, C$H_A$C$H_B$C$H_3$) 2.45 (1H, dq, 18.1, 7.2 Hz, C$H_A$C$H_B$C$H_3$) 1.95-1.85 (2H, m, C*H*($CH_3$)CHOBn, C*H*($CH_3$)$_2$) 1.09-0.99 (15H, m, C(=O)CH(C$H_3$)C(=O), C(=O)CH(C$H_3$)CHOTES, C(=O)CH(C$H_3$)CHOTBS, $CH_2$C$H_3$, CH(C$H_3$)$_2$) 0.93-0.83 (18H, m, 3*SiOC$H_2$C$H_3$, CH(OTBS)CH(C$H_3$)C(=O), CH(C$H_3$)$_2$, CH(C$H_3$)CHOBn) 0.54 (6H, q, 7.9 Hz, 3*SiC$H_2$CH$_3$) 0.07 (3H, s, SiC$H_3$) -0.05 (3H, s, SiC$H_3$) $^{13}$C NMR (150MHz; $CDCl_3$) 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.

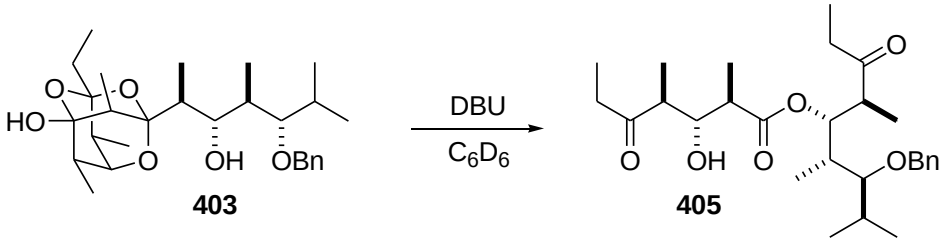
**5-(4-Benzyloxy-2-hydroxy-1,3,5-trimethyl-hexyl)-3-ethyl-8,9,10-trimethyl-2,4,6-trioxa-tricyclo[3.3.1.13,7]decan-1-ol (403)**




**400** **403**

To a solution of trione **400** (38 mg; 0.05 mmol) in DMF (0.4 mL) and $H_2O$ (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 ($Na_2SO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) produced a mixture of isomeric products which were treated with DBU (minimal amount in $C_6D_6$) to give trioxaadamantane **403** (22 mg; 94%) as a clear oil. $R_F$ = 0.5, $^1$H NMR (600MHz; $C_6D_6$) δ 7.40 (2H, d, 7.5 Hz, Ar*H*) 7.21 (2H, t, 7.6 Hz, Ar*H*) 7.10 (1H, t, 7.4 Hz, Ar*H*) 5.07 (1H, d, 12.0 Hz, OC$H_A$CH$_B$Ph) 4.67 (1H, d, 12.0 Hz, OCH$_A$C$H_B$Ph) 4.43 (1H, s, CHO*H*) 4.31 (1H, d, 8.3 Hz, C*H*OH) 3.78 (1H, dd, 9.3, 1.9 Hz, C*H*OBn) 3.37 (1H, s, C*H*(-O-)C) 2.62 (1H, brs CO*H*) 2.30-2.21 (2H, m, CH(OH)C*H*(CH$_3$)CHOBn, C*H*(CH$_3$)CHOH) 1.94-1.88 (2H, m, C*H*(CH$_3$)$_2$, C(OH)C*H*(CH$_3$)C) 1.58-1.51 (2H, m, C$H_A$CH$_B$CH$_3$, C(-O-)$_2$C*H*(CH$_3$)CH(-O-)) 1.38-1.31 (1H, m, CH$_A$C$H_B$CH$_3$) 1.22 (3H, d, 6.9 Hz, CH(OH)CH(C$H_3$)CHOBn) 1.22-1.18 (1H, m, C(-O-)OHC*H*(CH$_3$)CH(-O-)) 1.07 (3H, d, 6.9 Hz, CH(C$H_3$)$_2$) 1.06 (3H, d, 6.9 Hz, CH(C$H_3$)$_2$) 1.03 (3H, d, 6.9 Hz, C(-O-)OHCH(C$H_3$)CH(-O-)) 0.99-0.95 (6H, m, CH(C$H_3$)CHOH, C(-O-)$_2$CH(C$H_3$)CH(-O-)) 0.91 (3H, t, 7.4 Hz, CH$_2$C$H_3$) 0.60 (3H, d, 6.7 Hz, C(OH)CH(C$H_3$)C) $^{13}$C NMR (150MHz; $C_6D_6$) 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.

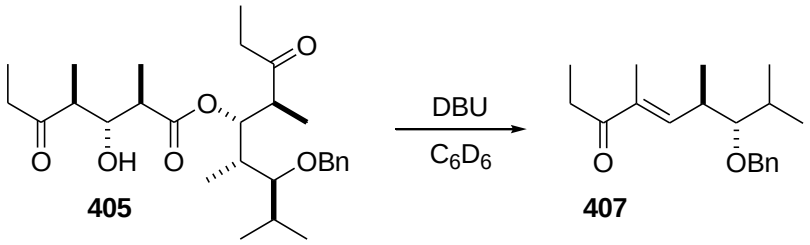
**3-Hydroxy-2,4-dimethyl-5-oxo-heptanoic acid 3-benzyloxy-2,4-dimethyl-1-(1-methyl-2-oxo-butyl)-pentyl ester (405)**




**403** **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% $Et_2O/CH_2Cl_2$) to obtain the ester **405** (18 mg; 81%) over two steps as a clear oil. $R_F$ = 0.47, $^{1}$H NMR (600MHz; $C_6D_6$) δ 7.40 (2H, d, 7.7 Hz, Ar*H*) 7.20 (2H, t, 7.8 Hz, Ar*H*) 7.10 (1H, t, 7.4 Hz, Ar*H*) 5.45 (1H, dd, 7.7, 4.1 Hz, C*H*OC(=O)) 4.66 (1H, d, 11.3 Hz, OC$H_A$$CH_B$Ph) 4.53 (1H, d, 11.3 Hz, OC$H_A$C$H_B$Ph) 3.77 (1H, brs, C*H*OH) 3.70 (1H, brs, CHO*H*) 3.19 (1H, dd, 7.1, 3.9 Hz, C*H*OBn) 3.08 (1H, qn, 7.1 Hz, C(=O)C*H*($CH_3$)CHOC(=O)) 2.67-2.62 (2H, m, C(=O)C*H*($CH_3$)CHOH, CH(OH)C*H*($CH_3$)) 2.22-2.10 (5H, m, 2*C$H_2$$CH_3$, C*H*($CH_3$)CHOBn) 2.02 (1H, dq, 18.2, 7.2 Hz, C$H_2$$CH_3$) 1.82 (1H, qnd 6.9, 4 Hz, C*H*($CH_3$)$_2$) 1.14 (3H, d, 7.1 Hz, CH(OH)CH(C$H_3$)) 1.00 (3H, d, 6.9 Hz, CH(C$H_3$)$_2$) 0.98 (3H, d, 7.2 Hz, C(=O)CH(C$H_3$)CHOH) 0.97 (3H, d, 6.9 Hz, CH(C$H_3$)$_2$) 0.95 (3H, t, 7.3 Hz, $CH_2$C$H_3$) 0.94 (3H, d, 7.1 Hz, CH(C$H_3$)CHOBn) 0.92 (3H, t, 7.3 Hz, $CH_2$C$H_3$) 0.88 (3H, d, 7.1 Hz, C(=O)CH(C$H_3$)CHOC(=O)) $^{13}$C NMR (150MHz, $C_6D_6$) δ 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.

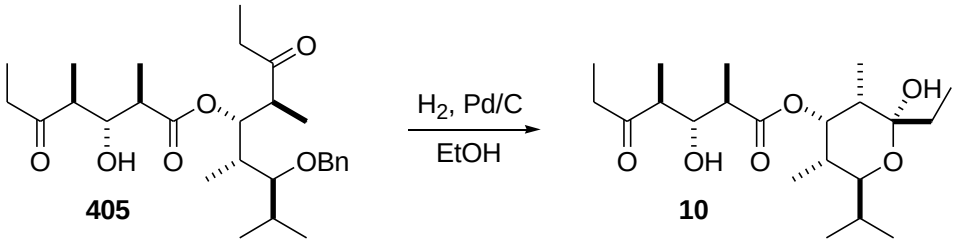
**7-Benzyloxy-4,6,8-trimethyl-non-4-en-3-one (407)**




**405** **407**

β-elimination product from the esterification and retro-Claisen reactions. Purified by column chromatography ($CH_2Cl_2$) gave the elimination product **407**. $R_F$ = 0.55, $^1$H NMR (600MHz: $CDCl_3$) δ 7.35-7.26 (5H, m, Ar*H*) 6.75 (1H, dd, 9.8, 1.3 Hz, $CH_3C$=C*H*) 4.63 (1H, d, 11.2 Hz, C$H_A$C$H_B$Ph) 4.57 (1H, d, 11.2 Hz, C$H_A$C$H_B$Ph) 3.09 (1H, dd, 6.7, 4.0 Hz, C*H*OBn) 2.91-2.85 (1H, m, C*H*($CH_3$)CHOBn) 2.67 (2H, qd, 7.3 Hz, C$H_2$$CH_3$) 1.82-1.76 (1H, m, C*H*($CH_3$)$_2$) 1.78 (3H, d, 1.3 Hz, C$H_3$C=CH), 1.08 (3H, d, 6.9 Hz, CH(C$H_3$)CHOBn), 1.07 (3H, t, 7.3 Hz, $CH_2$C$H_3$) 0.99 (3H, d, 6.7 Hz, CH(C$H_3$)$CH_3$), 0.88 (3H, d, 6.7 Hz, CH(C$H_3$)$CH_3$)

**Dolabriferol (10)**




**405** **10**

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 *in vacuo*. Purification by column chromatography (10% $Et_2O/CH_2Cl_2$) gave dolabriferol (**10**) (13.4 mg; 92%) as a white powder. $R_F$ = 0.35, $^1$H NMR (600MHz; $CDCl_3$) δ 5.24 (1H, t, 2.7 Hz, C*H*OC(=O)) 3.76 (1H, m, C*H*OH) 3.61 (1H, brs, CHO*H*) 3.60 (1H, dd, 10.5, 2.2 Hz, ($CH_3$)$_2$CHC*H*O) 3.46 (1H, brs, CO*H*) 2.79 (1H, dq, 7.2, 7.2 Hz, C(=O)C*H*$CH_3$) 2.73 (1H, dq, 7.1, 4.8 Hz, OC(=O)C*H*$CH_3$) 2.57 (1H, dq, 14.5, 7.2 Hz, C(=O)C$H_A$C$H_B$$CH_3$) 2.46 (1H, dq, 14.5, 7.2 Hz, C(=O)C$H_A$C$H_B$$CH_3$) 1.91 (1H, dq, 7.2, 2.8 Hz, C*H*($CH_3$)COH) 1.83 (1H, dqq, 6.9, 2.2 Hz, C*H*($CH_3$)$_2$) 1.79 (1H, dqd, 10.5, 6.9, 2.7 Hz, C*H*($CH_3$)CHO) 1.62 (2H, m, C$H_A$C$H_B$$CH_3$, C$H_A$C$H_B$$CH_3$) 1.33 (3H, d, 7.1 Hz, OC(=O)CHC$H_3$) 1.15 (3H, d, 7.2 Hz, C(=O)CHC$H_3$) 1.04 (3H, t, 7.2 Hz, C(=O)$CH_2$C$H_3$) 1.01 (3H, d, 6.9 Hz, CH(C$H_3$)$CH_3$) 1.00 (3H, d, 7.2 Hz, CH(C$H_3$)COH) 0.91 (3H, t, 7.3

Hz, $CH_2CH_3$) 0.83 (3H, d, 6.9 Hz, $CH(CH_3)CH_3$) 0.78 (3H, d, 6.9 Hz, $CH(CH_3)CHO$), **HRESIMS** calculated for $C_{21}H_{38}O_6^+$ $[M+H]^+$ : 387.2668; found 387.2611

## Appendix 1