Synthetic Studies Towards Spirangien A and Total Synthesis of (+)-Ascosalipyrone and *ent*-Micropyrone

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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Declaration

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

Claire Gregg

13th May 2011

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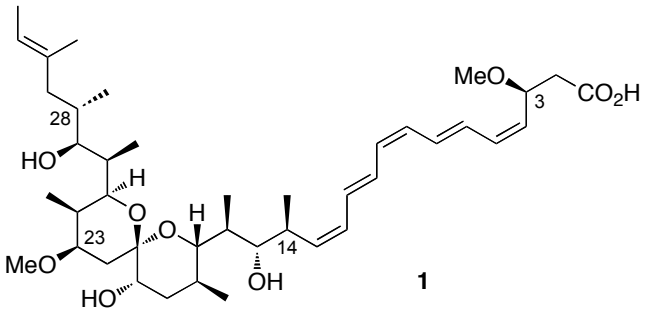
Abstract

Polyketides are considered not only the largest class of secondary metabolites that share a common biosynthesis, but are also one of the most interesting classes of natural products due to their enormous structural diversity and broad spectrum biological activities. Chapter one introduces the reader to polyketide natural products, including their origin, structure and activity. This is followed by an overview of the aldol reaction, a highly useful synthetic tool in the biomimetic construction of polyketide motifs. The aldol reaction will feature extensively in the studies to follow.

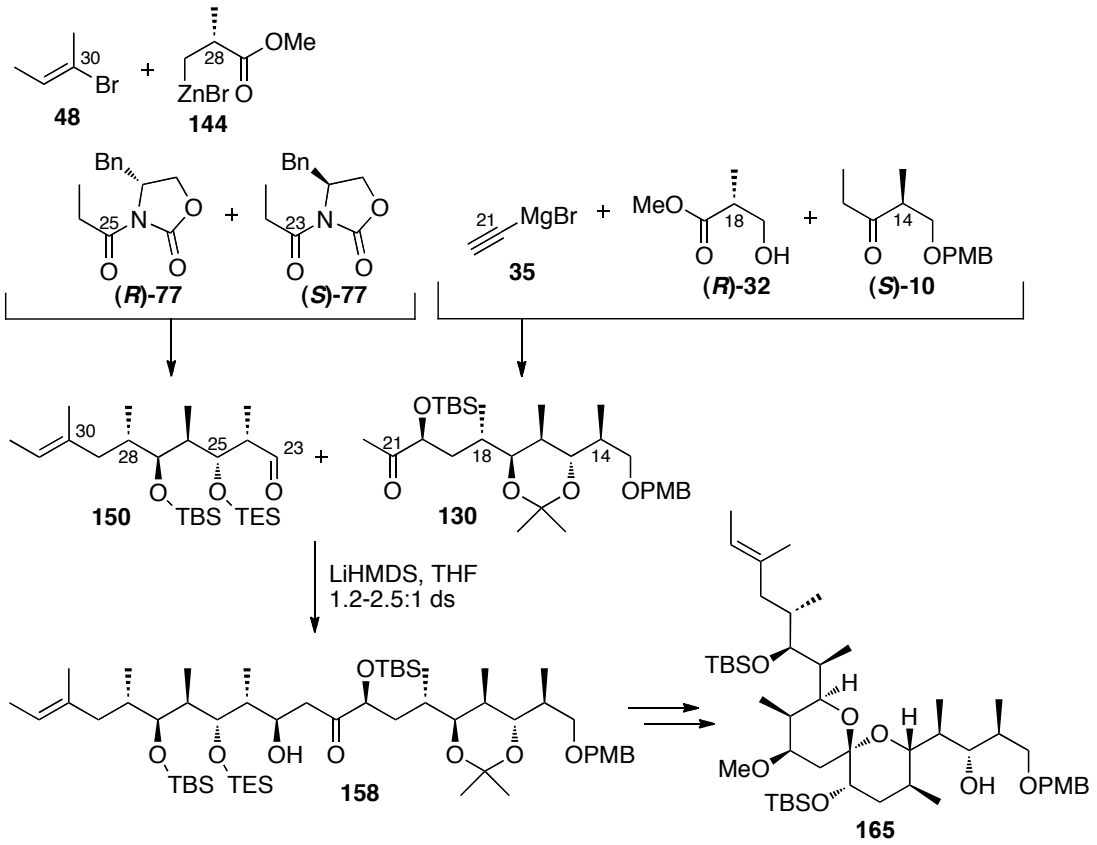
Chapter two describes studies towards the synthesis of spirangien A (**1**), a highly cytotoxic and antifungal polyketide metabolite, isolated from the myxobacterium *Sorangium cellulosum*. The synthetic approach to spirangien A exploited the obvious C22-C23 acetate aldol disconnection in linear precursor **158**. Model studies were conducted which showed that the diastereoselectivity of this aldol reaction is highly substrate controlled and depends heavily on the hydroxyl protecting group strategy. This model system lacked the C17 stereocentre of the natural product, which evidently exhibited strong 1,7-stereoinduction, therefore the model was concluded to be an inadequate representation of the natural product system.



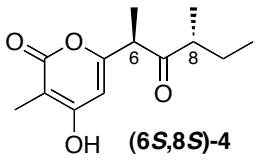
1

The aldehyde coupling partner **150** was synthesised in 10 steps (10% yield), utilising a highly efficient cross-coupling of zinc homoenolate **144** with (*E*)-2-bromo-2-

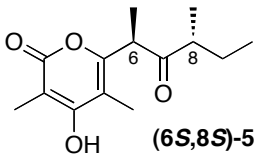
butene (**48**) to install the C28 stereocentre and two successive Evans *syn* aldol reactions to give the desired C24-27 stereotetrad and differential protection of the resulting hyroxyl groups. Ketone coupling partner **130** was synthesised from (*R*)-Roche ester **(*R*)-32** in 16 steps (22% yield), using a mercury catalysed hydration of the terminal alkynyl functionality derived from ethynylmagnesium bromide (**35**) to afford the methyl ketone, and a *syn,syn* selective aldol reaction with (*S*)-Roche ester derived dipropionate equivalent **(*S*)-10** to give the C14-17 stereotetrad. Coupling of the resulting aldehyde **150** and ketone **130** was achieved using a LiHMDS aldol to give 1.2-2.5:1 ds in favour of the desired product **158**. The stereochemistry of aldol adduct **158** was assigned by conversion to the corresponding hemiacetal and subsequent nOe analysis. Spirocyclisation of the major product hemiacetal gave **165**, from which stereochemical assignment was confirmed. Further manipulation of **165** in 3 steps (removal of the TBS groups, re-protecting with TES groups and finally cleavage of the PMB ether) would result in a formal synthesis of spirangien A, however limited availability of material prevented completion of the total synthesis.



Chapter three details the total synthesis of (+)-ascosalipyrone [**(6*S*,8*S*)-4**] and *ent*-micropyrone [**(6*S*,8*S*)-5**]. Ascosalipyrone (**4**), isolated from the obligate marine fungus *A. salicorniae*, and micropyrone (**5**), isolated from the plant *H. italicum*, are two novel, structurally related polyketide natural products. Both compounds have the same 4-hydroxy-α-pyrone containing core structure, differing only by an extra methyl group at C4 in micropyrone (**5**). Ascosalipyrone was reported as an inseparable mixture of diastereomers, while micropyrone was reported as a single isomer with a non-zero specific rotation.

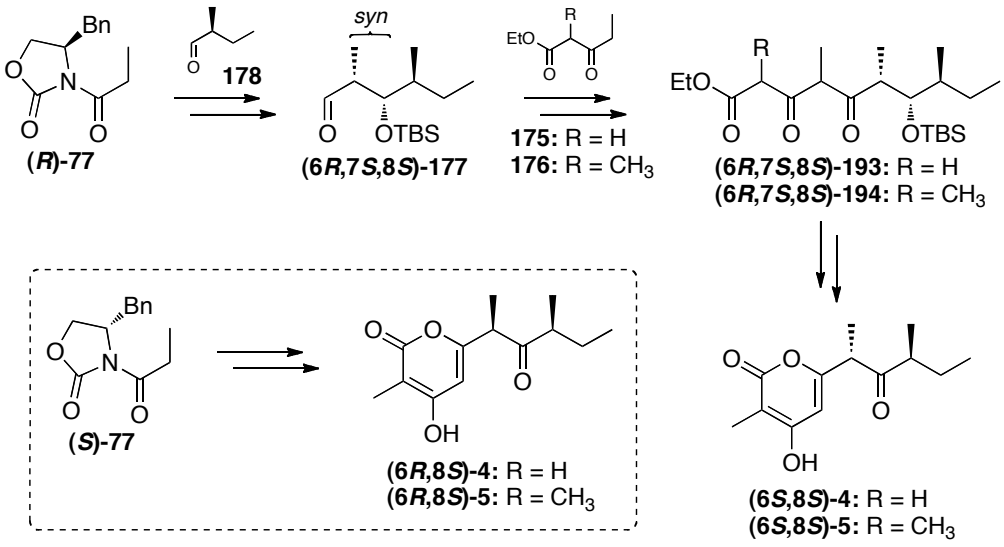


(6*S*,8*S*)-4



(6*S*,8*S*)-5

The synthesis of two potential diastereomers of each natural product from a common intermediate was achieved. A highly diastereoslective *syn* aldol reaction between both the **(*R*)-77** and **(*S*)-77** enantiomers of Evans' auxiliary and chiral aldehyde **178** was exploited to produce aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177**. The linear precursors **(6*R*,7*S*,8*S*)-193** and **(6*R*,7*S*,8*S*)-194** were constructed by addition of β-ketoesters **175** or **176** respectively to aldehyde **(6*R*,7*S*,8*S*)-177**, with DBU promoted cyclisation to install the 4-hydroxy-α-pyrone ring system. Removal of the protecting groups and Jones oxidation gave two possible isomers of each ascosalipyrone and micropyrone. No epimerisation of the α-stereocentre was observed for the micropyrone isomers but partial epimerisastion (3:1) was seen for ascosalipyrone isomers. This was attributed to less steric congestion for ascosalipyrone, which lacks one pyrone methyl. Comparison of the NMR and specific rotation assigned the structure of (+)-ascosalipyrone [**(6*S*,8*S*)-4**] and micropyrone [**(6*R*,8*R*)-5**].


Bn
O
N
O
O
(R)-77
178
syn
O
OTBS
(6R,7S,8S)-177
R
EtO
O
O
175: R = H
176: R = CH3
EtO
R
O
O
O
OTBS
(6R,7S,8S)-193: R = H
(6R,7S,8S)-194: R = CH3
Bn
O
N
O
O
(S)-77
O
O
O
OH
(6R,8S)-4: R = H
(6R,8S)-5: R = CH3
O
O
O
OH
(6S,8S)-4: R = H
(6S,8S)-5: R = CH3

Glossary

°C	degrees Celsius
Å	angstroms
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
aq.	aqueous
AR	analytical reagent
Ar	aromatic
atm	atmospheres
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bz	benzoyl
bp.	boiling point
Bu	butyl
Bz_2O	benzoic anhydride
c	concentration (g/100 mL)
cat.	catalytic
CAN	cerium ammonium nitrate
$CDCl_3$	deuterated chloroform
C_6D_6	deuterated benzene
CD_3OD	deuterated methanol
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$(c\text{-Hex})_2BCl$	dicyclohexylboron chloride
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

$(Sia)_2BH$	disiamylborane
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ds	diastereoselectivity
E	*entgegen* (opposite)
ee	enantiomeric excess
eq.	equivalents
ESI	electrospray ionisation
et al.	*et alia* (and others)
Et	ethyl
FGI	Functional Group Interconversions
GC	gas chromatography
HF	hydrofluoric acid
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence
HRESIMS	high resolution electrospray ionization mass spectroscopy (spectrum)
Hz	hertz
ie.	id est (that is)
i-	*iso-*
Ipc	diisopinocampheyl
IBX	2-iodobenzoic acid
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilaside
LC	liquid chromatography
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
Me	methyl
MHz	megahertz
mmol	millimole

mol	mole
mp.	melting point
MS	mass spectrum
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
OTf	trifluoromethanesulfonate (triflate)
[O]	oxidation
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr	pyridine
R*f*	retention factor
rt	room temperature
sat.	saturated
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-	*tertiary*
$(Thex)BH_2$	thexylborane
TES	triethylsilyl
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
p-TsOH	*para*-toluenesulfonic acid
p-TsCl	*para*-toluenesulfonyl chloride
Ts	toluene sulfonyl (tosyl)
UV	ultraviolet
X4	hexanes

Xp	Evans auxiliary
μmol	micromole
Z	*zusammen* (together)
<	less than
>	greater than

Contents

Chapter Four: Experimental

Appendices

Chapter One:

Introduction

1.1 Natural Products Chemistry

1.1.1 A Historical Perspective

Natural products chemistry is a science as old as mankind itself, manifesting itself in the preparation of food, pigments, fibres, toxins, medicinals, fragrances and stimulants.[1,2] The science has evolved over many centuries, beginning with trial and error testing of extracts from plants and other natural sources by healers and shamen.[3] However, it wasn't until the late 19th century with the inception of modern science that the true properties of extracts of natural products really began to arouse the curiosity of scientists. It was then that scientists began to separate, purify and analyse compounds produced by living cells.[1,4] This gave access to the pure active ingredients which generally displayed greater potency than the crude extracts.[3]

Initially structural elucidation was carried out by degradation of the compound into smaller fragments of known structure, coupled with elemental analysis and reactivity pattern studies.[1] These studies led to the discovery of a wealth of new reactions and rearrangements. However, it wasn't until the birth of spectroscopic techniques such as UV, IR, MS and NMR that natural products chemistry evolved into what it is today, where milligram or even sub-milligram quantities of target metabolites can be isolated, purified and characterised without destruction of the material under investigation. As a result, organisms that have previously been studied can be revisited and those that were once considered too small or rare for adequate research can be sampled and tested.[4]

As the usefulness of natural products became increasingly relied upon, the need for preparative procedures grew. As more novel structures and structural features emerged, new methods were required and developed, continually pushing the boundaries of organic synthesis and inspiring increasingly sophisticated analytical methodology. As such, natural products chemistry has contributed invaluably to the enormous body of reactions, rearrangements and techniques that modern day chemists rely heavily upon.

1.1.2 Secondary Metabolites

Natural products chemistry as it is known today concerns mainly the formation, structure and properties of secondary metabolites, that is those compounds that are produced by living organisms that are not part of the organism's primary metabolism, but contribute to the survival of the organism.[1] Over the last several decades a set of principles governing the biosynthesis of natural products have been arrived at, leading to several distinct classes of natural products based on the structural units they incorporate or are derived from.[1] These biosynthetic principles contribute not only to structure elucidation by the exclusion of so-called "unnatural" structures, but also provide valuable information to the synthetic chemist who can try to mimic these processes in the laboratory.

Secondary metabolites, isolated from both terrestrial and marine sources, are a rich source of pharmaceutically important compounds. Recent reports indicate that natural products and their derivatives, mimics or compounds inspired by them make up approximately 40% of all current trade drugs.[5,6] In fact, in antibiotic and anticancer research, up to ¾ of all drugs are natural product derived.[5] This makes new secondary metabolites prime candidates for future drug development and an extensively explored area of research throughout the world.

1.2 Polyketide Natural Products

Polyketides are considered not only the largest class of secondary metabolites that share a common biosynthesis, but are also one of the most interesting classes of natural products due to their enormous structural diversity and broad spectrum biological activities. Although the role of polyketides in their native organisms is largely unknown, an extraordinary range of pharmaceutical properties have been identified amongst this group of naturally occurring compounds.[7]

Apart from the penicillins, polyketides are the most important chemical class of antibiotics,[8] but their scope of biological activity also includes anticancer,

immunosuppressant, antifungal, anticoagulant, cholesterol lowering and antiparasitic properties.[9-12] There are 5000 to 10000 known polyketides, 1% of which have been shown to possess drug activity.[9,10] This is approximately five times the average found in all natural products combined, making polyketides one of the most important sources for discovery of new and potential drug molecules.[9,10] The combined sales of the more than 40 polyketide pharmaceuticals on the market generate more than $25 billion a year,[13] and it is the unrivalled array of biological activities and the enormous commercial value of polyketides that drives current research.[14] Figure 1.1 shows some examples of natural polyketides that have achieved success as commercially available pharmaceuticals.

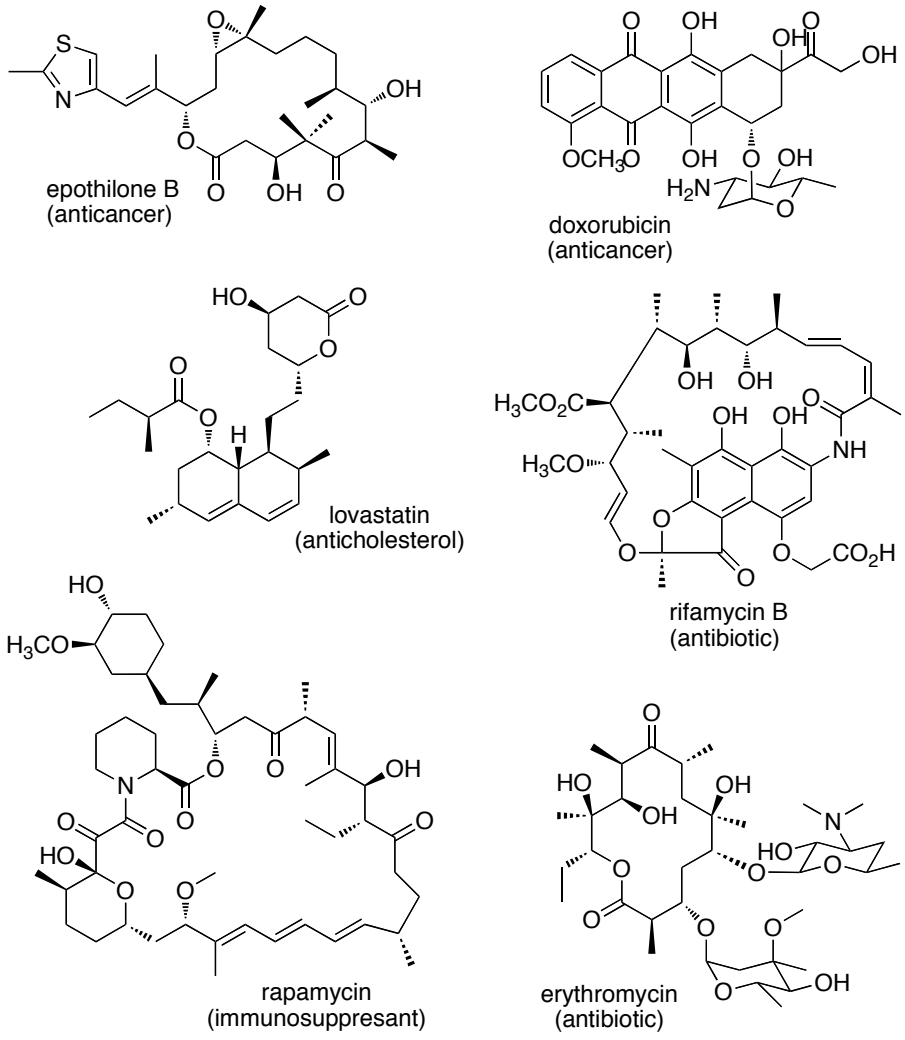
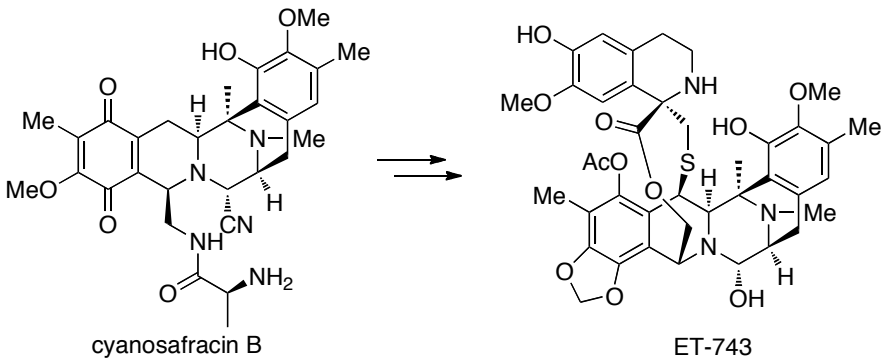


Figure 1.1: Commercially available polyketide natural products.

The concentration of many highly active polyketide compounds inside their host organism is often minute, in the millimolar and even micromolar range, often constituting as little as 10^{-6}% of the net weight of material.[15,16] As a consequence of their limited availability in nature, isolation can be difficult and results in the undesirable destruction of many kilograms of the organism to obtain these products. For example, in order to obtain approx. 1 g of the alkaloid anticancer agent Ecteinascidin-743 (ET-743), approximately one metric tonne of the host organism has to be harvested and extracted.[15] To conduct clinical studies, gram quantities of a compound are required, and if this compound were to be licensed and marketed as a drug, to isolate the quantities required would undoubtedly result in the extinction of the host species if it were the sole source of the drug.[16] Fortunately, ET-743 can be mass-produced *via* a partial synthesis from the antibiotic cyanosafracin B, a precursor compound that can be obtained by bacterial fermentation (scheme 1.1).[17]



Scheme 1.1: Partial synthesis of ET-743 from cyanosafracin B.

Their medicinal potential, combined with their challenging structural complexity, makes polyketides an attractive synthetic target. Due to the minute quantities of natural product typically obtained, assignment of the absolute or even relative configuration can be difficult and tentative. Therefore, despite the emergence of powerful methods such as NMR spectroscopy for structure determination, partial or complete stereocontrolled syntheses and biosynthetic studies are still required not

only for biological testing, but to validate stereochemical detail in large, highly functionalised molecules.[18,19]

1.2.1 Biological Activity

Up until the mid 1980s, most of the research into marine natural products was focused on the chemistry of new compounds, rather than their biological activity. It wasn't until the provision of research funding was linked with a compounds bioactivity that this became the primary focus of marine natural products chemistry.[12] As such, comprehensive biological testing of many polyketides that were discovered prior to this period was not carried out. Most compounds were typically tested only for antimicrobial activity, and this was only later extended to testing for cytotoxicity as interest in anti-cancer agents grew.[12]

Polyketides exhibit a vast array of higher than average pharmaceutical activities, making them highly useful as ready-made drugs or lead compounds. However, this is invariably not the same function that it exerts in the native organism, and quite often its role in the organism is not even known. Typically, polyketides are produced by an organism as a defense mechanism (and are generally believed to also act as pigments, virulence factors and infochemicals)[20] and as such are prevalent in the marine environment due to the lack of morphological defense structures such as spines or shells in soft-bodied sessile or slow-moving invertebrates.[15] In fact, it has been postulated that shell-less molluscs evolved by loss of the shell after the ancestral mollusca acquired defensive chemicals through their diet.[21] These compounds are secreted to help deter predators, keep competitors at bay or paralyse their prey.[22] Therefore these compounds have obviously been designed by nature to interact with macromolecules such as DNA and proteins and hence alter their function.[3] As such, the evolutionary optimisation of these natural compounds ensures that they have far better odds of showing biological activity than random synthetic compounds.[3,23]

Some of the most highly toxic non-peptide toxins in nature also belong to the polyketide family and are isolated from marine creatures. These compounds, which pose a risk to humans who consume seafood, are paralytic, diarrhetic or amnesic shellfish poisons.[12] The most potent, maitotoxin and palytoxin, both have highly complex and enormous polyether structures. The structural elucidation of both these compounds and the total synthesis of palytoxin (figure 1.2) are considered some of the greatest feats ever achieved in organic synthesis.[21,24-30] Unfortunately, it is precisely these incredible achievements which have deterred interest from the study of marine toxins as smaller and less complex structures are no longer considered challenging.[21] It is however important to study these toxic compounds so that consumption can be avoided or treated. Nevertheless, potential medicinals remain the driving force for polyketide research due to their commercial value and synthetic complexities.

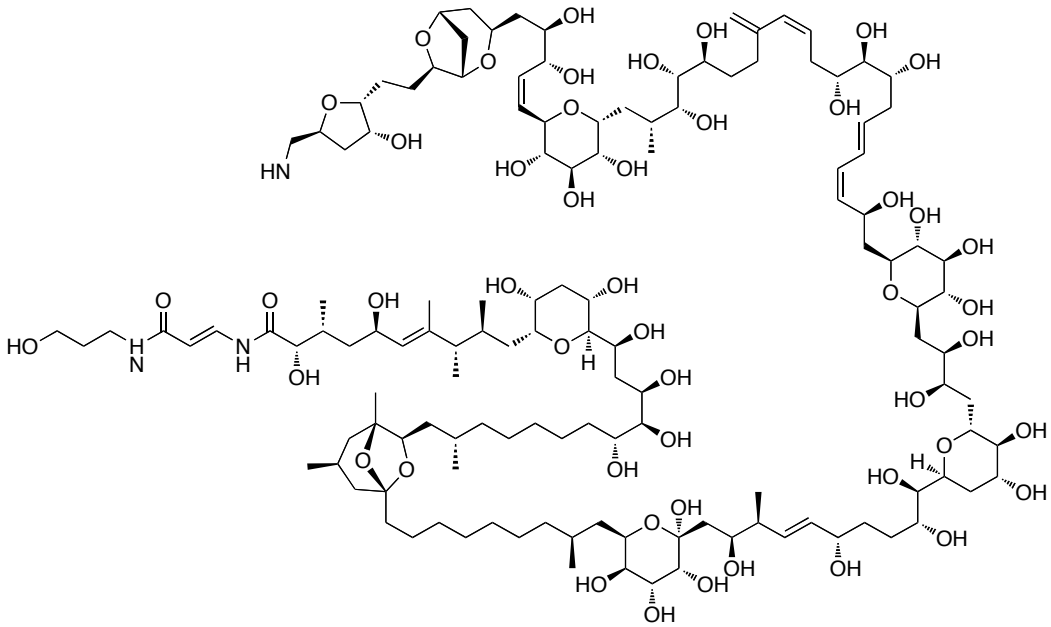


Figure 1.2: The chemical structures of the marine toxin palytoxin (PTX).

Discussion of the biological activity of polyketides, particularly given their role inside the native organism is not necessarily the same as in human cells, pre-empts a

discussion of the origin of such activity. Of course, millions of years of adaptation and natural selection by the native organism has resulted in an arsenal of highly useful compounds which also must have the ability to reach a specific site of action.[5] Less obvious however is the hypothesis that certain compounds or groups of compounds bind to specific and highly conserved, or otherwise structurally related protein domains, regardless of the organism expressing them.[5] This theory is supported by the observation that two structurally but not functionally related proteins can be inhibited by natural product derivatives, and the fact that the native biological target is usually different from the pharmaceutical target.[5]

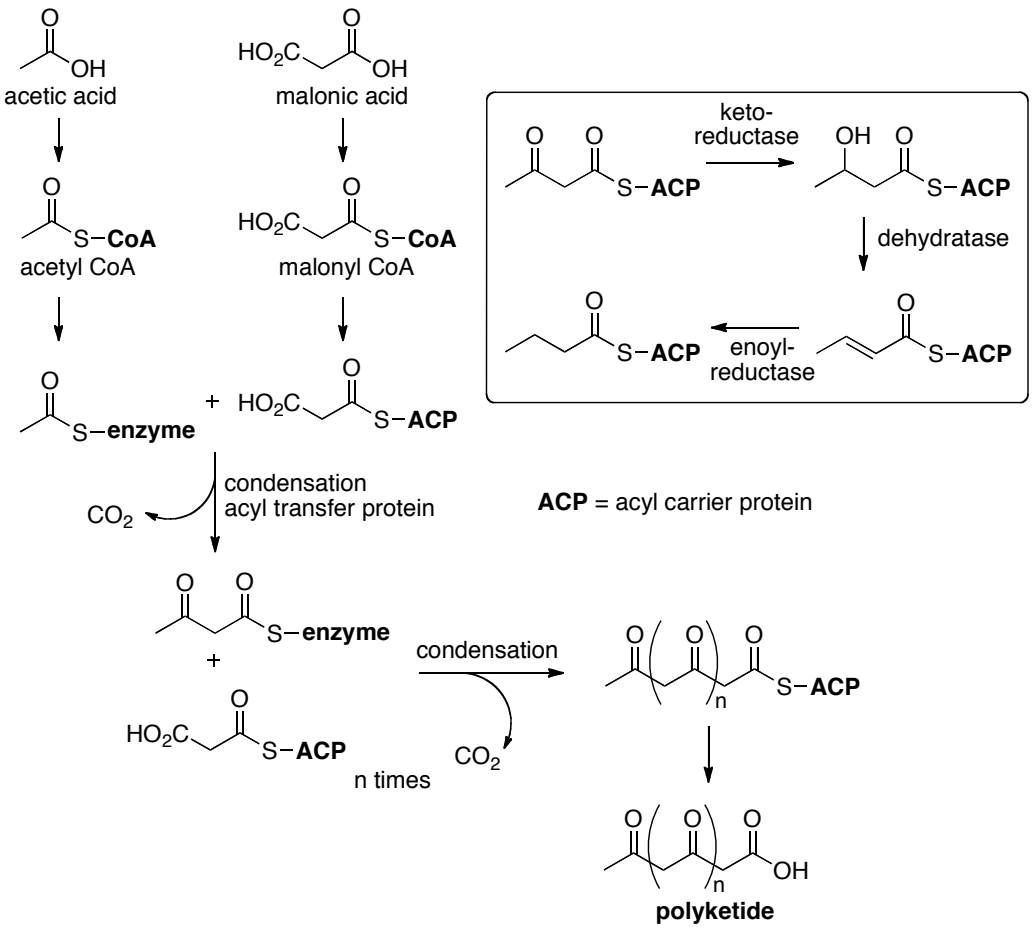
Unfortunately, many compounds that have shown excellent pharmaceutical potential are simply too complex and costly to synthesise for clinical purposes.[16,12] These compounds are more useful as lead compounds, for unless a compound or a derivative thereof can be readily and economically manufactured it is of little commercial interest to the pharmaceutical industry.[12] While bulk production of these metabolites by synthesis or fermentation can be highly impractical, technology is leaning towards the cloning of biosynthetic gene clusters.[31] It is also hoped that by manipulating DNA to add, subtract or swap sections of the genetic code in the "assembly line" in a combinatorial fashion, libraries of 'unnatural natural products' can be generated which may be of pharmaceutical importance as new drugs or leads.[3,13] To date this relatively new approach has lead to over 100 new compounds, some of which have shown potential drug activity.[13]

1.2.2 Biosynthesis

Polyketides are synthesised in nature by the stepwise building of long carbon chains, two carbon atoms at a time, by exceptionally large, complex and multifunctional enzyme clusters called polyketide synthases (PKSs).[8] These highly complex proteins are organised into coordinated groups of active sites (modules), in which each module is responsible for catalysis of one cycle of polyketide chain elongation and the associated functional group modification.[7] This process is a complicated one and can involve up to a hundred different enzymes.[13] The order,

number and type of these catalytic domains determines the chain length, oxidation state, pattern of branching, cyclisation and stereochemistry of the resulting natural products in a combinatorial fashion to produce an enormous variety of structures.[8]

In simple terms, the primary role of the PKS is to facilitate the condensation of small organic acids to form long carbon chains. These acids, typically acetic acid and malonic acid, are in the form of their activated derivatives – coenzyme A (CoA) thioesters. Successive linear Claisen condensation of these units with loss of CO_2 gives rise to poly-β-ketoesters (polyketides) (scheme 1.2). Each module on the PKS contains a carrier protein domain at the heart of the module to which the growing chain is tethered and which ensures the growing chain is shepherded correctly amongst the various active centres.[13] Each module also includes an acyl transferase to load the extender unit onto the enzyme, a ketosynthase to perform the condensation, and exactly those reductive activities required to generate the desired functionality at the β-carbon as each unit is added.[8] The β-keto group can either remain intact or be reduced to a hydroxyl, olefin or methylene functionality by the reductive enzymes ketoreductase, dehydratase and enoyl reductase (scheme 1.2). This cycle is repeated until the action of a terminating domain releases the chain. The intermediate linear precursor is highly reactive and is temporarily stabilised by chelation or hydrogen bonding to the enzyme surface so that it does not cyclise before assembly is complete.[1] The topography of the enzyme then dictates the mode of cyclisation.



Scheme 1.2: Simplified schematic of linear polyacetate chain construction by condensation of small organic acids.

Enormous variation in the final polyketide structure results from a number of variables in the biosynthetic process. First, the "starter" unit can theoretically be any acyl coenzyme A found in nature, but is typically either acetyl-CoA or propionyl-CoA. The "extender" units can also vary by addition of acetate, propionate or butyrate units, as their malonyl-CoA equivalents. The latter two lead to methyl and ethyl side chains respectively and the introduction of a chiral centre which can have one of two configurations. The number of such ketide units added dictates the chain length, and the resulting keto groups can be left untouched, modified or removed. If reduced to a hydroxyl group, this also creates a new stereogenic centre, while olefinic bonds can have *E* or *Z* geometry. Finally, the linear polyketide can

cyclise to give aromatic compounds, or lactonise to give macrolides and other "tailoring" enzymes can introduce sugars or other new functional groups at varying positions.[8] Variation can also come from condensation of separately produced polyketides and secondary processes such as halogenation, alkylation, rearrangements, etc.[1]

1.2.3 Sources of Novel Bioactive Compounds

Most polyketides are made by bacteria and fungi, though they have also been isolated from plants and animals, so the primary approach to date has been to scour the soil and the oceans for previously undiscovered microorganisms and to isolate and test the metabolites they produce.[13] As there are still an enormous number of microorganisms yet to be characterised, particularly in the marine environment which is a relatively recent searching ground, this approach will continue to reveal novel bioactive compounds for a long time to come.[13,32] Novel structures of therapeutic potential are also being created in the laboratory by modification of existing natural structures, or by manipulation of the genetic code to incorporate new features or modify existing features generated by the organism.

It is generally believed that the diversity of organisms in the marine environment is greater than that found in the terrestrial environment. Indeed, the world's oceans cover more than 70% of the Earth's surface, house 34 of the 36 phyla of life represented on Earth and more than 300 000 known species of plants and animals (only a small percentage of those yet to be discovered).[16,31] Despite this fact, marine natural products chemistry is only now beginning to reach maturity. This is largely due to the accessibility of marine habitats, with advances in diving technology opening up vast and yet unexplored areas in recent years.[2] Every year an increasing number of new marine polyketides are reported in the literature, and this is expected to continue for many years to come as more marine environments become accessible and interest in this area continues to escalate.[33,34] Of the marine creatures studied to date, a seemingly endless parade of novel structures have been

isolated.[21] These structures have great potential as pharmaceuticals, nutritional supplements, cosmetics, agrichemicals and enzyme mimics, all of which have prospective marketability.[31]

Many terrestrial polyketide natural products have made it onto the market as licensed drugs, such as the antibiotic rifamycin, which is biosynthesised by the soil-dwelling bacterium *Amycolatopsis mediterranei*. However, no marine polyketide has yet reached this stage due to the relatively recent emergence of the marine environment as a viable searching ground for polyketides. It is estimated that there are over 14,500 marine natural products currently known, 20 of which have shown promising progress in clinical development, and a growing number of marine natural products are entering clinical trials every year.[19,35] The most advanced marine natural product in clinical trials is the alkaloid (not polyketide) anti-tumour agent ET-743, which is currently in phase III trials. Some polyketides of marine origin are currently involved in phase II trials, including bryostatin (anticancer), dolastatin 10 (anticancer) and curacin A (antimitotic) (figure 1.3).[21]

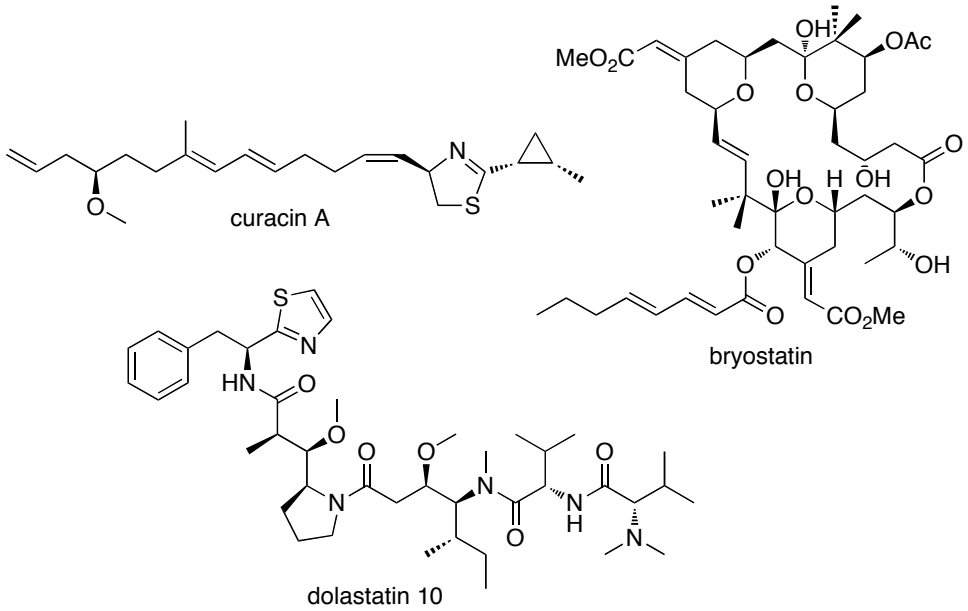


Figure 1.3: Marine polyketides currently in clinical trials.

The polypropionates, a major structural sub-class of polyketides resulting from the condensation of multiple propionate units, have received a lot of attention owing to their complexity and biological potential. Over the last 40 years polypropionates have been isolated from marine organisms ranging in diversity from bacteria to sponges.[36] In particular, the Mollusca have been identified as the most important source of marine polypropionates, often giving rise to structures belonging to a rare group that are entirely propionate unit derived.[36] Some such metabolites have been demonstrated to display biological activity and a select few have gone on to clinical trials as potential pharmaceuticals. Studies into terrestrial polypropionates have shown considerably more progress in this area, owing to the several decades head start that terrestrial natural products chemistry has enjoyed. The marine environment as a source of polypropionates is literally an enormous pool of potential for further discovery in this area.

The successive polymerisation of propionate units results in a structure containing multiple contiguous stereocentres carrying alternating centres of oxygenation and methylation (the polypropionate motif). These compounds (containing multiple propionate units, though not necessarily strict polypropionates) can be highly complex in structure with multiple ring systems, such as auripyrone A[37] and discodermolide,[38] or simpler and even acyclic, such as pteroenone[39] (figure 1.4). The installation of these motifs has been an ongoing challenge to synthetic chemists and remains a topic of intense research interest.[40] Many stereocontrolled strategies for installing these arrays have been developed and more efficient and selective methods are continually pursued. Perhaps the most important and widely utilised reaction in polypropionate synthesis is the aldol reaction because it gives immediate access to the polypropionate motif, and will be described in more detail in section 1.3.1.

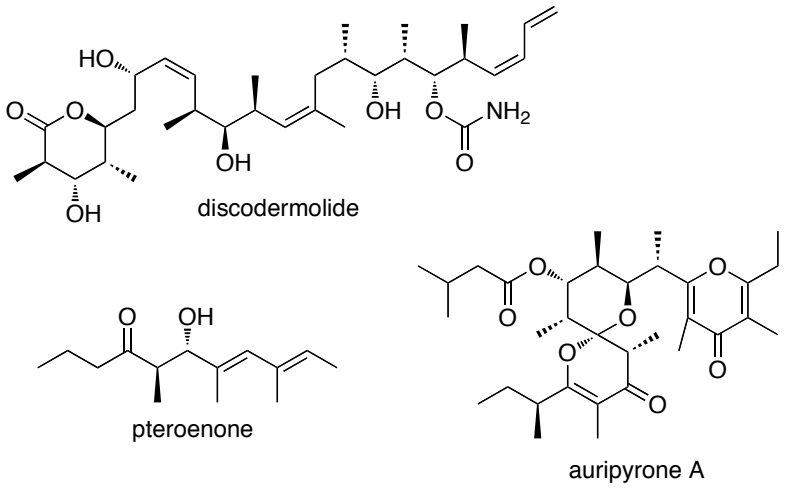
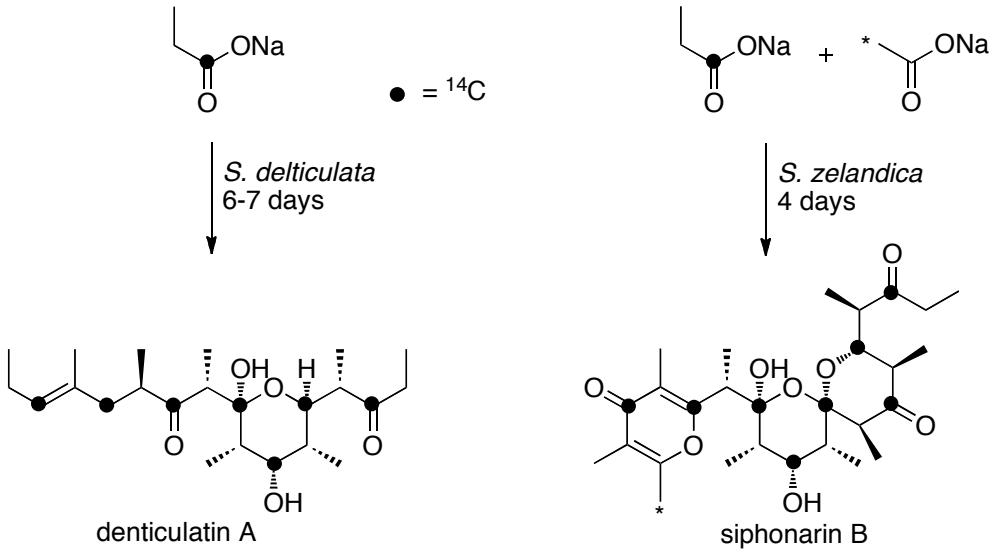


Figure 1.4: Structures of the polyketide natural products discodermolide, auripyrone A and pteroenone.

Traditionally, ^{14}C labeled acetate-feeding studies were conducted to determine the starter units for polyketide synthesis in nature. This method required degradation, separation and isolation of the sample into single carbon units for radioactive testing and complete biosynthesis elucidation.[1] These studies showed in many cases that what appears to be a propionate unit is in fact derived in nature from an acetate-methionine pathway, whereby the methyl group is introduced by methionine after condensation of the acetate units.[36] These studies served to highlight a significant difference in the biosynthetic approaches of bacteria and fungi, in that bacteria use propionate units for macrolide and polyether synthesis, while there are a very limited number of examples of propionate-based biosynthesis in fungi.[36] Scheme 1.3 shows the outcome of isotope labeled feeding experiments in the organisms that produce denticulatin A (*S. denticulata*) and siphonarin B (*S. zelandica*).[36] Denticulatin A was shown to be entirely propionte unit derived, while siphonarin B incorportates a single acetate unit and eight propionate units.



Scheme 1.3: ^{14}C acetate and propionate feeding studies to produce isotopically labeled denticulatin A and siphonarin B.[36]

1.2.4 Structural Features of Polyketides

The enormous scope for variation in the biosynthetic process, coupled with modifications that can be made in the laboratory, suggest an almost infinite array of structural diversity for polyketides. Limitations are however inherent in the biosynthetic process, which excludes certain 'unnatural' structural features.[41] Polyketides are characterised by their make-up from acetate, propionate and (less commonly) butyrate units, and their β-polyoxygenated carbon backbones. Methylation can also occur at other carbon, oxygen or nitrogen atoms in the structure, which cannot be explained by the biosynthetic process represented in section 1.2.2. This structural feature results in nature from addition of a one carbon fragment by methionine, formate, formaldehyde, serine or glycine.[1]

1.2.4.1 Structural Sub-Classes of Polypropionates

Polypropionates are loosely divided into three further structural sub-groups: polyethers, macrolides and spiroketals.[10] Polyether antibiotics usually contain a

mixture of 1,2- and 1,3-diols and these alcohol groups are frequently etherified (lonomycin C), esterified or bound into spiroketals (lonomycin C and calcimycin) (figure 1.5).[42] These compounds act by encapsulating cations in nature and creating a hydrophobic environment around them so that they can be transported in and out of cells.

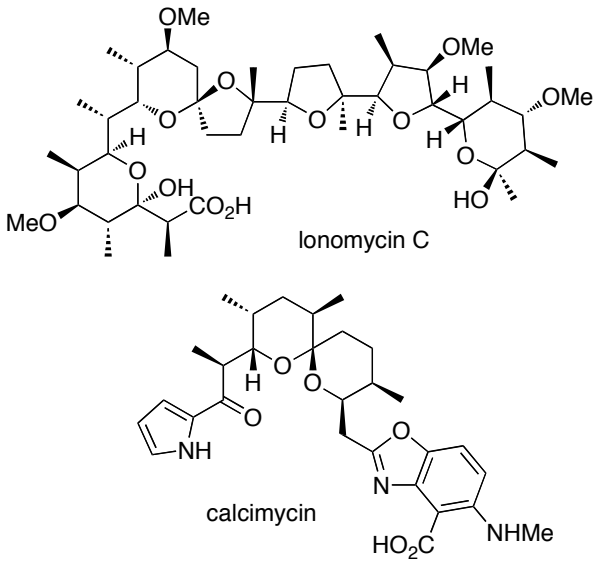


Figure 1.5: Polyether antibiotics lonomycin C and calcimycin.

Macrolide antibiotics are a large class of polyketides characterised by the presence of a macrocycle containing the lactone moiety. There are four main types of macrolides: polyoxo, ionophore and ansamycin, which all display antibacterial activity, and the polyenes, which typically display antifungal activity. The polyoxo macrolides have 12, 14 or 16 membered rings that are constructed from acetate and propionate units, though the 16-membered rings also incorporate a single butyrate unit.[42] These structures also incorporate at least one carbohydrate unit, usually in the form of an amino sugar, as in erythromycin A. Ionophores are formed by the cyclopolymerisation of two or more carboxylic acids and are able to transport alkali metal cations through biological systems (eg. Nonactin, figure 1.6).[42] The ansamycins typically contain an aromatic nucleus bridged through non-adjacent

carbons, such as in rifamycin S (figure 1.6), and are frequently associated with powerful anti-tumour activity.[42] Polyene macrolides are characterised by the presence of a conjugated polyene moiety and a low degree of alkylation on the lactone ring, eg. amphotericin B (figure 1.6).

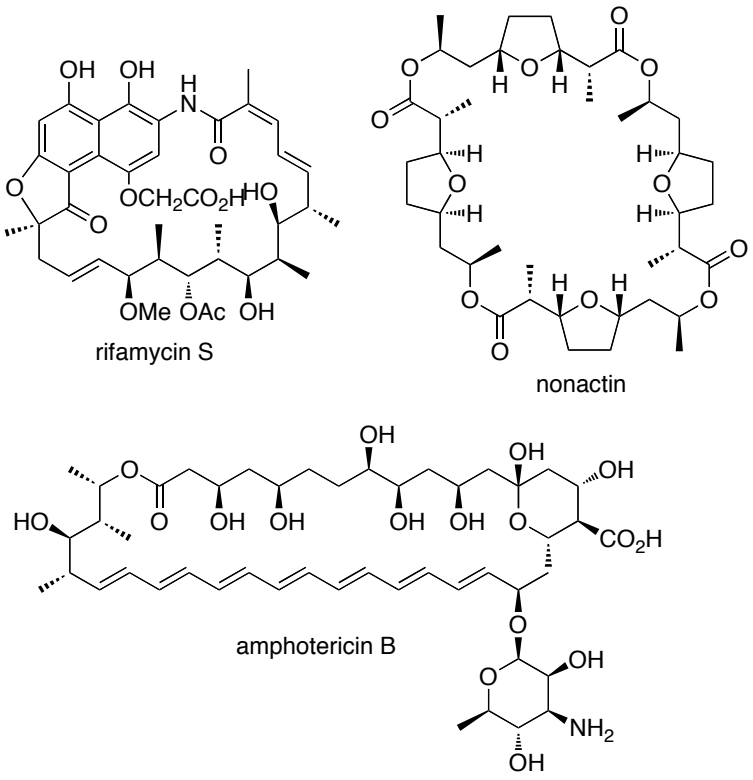


Figure 1.6: Macrolide antibiotics erythromycin A, nonactin, rifamycin S and amphotericin B.

The spiroketal unit is a common structural feature found in polyketides isolated from almost all walks of life and is often associated with pharmacological activity. These structural units consist of a cyclic ketal in which two rings are joined by a single atom, the spiro atom, and the two ketal oxygens that are attached to the spiro atom each form part of one of the rings.[43] There are three main types of ring systems observed in spiroketals and most spiroketal containing natural products fall into one of these structural categories: [6,6]-spiroketals such as the diarrhetic shellfish toxin okadaic acid; [6,5]-spiroketals such as the protein phosphatase

inhibitor calyculin A; and [5,5]-spiroketals like asperketal A (figure 1.7).[44,18] Interest in the synthesis of spiroketal containing natural products has grown over the past two decades as an increasing number of pharmacologically active spiroketals are identified.[44]

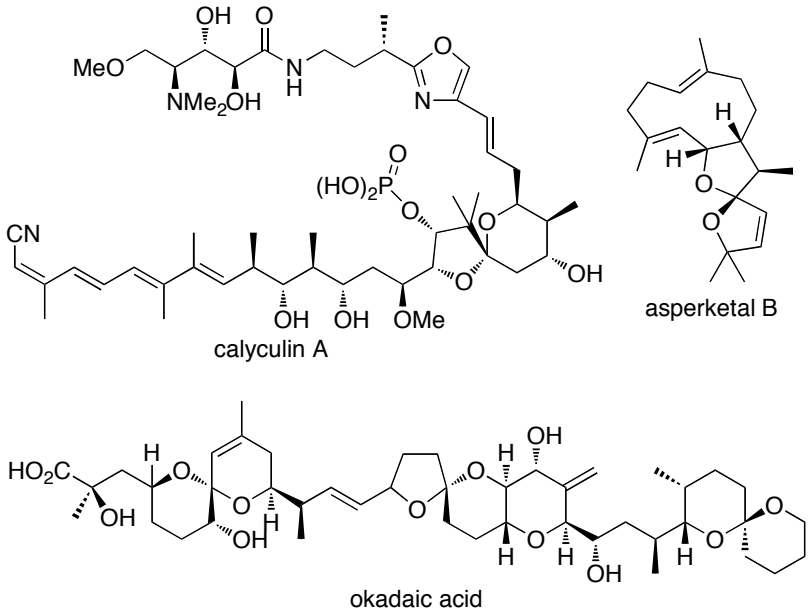


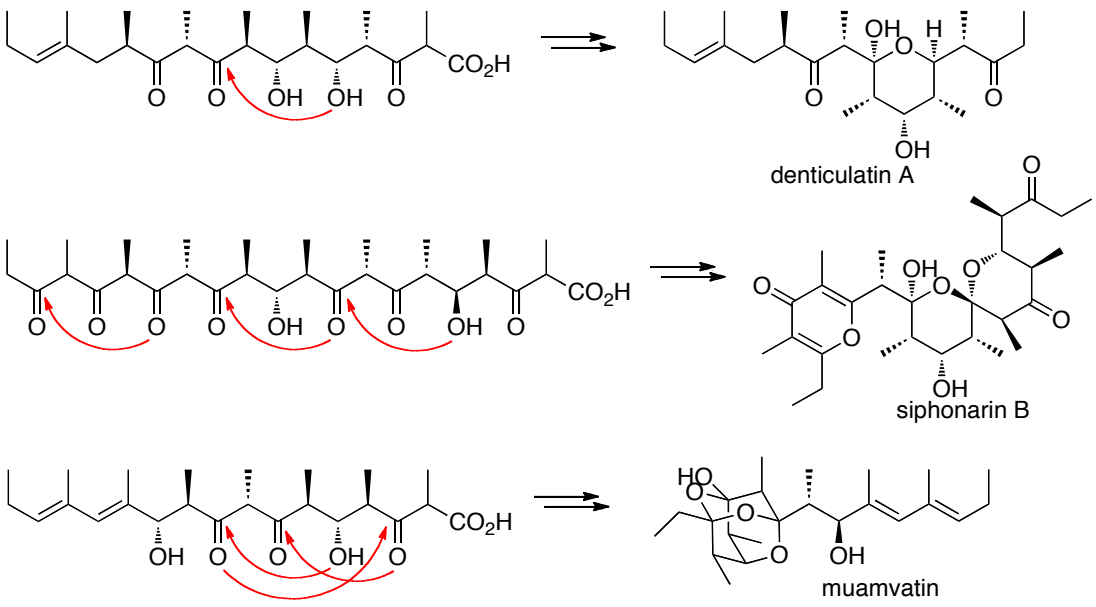
Figure 1.7: Spiroketal containing polyketides calyculin A, asperketal and okadaic acid.

1.2.4.2 Cyclisation Modes

The polyketide structural motif contains many electrophilic (eg. carbonyl carbons) and nucleophilic (eg. hydroxyl groups and carbons situated next to carbonyl groups) sites, making them highly susceptible to intramolecular cyclisation reactions. Other thermodynamically favoured processes may also accompany cyclisation, including dehydration, rearrangement or cycloaddition reactions.

Six membered oxygen heterocycles are a common feature of many polyketides, and a number of different cyclisation modes account for these motifs. They result from nucleophilic attack of an oxygen atom on an electrophilic carbon atom situated 5

carbon atoms away on the polyketide chain. The modes of cyclisation of polyketides are determined by unraveling the ring structure in a retro-synthetic fashion to reveal the proposed biosynthetic linear precursor. Often this reveals several possible modes of cyclisation, however typically the most thermodynamically favoured mode is preferred, leading to the most stable product. Cyclisation proceeds *via* a six membered chair transition state in which the most stable conformation is the one in which the largest and most sterically demanding groups are situated in an equatorial position, while the anomeric effect is responsible for hydroxyl groups assuming the axial position when situated on a carbon adjacent a heteroatom. The stereochemistry of the compounds dictates the precise positioning of the substituents on the ring. The thermodynamically favoured mode of cyclisation of a number of polypropionates is highlighted in scheme 1.4.[45] Interestingly, these 3 compounds share a common 5-propionate unit motif, however they display very different modes of cyclisation due to the effects discussed above.

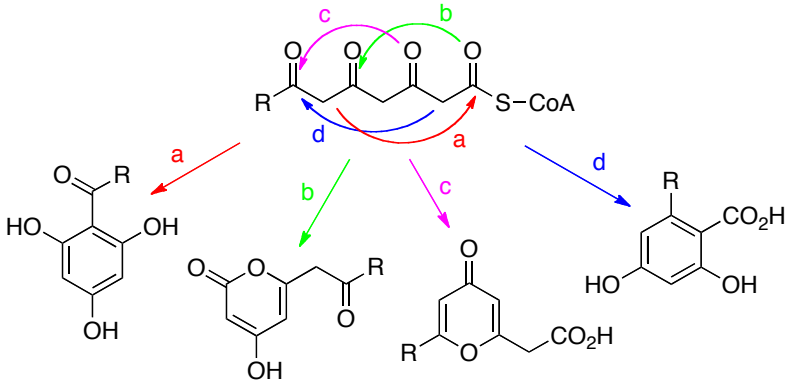


Scheme 1.4: Thermodynamic cyclisation modes for the related siphonariid metabolites denticulatin A, siphonarin B and muamvatin.[46]

It has been postulated that the formation of some cyclic acetals occurs as a result of thermodynamic cyclisation during the isolation process rather than as a result of enzymatic processes inside the organism.[45,46] This theory is supported by the observation that the cyclic product is typically the thermodynamic product, a process which does not require enzymatic intervention.[47] This was highlighted by Paterson and Perkins who observed the same stereochemical arrangement in the linear precursor to muamvatin and the related siphonariid metabolites siphonarin B and denticulatin A (scheme 1.4, above).[45,46] Cyclisation of the linear precursor to form the trioxaadamantane ring in muamvatin was achieved readily upon silica gel, which suggests that muamvatin is an artifact of the chromatographic purification process used in the isolation of the natural product and that the natural product is in fact an unstable acyclic polypropionate.[46] The natural product status of several other polypropionates has been called into question as their elucidated structures are believed to arise *via* dehydration or rearrangement upon isolation.[36]

This observation does not however hold true for all cyclic acetal polypropionates. Spiroacetal formation from the dihydroxy ketone linear precursors is a highly thermodynamically favoured process and these are almost certainly formed inside the organism. In fact, this type of cyclisation is almost impossible to prevent, particularly under acidic conditions.[44]

Aromatic antibiotics are one of the major groups of polyketides and the planarity of these compounds is an important factor in their bioactivity.[48] The cyclisation modes that lead to aromatic polyketides are summarised in scheme 1.5. If we consider the tetraketide unit shown scheme 1.5, the activated methylene groups act as nucleophiles upon enolisation by removal of a proton, as do the oxygen atoms due to their lone pairs. The carbonyl carbons have carbonium ion character and are thus the electrophiles. Interaction of these active sites leads to an array of possible cyclisation modes giving rise to the aromatic products shown.[1,49] Penta- and higher order ketides have several additional cyclisation pathways available to them and this can lead to a vast number of fused and tethered biaryl and polyaryl systems incorporating both the carbocyclic and heterocyclic aromatic units.



Scheme 1.5: Cyclisation modes of a tetraketide to give carbocyclic or heterocyclic aromatic polyketides.

The α-pyrones, formed *via* pathway b in scheme 1.5 above, are a class of polyketides that are of significance to this research project. These compounds share a common structural motif of a six-membered cyclic unsaturated ester (lactone) that has chemical properties related to alkenes and aromatic compounds (figure 1.8).[50] This structural moiety is prevalent in a diverse range of species and is involved in many key biological processes including defense and intercellular communication.[50] Many biologically important compounds contain the α-pyrone moiety, including pheromones, coumarins and elasnin, and they have broad spectrum pharmaceutical properties including use in the treatment of HIV, Alzheimer's disease and cancer.[50] 4-hydroxy-α-pyrones (figure 1.8) in particular have become one of the most important classes of anti-HIV agents.[51]

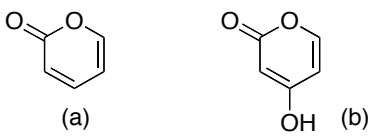


Figure 1.8: The α-pyrone (a) and 4-hydroxy-α-pyrone (b) moieties.

1.3 Asymmetric Synthesis of Natural Products

For chiral compounds, particularly those with drug activity, it is often imperative that they are synthesised as single isomers. While it is typically only one isomer that displays the desired activity, sometimes its enantiomer can display entirely different and often detrimental activity on biological systems. For example, the infamous thalidomide, where the (*R*)-enantiomer has sedative and hypnotic effects, while the (*S*)-enantiomer is potently teratogenic; or timolol, which has only one active isomer that acts as an adrenergic blocker (figure 1.9).[42] Synthesis of a single isomer also helps in the determination of the absolute stereochemistry of a natural product. Several asymmetric synthetic methods exist which have evolved as a response to this crucial requirement of enantio- and diastereopurity. These include the asymmetric reduction of carbonyl compounds by addition of nucleophiles to α-chiral carbonyls or addition of chiral nucleophiles to carbonyls, addition of chiral or achiral allyl and crotylmetal reagents to chiral or achiral aldehydes, hydroboration or conjugate addition to alkenes and free radical processes.[52]

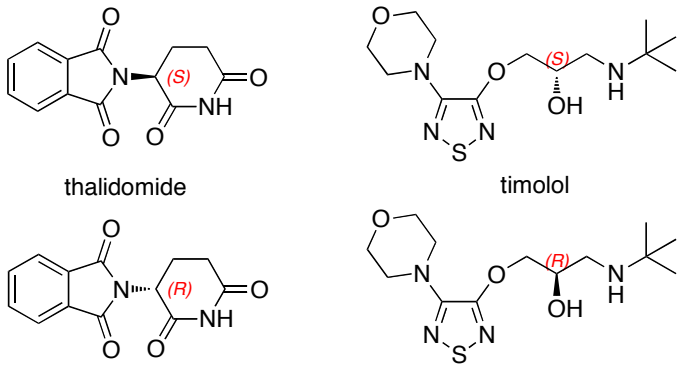


Figure 1.9: The (*R*)- and (*S*)- enantiomers of thalidomide and timolol.

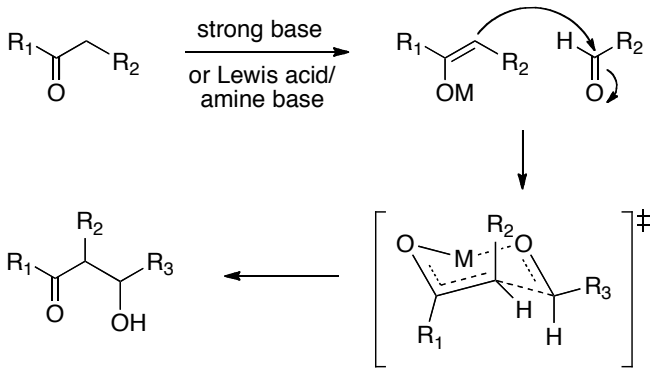
Pericyclic reactions are also a very important class of asymmetric reaction, including the Diels-Alder and hetero-Diels-Alder reactions, the [3,3]-Claisen, Cope, oxy-Cope and Ireland-Claisen rearrangements, the [2,3]-Wittig rearrangement and the ene reaction. However, perhaps no reaction is more important to polyketide synthesis

than the aldol reaction, as it is an efficient method for installing the characteristic carbon chain bearing oxygen atoms at alternating positions, often incorporating multiple contiguous stereocentres.

1.3.1 The Aldol Reaction

The aldol reaction has found widespread application in the synthesis of polyketides (particularly polypropionates), not only because it is a major C-C bond forming reaction, but because it leads to the installation of up to two new stereocentres and the β-polyoxygenation that is characteristic of polyketides.[53] Furthermore, this type of reaction can lead to the formation of C-C bonds in a regio-, stereo- and enantioselective manner.[54]

The aldol reaction traditionally involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β-hydroxyketone, a structural motif common to many polyketide natural products. Enolate formation is facilitated by a strong base or Lewis acid/weak base and the reaction proceeds *via* a rigid six-membered chair transition state in which the enolate metal coordinates to the aldehyde oxygen, defining the stereochemistry of the aldol product (scheme 1.6).

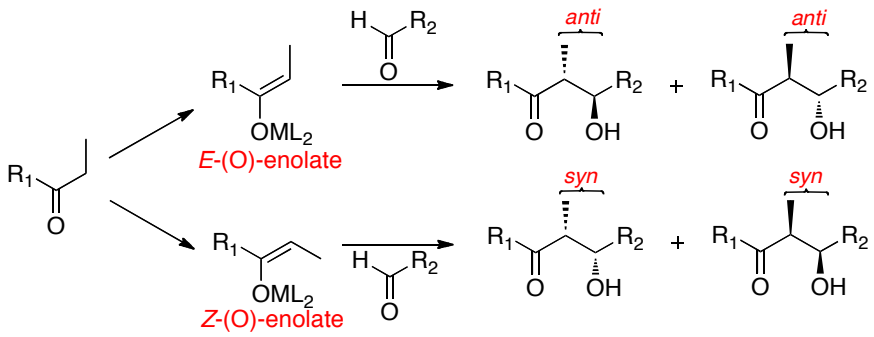


Scheme 1.6: Mechanism for the aldol reaction.

Addition of ethyl ketone enolates to aldehydes results in two new stereocentres and the characteristic alternating methyl and hydroxyl groups of polypropionates. For the purposes of this discussion the use of ethyl ketones will be considered exclusively, though this can be extended to higher order ketones. Achieving selectivity in methyl ketone aldol reactions can be somewhat more difficult and will not be elaborated upon here, but will be investigated further in chapter 2.

1.3.1.1 Enolate Geometry

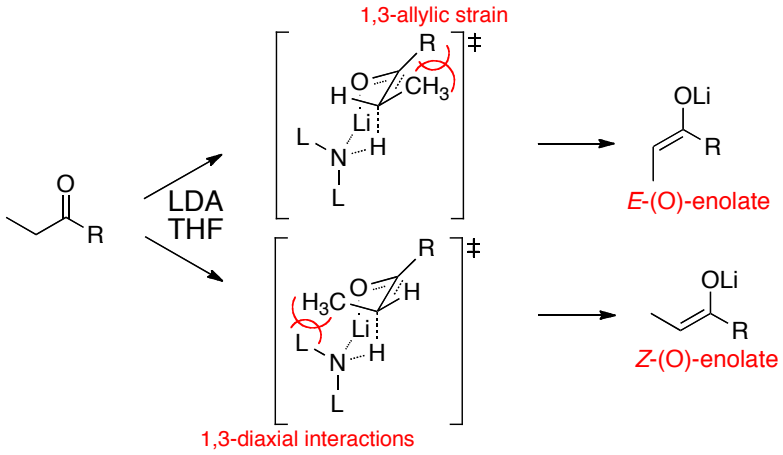
In order to produce a single isomer of an aldol adduct, control of both the geometry of the enolate and the π-face selectivity of the reaction is essential. First, consider the enolate geometry for the reaction between an achiral ketone and achiral aldehyde, from which there are four possible stereoisomers of the resulting adduct. Where *E*-(O)-enolisation is achieved the two products are enantiomeric with an *anti* relationship between the two stereocentres. The *Z*-(O)-enolate adducts are the two enantiomeric *syn* isomers (scheme 1.7). The enolate geometry can be controlled by a number of variables: usually the Lewis acid and base employed for enolisation; the ligands on the Lewis acid metal; substituents on the ketone; and the reaction conditions.



Scheme 1.7: The four possible stereoisomers produced by the reaction of an ethyl ketone enolate with an achiral aldehyde.

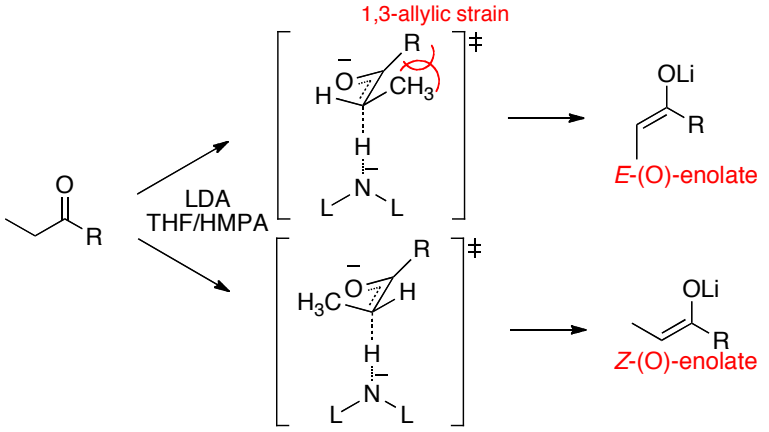
Geometry aside, there is often more than one possible enolate that can be generated when an asymmetric ketone is treated with base. Therefore the first consideration is the regiochemistry of the ketone. Abstraction of the less hindered proton gives rise to the kinetic enolate, while thermodynamic enolisation results in removal of the α-proton that gives rise to the most substituted (and hence most stable) olefin. It is often possible to control which enolate is formed by controlling the conditions of the reaction. For example, low temperatures tend to favour the kinetic enolate, while the choice of base can also play an influential role. An excess of strong, hindered base and a relatively ionic metal oxygen bond favours kinetic enolates, while a sub-stoichiometric amount of base and a more covalent metal-oxygen bond favours thermodynamic enolates.

The stereochemistry of enolate formation from ethyl ketones is influenced by the nature of the R group, the base and the solvent.[52] A six-membered transition state model was proposed by Ireland *et al*.[55] to rationalise the outcome of lithium enolate formation using a dialkylamide base in THF (scheme 1.8). The transition state leading to the *Z*-(O) isomer is disfavoured by 1,3-diaxial interactions between the methyl group on the enolate and the ligands (L) on the nitrogen. This interaction increases as the size of L increases. The transition state leading to the *E*-(O) enolate is disfavoured by 1,3-allylic strain between the R group and the methyl on the enolate, which increases as the size of R increases. This leads to a general rule for lithium enolate formation whereby large ligands on the base favour *E*-(O)-enolate formation while larger R groups favour *Z*-(O)-enolates.



Scheme 1.8: Transitions state models for the enolisation of an ethyl ketone with a lithium dialkylamide base in THF.

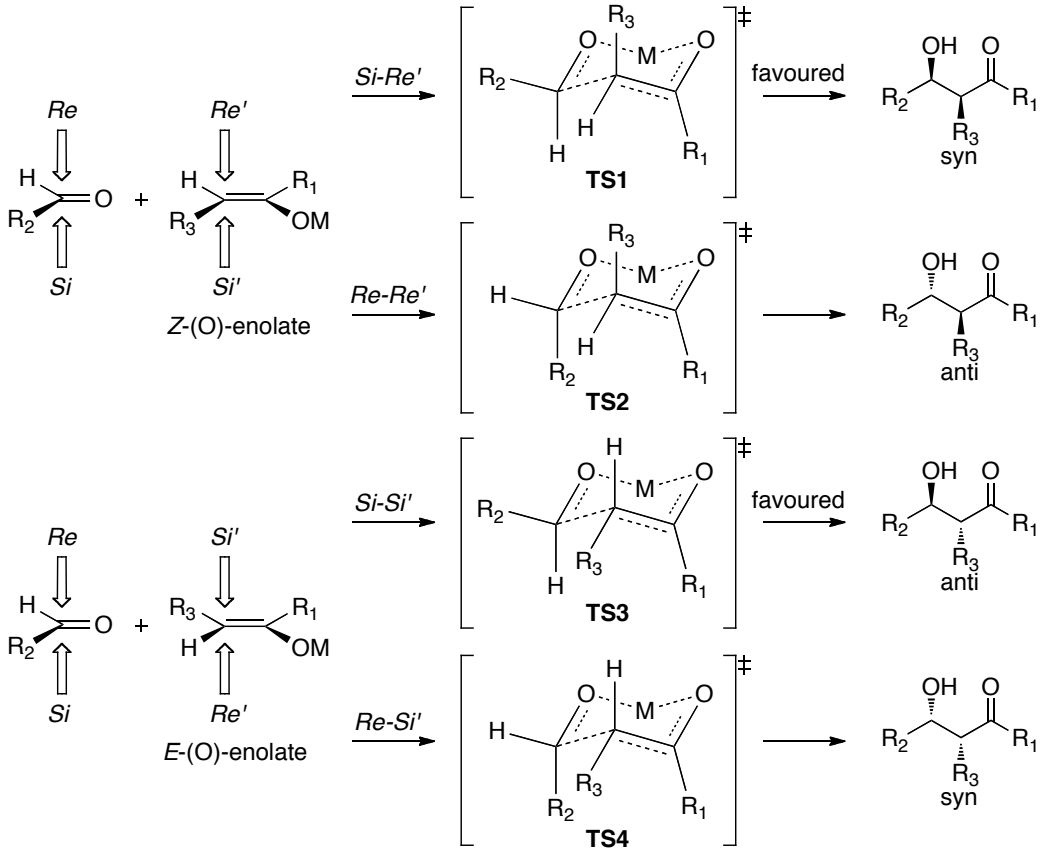
In the presence of HMPA, which acts to solvate the lithium ion in solution, the six-membered chair transition state is interrupted and the 1,3-diaxial interaction is removed from the transition state leading to the *Z*-(O) isomer (scheme 1.9).[52] The 1,3-allylic strain is however still present in the transition state giving rise to the *E*-(O) isomer and therefore *Z*-(O) enolate formation is typically favoured.



Scheme 1.9: Transitions state models for the enolisation of an ethyl ketone with a lithium dialkylamide base in THF/HMPA.

1.3.1.2 π-Face Selectivity

As previously mentioned, the reaction of ethyl ketone enolates with aldehydes gives rise to four possible products (scheme 1.10). The generation of these products is rationalised by six-membered cyclic Zimmerman-Traxler transition states. The four possible transition states shown in scheme 1.10 arise due to attack of the *re* or *si* face of either the *Z*-(O) or *E*-(O) enolate on either the *re* or *si* face of the aldehyde. Each of the chair transition states represented here also has an enantiomeric chair transition state of equal energy, which gives rise to the enantiomeric product (provided R_1, R_2 and R_3 are achiral). *Z*-(O)-enolates favour *syn* products due to destablising 1,3 steric interactions between R_1 and R_2 in **TS2** leading to the *anti* adduct, while *E*-(O)-enolates favour *anti* adducts for the same reason (**TS4**).



Scheme 1.10: Zimmerman-Traxler transition states for the aldol reaction of an enolate with an aldehyde.

When one of R_1, R_2 or R_3 is chiral, all eight possible diasteromeric transition states give rise to different diastereomeric products. These chiral elements, particularly on the enolate, can give rise to high selectivity in the aldol reaction. Typically, chiral aldehydes have less influence on the outcome of the reaction, however in some cases it has been shown to exert a significant effect on the selectivity of the reaction.[52] Where both a chiral enolate and aldehyde are employed, the facial selectivity of both species competes and this is referred to as a double stereodifferentiating reaction. Chiral ligands on the Lewis acid metal also give rise to diastereomeric transition states (though not necessarily diastereomeric products), which gives the transition states different energies and hence can be used to control the stereochemical outcome of the reaction.

As indicated above, the π-face selectivity of the aldol reaction can be influenced by the introduction of an asymmetric element into the reaction. This can be done three ways: reagent control, substrate control or auxiliary control. Reagent control typically refers to the use of chiral ligands on the Lewis acid metal used for enolisation, but can also refer to chiral catalysts or solvents. This method is often employed where the coupling of two achiral substrates is required. There are a number of Lewis acid metals employed in the aldol reaction (tin, lithium, titanium, boron, etc), the most widely used of which is boron. Boron is useful in these reactions due to the short length of the boron to oxygen bond, making the transition states for these reactions tighter than with other metals and more highly ordered. Some commonly utilised chiral boron reagents that can be used to give high diastereoselectivity in aldol reactions include the α-pinene derived (-)-diisopinocamphenylboron chloride ((-)-Ipc_2BCl) (a), the menthone derived [(-)-$(menth)CH_2]_2BCl$ (b) and borolone (c) (figure 1.10).[56]

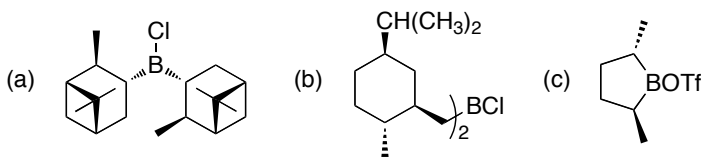
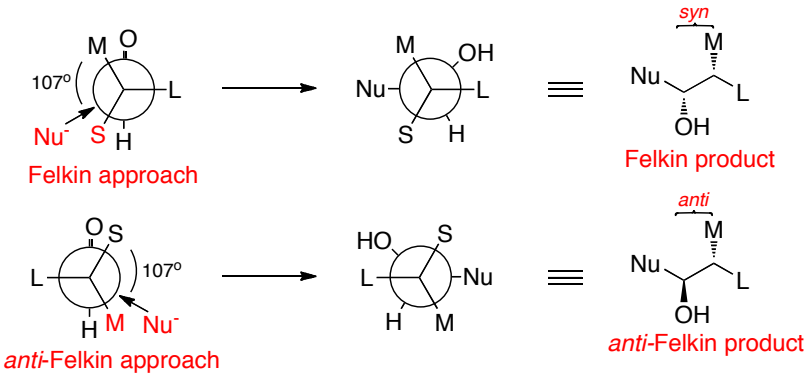


Figure 1.10: Chiral boron reagents used for asymmetric control of aldol reactions.

1.3.1.3 Substrate Control

Substrate controlled aldol reaction are ones in which the aldehyde, ketone or both are chiral and hence exert some facial selectivity on the reaction. These reactions can be highly stereoselective without the aid of a chiral reagent, though chiral reagents have been employed in limited examples where triple asymmetric induction is achieved using a chiral ketone, chiral aldehyde and chiral ligands on the Lewis acid metal.[52]

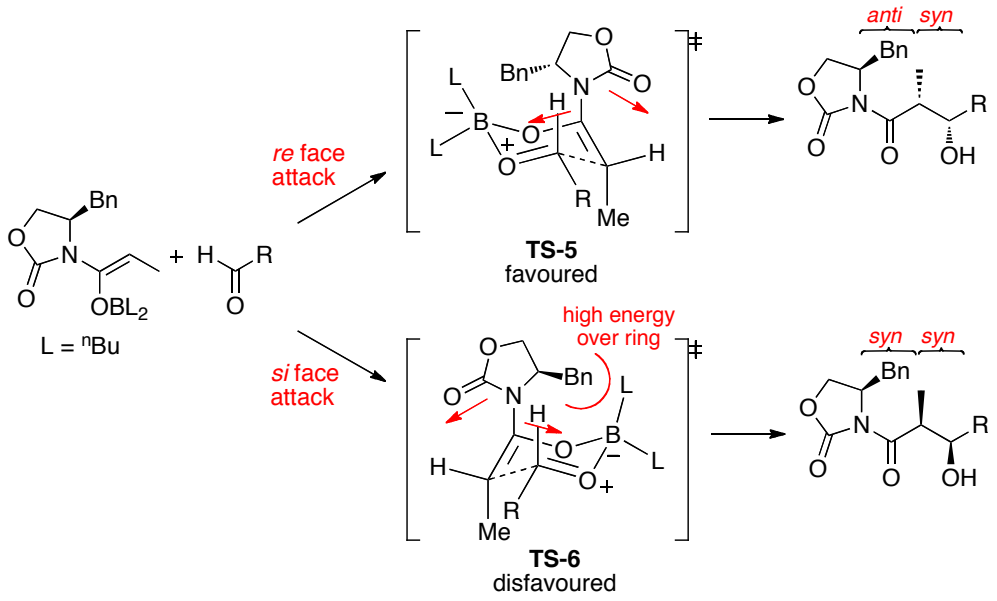
A useful tool for predicting the stereochemistry of the addition of nucleophiles to α-chiral carbonyl compounds is the Felkin model,[57] modified by Anh.[58] The Felkin-Anh model invokes a reactant-like transition state in which the torsional strain between the partially formed bonds corresponds to a substantial fraction of the strain between the fully formed bonds. This results in a staggered conformation in the transtion state, where the bulkiest ligand (L) is situated perpendicular to the carbonyl to minimise steric strain. The nucleophile (which approaches along the Burgi-Dunitz trajectory, $\sim 107^{o}$ from the C=O bond)[59] attacks from the least hindered face, where the partially formed bond overlaps with the smallest ligand (S) to minimise steric interactions, giving the *syn* product (scheme 1.11). The *anti*-Felkin product is the one in which the nucleophile approaches along the more hindered trajectory alongside the medium-sized ligand (M), leading to the *anti* adduct, and is significantly less favoured because of the associated torsional strain. Typically, aldehydes show inherent Felkin selectivity when reacting with *E*-(O)-enolates, while *Z*-(O)-enolates experience a *syn*-pentane interaction between the medium ligand (M) and the axial methyl on the enolate in the Felkin transition state, resulting in an *anti*-Felkin preference.[60,61]



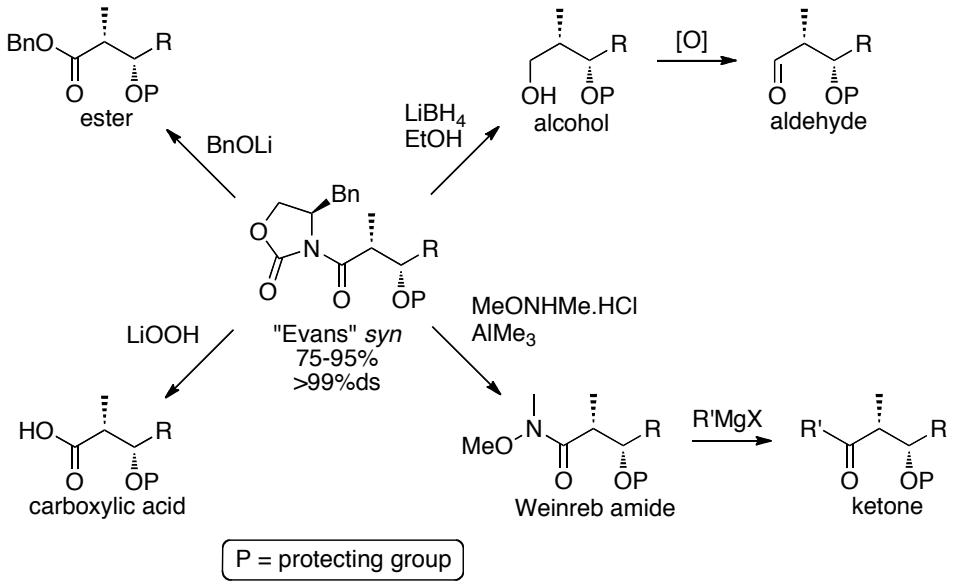
Scheme 1.11: Rationalistion for the Felkin-Anh model.

An interesting and highly useful form of substrate control involves the use of a chiral auxiliary. This group attached to the ketone, directs the reaction and can be modified or removed afterwards. Ideally, this auxiliary should result in highly selective enolisation, provide a strong bias for enolate diastereofacial selectivity and be cleaved without destruction of the desired products.[62]

One of the most commonly employed classes of chiral auxiliaries in polypropionate synthesis are the oxazolidinone auxiliaries developed by the Evans group.[63,64] These auxiliaries give diastereomeric ratios of up to 100:1 in the aldol adduct, and the outcome of these reactions can be rationalised by considering the chair transition states for the reaction (scheme 1.12). The relative stereochemistry of the benzyl substituent controls the π-facial attack of the enolate on the aldehyde, giving the Felkin product with the two newly generated stereocentres in a *syn* relationship. Scheme 1.12 shows the proposed lowest energy chair transition states for *re* and *si* face attack, in which the aldehyde R group assumes an equatorial orientation to minimise 1,3-diaxial interactions, and the oxazolidine carbonyl and the enolate oxygen have opposing dipoles. This defines the rotamer around the carbon-nitrogen bond so that the bulky benzyl group is situated away from the ring (**TS-5**) or over the ring (**TS-6**). The steric strain associated with **TS-6** leads to **TS-5** being the favoured transition state, giving the *anti-syn* product as shown. These auxiliaries are highly versatile and (with the hydroxyl protected) can be transformed or removed as summarised in scheme 1.13.

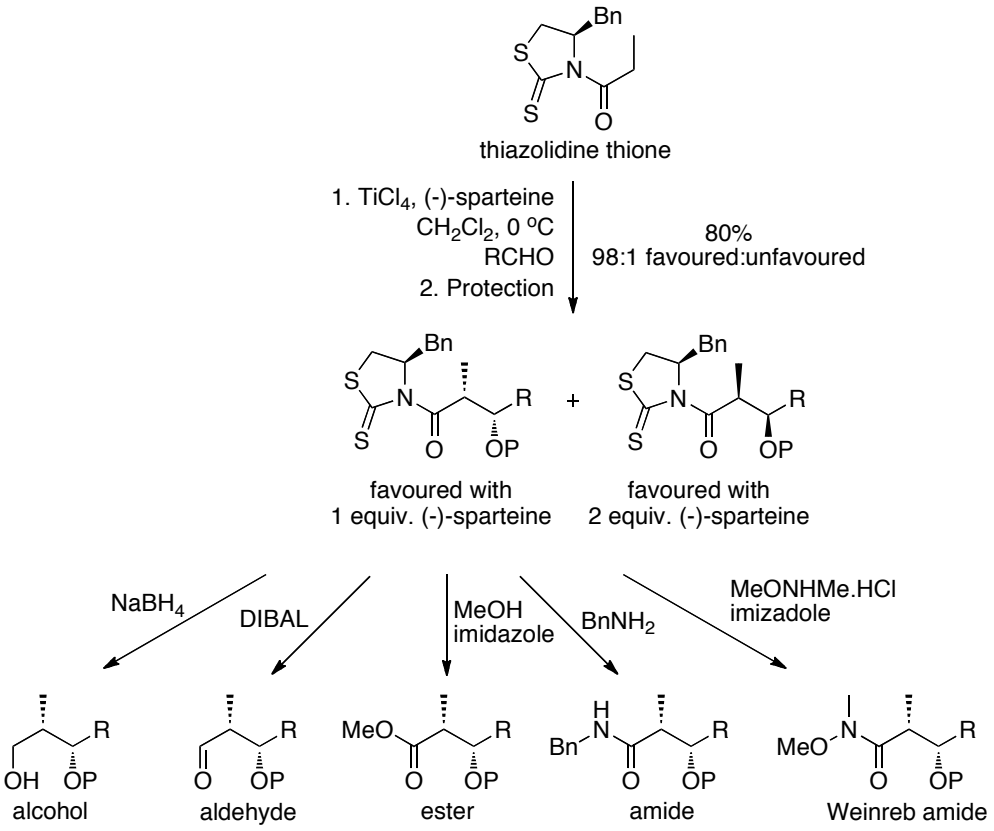


Scheme 1.12: Transition state rationalisation for the *anti-syn* outcome of the Evans aldol reaction.



Scheme 1.13: Possible transformations of the Evans auxiliary.

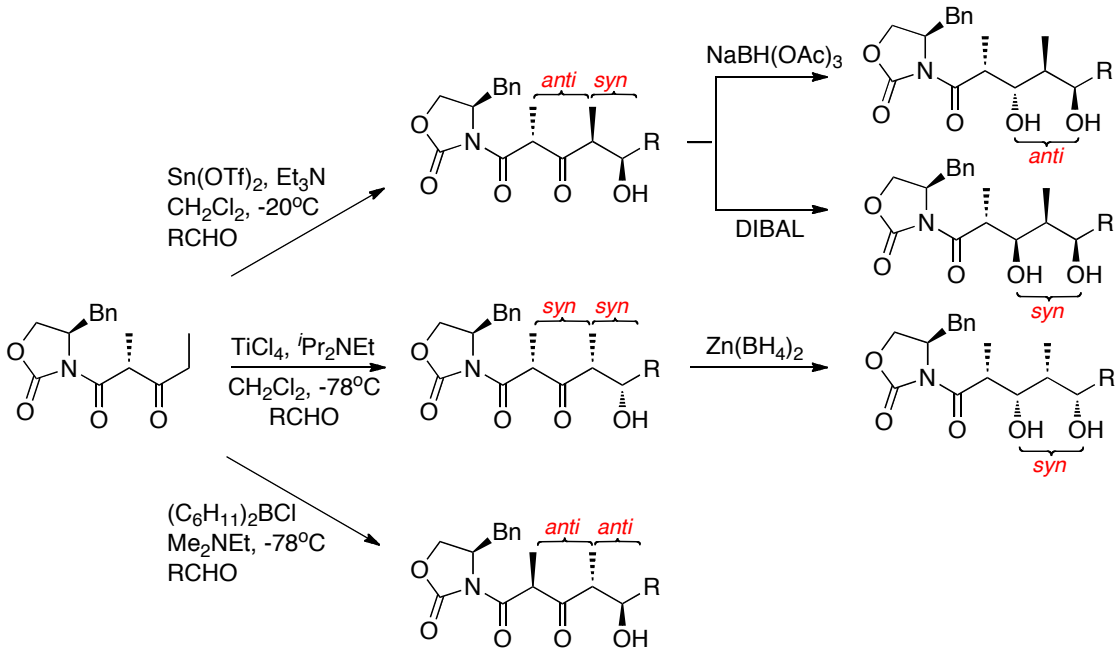
The selectivity of these aldol reactions can be altered by altering the reaction conditions. For example, enolisation using 20 mole% of $MgCl_2$, Et_3N and TMSCl in EtOAc favours the "non-Evans" *syn-anti* adduct.[65] Analogously, the aldol adduct of a thiazolidine thione derivative (scheme 1.14) can be elaborated to give a remarkable range of products with high selectivity (>98%) depending on the stoichiometry of sparteine employed for enolisation.[66,67]



Scheme 1.14: The aldol reaction and possible transformations of the thiazolidine thione auxiliary.

The dipropionate motif is a common structural element of polypropionates and Evans chemistry has been extended to incorporate these units.[68] Depending on the enolising conditions, the dipropionate equivalent (schemee 1.15) can give rise to *anti-syn*, *syn-syn* or *anti-anti* adducts as shown in diastereoselectivities of >95%.[68] The enantiomeric products are available from the enantiomer of the starting

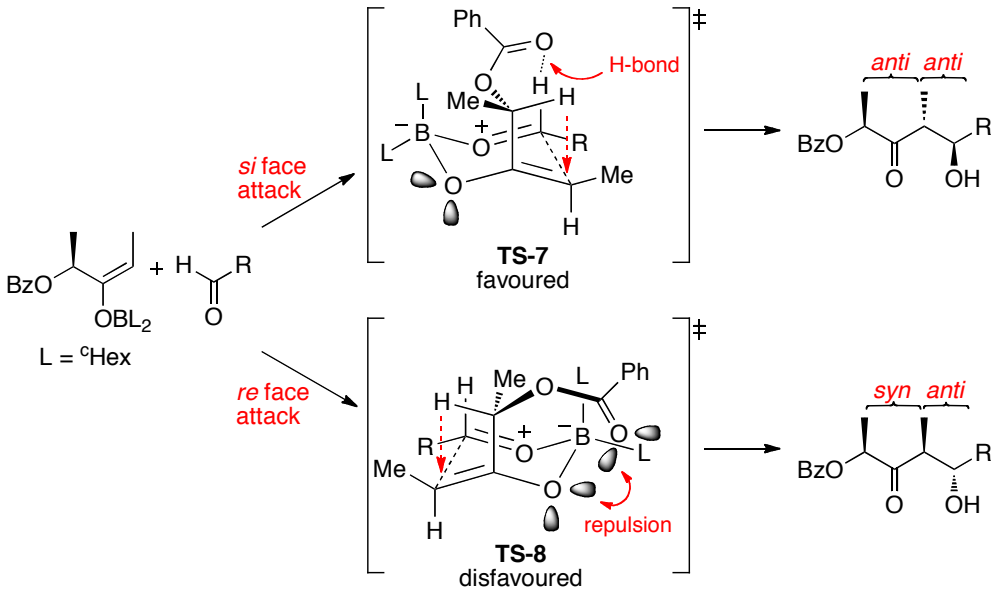
material. This method provides a means of incorporating a dipropionate unit without the additional synthetic steps required to obtain an aldehyde ready for further condensation after the addition of a single propionate unit. Furthermore, the β-keto groups of these species can be reduced under the conditions shown to give *syn* or *anti* 1,3-diols with >20:1 selectivity, owing to internal direction by the δ-hydroxy substituent.[68]



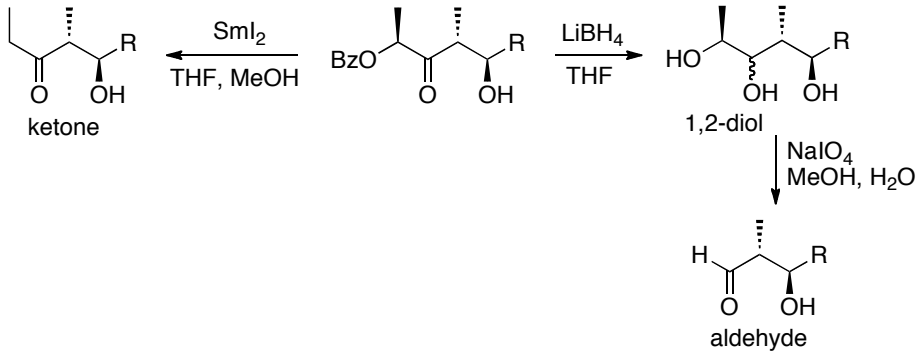
Scheme 1.15: The aldol reactions of the Evans dipropionate equivalent.

The Paterson group has developed a set of chiral ketones that can be used to direct the stereochemical outcome of the aldol reaction, and of particular interest to this project are the lactate-derived chiral ketones.[53,69-71] These compounds give rise to *anti-anti* aldol adducts and Paterson *et al*.[53] rationalised the outcome of these aldol reactions by considering the lowest energy chair transition state models for the reaction (scheme 1.16). The enolisation conditions employed ((*c*-C_6H_{11})$_2$BCl and Me_2NEt) [72] give exclusive formation of the *E*-(O)-enolate and the high π-face selectivity of this boron enolate overrides the Felkin-Anh induction by the aldehyde to give *anti* aldol adducts.[53] The two most stable chair transition states arising from the two potential π-facial attacks (ie. *re* or *si* face) of the enolate on an aldehyde are

the ones in which the aldehyde R group is situated in an equatorial position and the proton attached to the enolate stereocentre eclipses the double bond in order to minimise A(1,3) strain (scheme 1.16). Steric and electronic factors in the ketone lead to **TS-7** (resulting from *si* face attack of the enolate on the aldehyde) being the favoured transition state for the formation of the aldol product, as **TS-8** is destabilised by lone pair repulsions between the benzoate and enolate oxygens.[53] It has also been postulated that a hydrogen bonding-like interaction occurs between the benzoate oxygen and the aldehyde proton, stabilising **TS-7**.[53,73] These aldol adducts can also be elaborated into a range of carbonyl species (scheme 1.17), which can undergo further nucleophile addition. As the α-methyl group is often retained in the final product, it is considered to play an "optional auxiliary" role.[56] A variation of this chiral ketone, which bears a benzyl protecting group in place of the benzoyl, can be used to produce *anti-syn* adducts in high diastereoselectivity under the same conditions *via* the *Z*-(O)-enolate.[71]

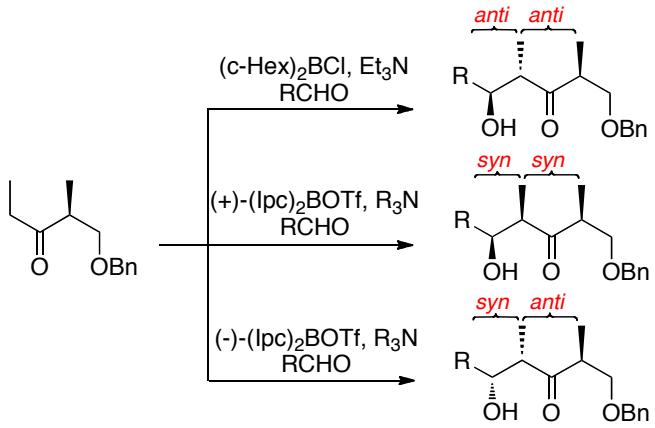


Scheme 1.16: Transition state rationalisation for the *anti-anti* outcome of the Paterson aldol reaction.



Scheme 1.17: Possible transformations of Paterson's lactate-derived chiral ketone.[69]

Paterson and coworkers[74-77] have also developed a dipropionate aldol equivalent which was found to give high diastereoselectivity (>96%) in favour of the *anti-anti* adduct using (*c*-Hex)$_2$BCl/Et$_3$N to produce the *E*-(O)-enolate.[75] The use of (+)-Ipc$_2$BOTf and (-)-Ipc$_2$BOTf with an amine base give rise to the *Z*-(O)-enolate, resulting in the *syn-syn* and *syn-anti* configurations respectively (up to 93% ds) as the stereochemistry of the isopinocamphyl ligands controls the facial selectivity of the enolate (scheme 1.18).[74,75] Sn(OTf)$_2$/Et$_3$N can also be used to generate *syn,syn* adducts, however Sn(OTf)$_2$ is a highly sensitive reagent that can be difficult to handle.[78] This process was later extended by Solsona *et al.*[79] to the use of the PMB protecting group in place of the benzyl, which gave rise to *syn,syn* adducts using the less cumbersome Ti(O*i*-Pr)Cl$_3$/*i*-Pr$_2$NEt. Variations of this dipropionate aldol are illustrated in scheme 1.19.[80-82]



Scheme 1.18: The various stereochemical outcomes of the aldol reaction of Paterson's dipropionate equivalent.

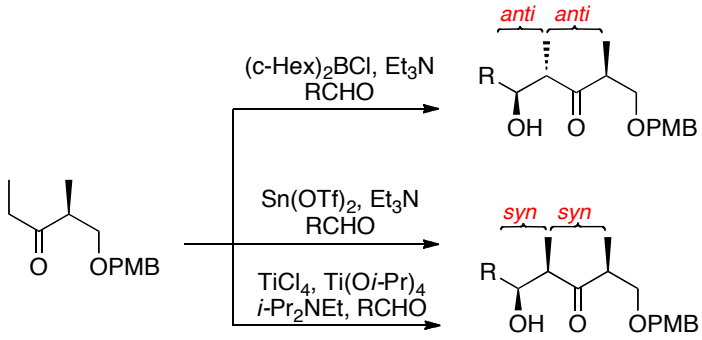


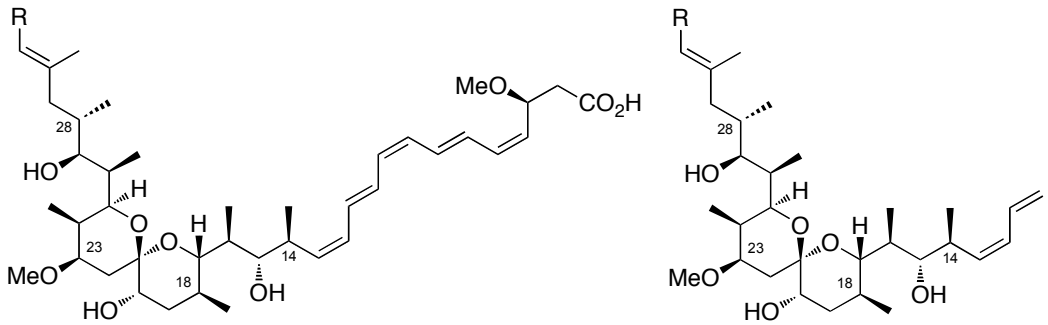
Figure 1.19: The various stereochemical outcomes of the modified Paterson dipropionate equivalent.

While there are a plethora of other chiral auxiliaries, catalysts and so on that are available to control the π-face selectivity of the aldol reaction, these are far too numerous to expand upon in this context and the interested reader is directed to a number of reviews and books on this topic.[52,15,83-85] As chemists strive to design and execute shorter and more efficient polypropionate syntheses, stereocontrolled aldol reactions have become increasingly important and as such will play a key role in the synthetic studies to follow.[56]

1.4 Synthetic Targets

The research presented herein describes the synthetic efforts towards two groups of polyketide natural products. These studies were conducted with the primary objective of determining the absolute configuration of the natural products, by designing and implementing a novel, stereocontrolled strategy for their synthesis.

Chapter two focuses on synthetic efforts towards the potent anticancer agent spirangien A (**1**) (figure 1.11), a highly complex 6,6-spiroketal containing compound isolated from the soil-dwelling myxobacterium *Sorangium cellulosum*. Spirangien A (**1**) (and the structurally related spirangien B (**2**)), contains 14 stereogenic centres, a novel spiroacetal core and delicate conjugated pentaene side-chain. While this compound had not been synthesised at the outset of these studies, owing to its potent anti-cancer activity and highly challenging structural complexity the structure of spirangien A was simultaneously pursued by a number of research groups world-wide. This resulted in the complete stereochemical assignment *via* total synthesis of spirangien diene (**3**)[86] and spirangien A (**1**)[87,88] in 2007 and 2008 respectively by the Paterson group. The purpose of these studies was therefore amended to a formal synthesis, with a particular focus of improving the selectivity of the key aldol reaction associated with the synthesis of its linear precursor (formation of the C22-23 bond).

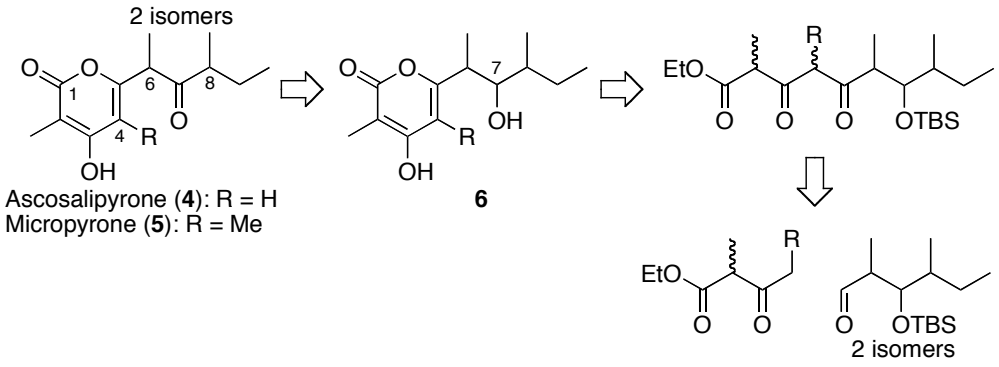


Spirangien A (**1**): R = Me
Spirangien B (**2**): R = Et

3

Figure 1.10: Spirangiens A (**1**) and B (**2**) and spirangien diene (**3**).

Chapter three details the total synthesis of the two structurally related 4-hydroxy-α-pyrone containing compounds ascosalipyrone (**4**) and micropyrone (**5**) (scheme 1.20). Ascosalipyrone (**4**) was isolated in 2000 from the obligate marine fungus *Aschochyta salicorniae*, which in turn was isolated from the inner tissue of the green alga *Ulva* sp.[89] The structurally related micropyrone was isolated in 2007 from the terrestrial plant *Helichrysum italicum*.[90] The two compounds differ in structure only by the presence or absence of a methyl substituent at C4 (scheme 1.20), however, ascosalipyrone was isolated as an unequal mixture of diastereomers, while micropyrone was isolated as a single isomer. A stereocontrolled synthesis of two diastereomers (8*S*) of each natural product from a common intermediate was sought in order to determine the relative and absolute stereochemistry of the natural products. It was hoped that the oxidation of C7 hydroxyl in compound **6** as the final synthetic step would give the β-keto pyrones without epimerisation at C6.



Scheme 1.20: A retrosynthetic overview of ascosalipyrone (**4**) and micropyrone (**5**).

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Chapter Two:

Synthetic Studies Towards Spirangien A

2.1 Introduction

2.1.1 Isolation of Spirangiens A and B

Myxobacteria are predominantly soil-dwelling organisms that have long been a source of structurally diverse, biologically active secondary metabolites. The enormous genome of these organisms lends itself to an extraordinary ability to produce secondary metabolites, with the genus *Sorangium* the most prolific source of versatile, biologically active secondary metabolites amongst the myxobacteria.[1,2] *Sorangium cellulosum* strain So ce90, first found in soil collected from the banks of the Zambesi River, South Africa, was identified on the basis of its antifungal activity, a common feature of the *Sorangia*.[2,3] Probing for the antifungal component of this species led to the isolation of two novel classes of compounds, the epothilones[4,5] and spirangiens.[4,6]

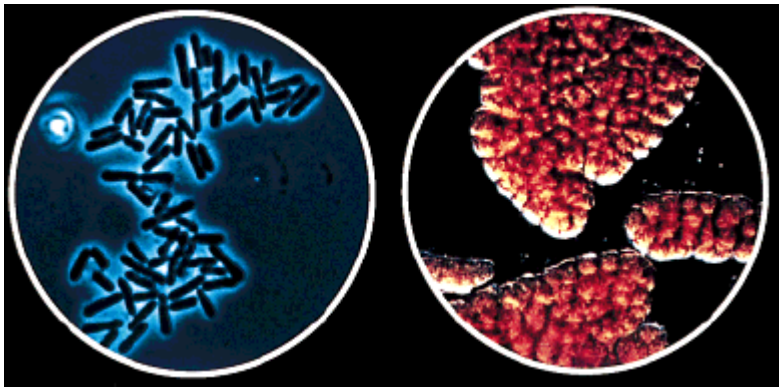


Figure 2.1: Growing cells of *Sorangium cellulosum* So ce90 (left) and spore capsules of the same organism (right).[3]

The most well known and well studied of these secondary metabolites are the epothilones, which exhibit potent antineoplastic activity comparable to that of Taxol®. The success of these compounds as lead structures for anti-cancer agents has manifested in the approval of ixabepilone, (a semi-synthetic aza-analogue of epothilone B, marketed under the name of Ixempra®, figure 2.2) by the United

States Food and Drug Administration in 2007 for the treatment of taxane-resistant metastatic breast cancer.[7] Several other epothilones and their derivatives are currently in various phases of clinical trials for the treatment of a variety of cancers including ovarian, prostate and lung cancer, and are expected to replace Taxol-derived agents once approved for human therapy.[1]

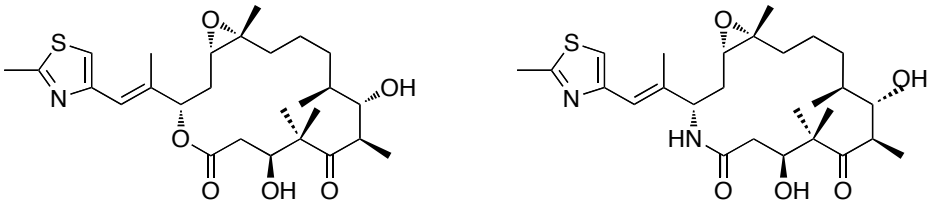


Figure 2.2: Epothilone B (left) and its semi-synthetic analogue ixabepilone (right).

The other, lesser-known family of compounds to be isolated from *Sorangium cellulosum* So ce90 were spirangiens A and B (figure 2.3). Spirangien A was tested for biological activity against a broad spectrum of bacteria, yeasts and fungi and was active against selected yeasts and fungi.[8] Spirangien A (**1**) was also found to be highly cytotoxic against the L929 mouse fibroblast cell line, exhibiting an IC_{50} value of 0.7 $ngmL^{-1}$.[8] Close consideration of the structure of spirangiens A and B reveals their polyketide nature, made up largely of propionate units and a few acetate units. The only discrepancy in the structure arises at C20, with the presence of a hydroxyl group that does not fit the classic polyketide pattern. This inconsistency has been attributed to a post-PKS oxygenation by examination of the gene cluster responsible for spirangien production.[9]

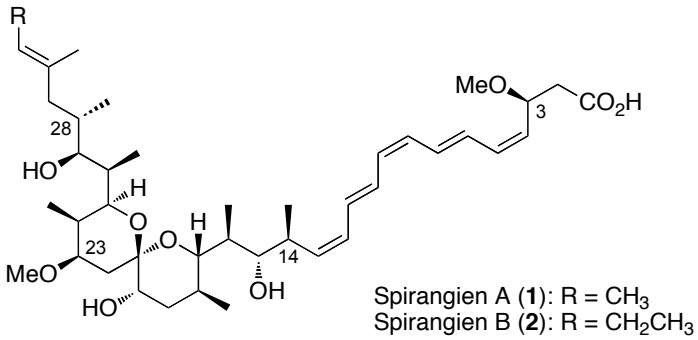


Figure 2.3: Spirangiens A and B.

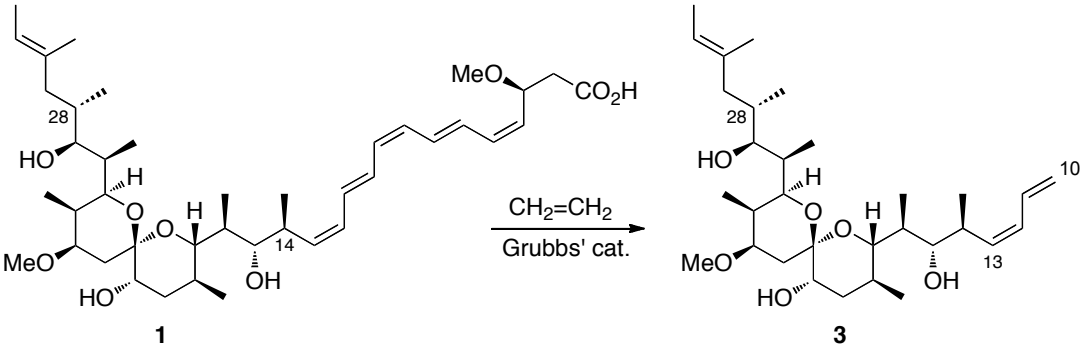
2.1.2 Structure Elucidation and Modification

It was not until 1995 that the complete relative configuration of spirangiens A and B were reported by Niggemann *et al*.[8] as a result of comprehensive NMR analysis and chemical modifications of spirangien A. Spirangiens A and B were both isolated as amorphous solids and high resolution mass spectrometry (HR-MS) and ^{13}C NMR used to deduce their molecular formulae: $C_{41}H_{66}O_9$ and $C_{42}H_{68}O_9$ respectively. Complex 1D and 2D NMR analysis (including COSY, HMQC, HMBC and NOESY) accompanied by UV absorption maxima led to the assignment of the skeletal structure, which was found to differ only by a single CH_2 group between spirangiens A and B. The core structure was also discovered to contain a complex pentaene system (the geometry of which was assigned on the basis of vicinal coupling constants), a heavily functionalised 6,6-spiroacetal core, 14 stereocentres and a terminal carboxyl group. The optical rotation of the natural products was reported [spirangien A (**1**): $[\alpha]^{20}_D$ = -19.4 (c 1.0, MeOH); spirangien B (**2**): $[\alpha]^{20}_D$ = -8.8 (c 0.4, MeOH)].

The absolute configuration of the remote C3 stereocentre was determined by chiral GC analysis. First, degradation of spirangien A was performed by ozonolysis, followed by oxidative workup. The resulting 2-methoxysuccinic acid was esterified with diazomethane, enabling GC comparison with known standards obtained from (*S*)-hydroxysuccinic acid and (±)-hydroxysuccinic acid in order to establish the (3*S*) configuration of spirangien A. This centre was however too remote from the core

structure to enable complete relative stereochemical assignment based on nOe analysis.

A number of structural modifications of spirangien A were achieved, the most significant of which was the generation of spirangien diene (**3**) (scheme 2.1) from cross-metathesis of spirangien A with ethylene and Grubbs' second-generation catalyst. X-ray crystal structure analysis of spirangien diene (**3**), which does not contain the remote C3 stereocentre, revealed the relative stereochemistry of C14-28. An optical rotation was also reported for compound **3** ($[\alpha]^{20}_{D}$ = +33.1 (c 1.0, MeOH)), making it possible to assign the absolute configuration of the natural products upon synthesis of an enantiomer of spirangien diene (**3**). Compound **3** was also tested for biological activity and was found to retain one tenth the biological activity of spirangien A, with an IC_{50} value of 7 $ngmL^{-1}$, highlighting the importance of the spiroacetal unit to the overall pharmacophore.[9,8]



Scheme 2.1: Cross-metathesis of spirangien A (**1**) to produce spirangien diene (**3**).

Attempts were made by the Niggemann group[8] to determine the absolute stereochemistry by synthesis of Mosher esters of spirangien diene (**3**), however this was unsuccessful. In 2007, Paterson *et al*.[10] achieved the synthesis of spirangien diene (**3**), confirming the absolute stereochemistry to be that shown in scheme 2.1.

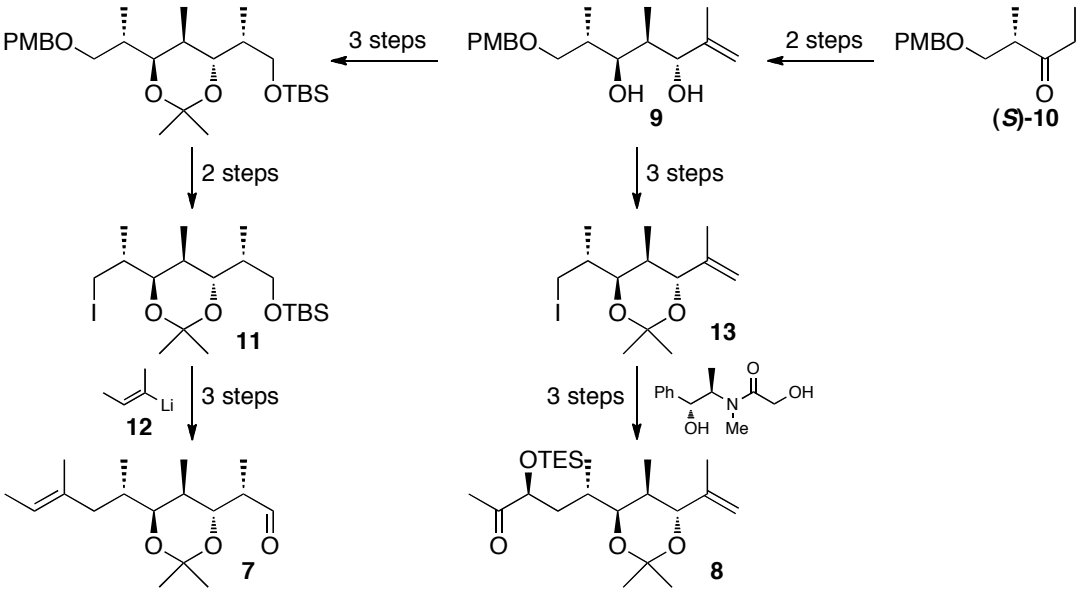
2.2 Previous Work

It is important to note here that at the outset of the synthetic studies described herein, no attempts towards the synthesis of spirangiens A and B had been reported in the literature. Since that time however, owing to the potent biological activity and interesting synthetic challenges associated with these natural products, a number of research groups around the world have published their efforts towards these natural products. This steady stream of publications culminated in the first total synthesis of (-)-spirangien A and its methyl ester in 2008 by the Paterson group.[11] The following sections contain a brief overview of the synthetic efforts published to date towards the synthesis of spirangiens A and B.

2.2.1 Paterson's Total Synthesis of Spirangien A

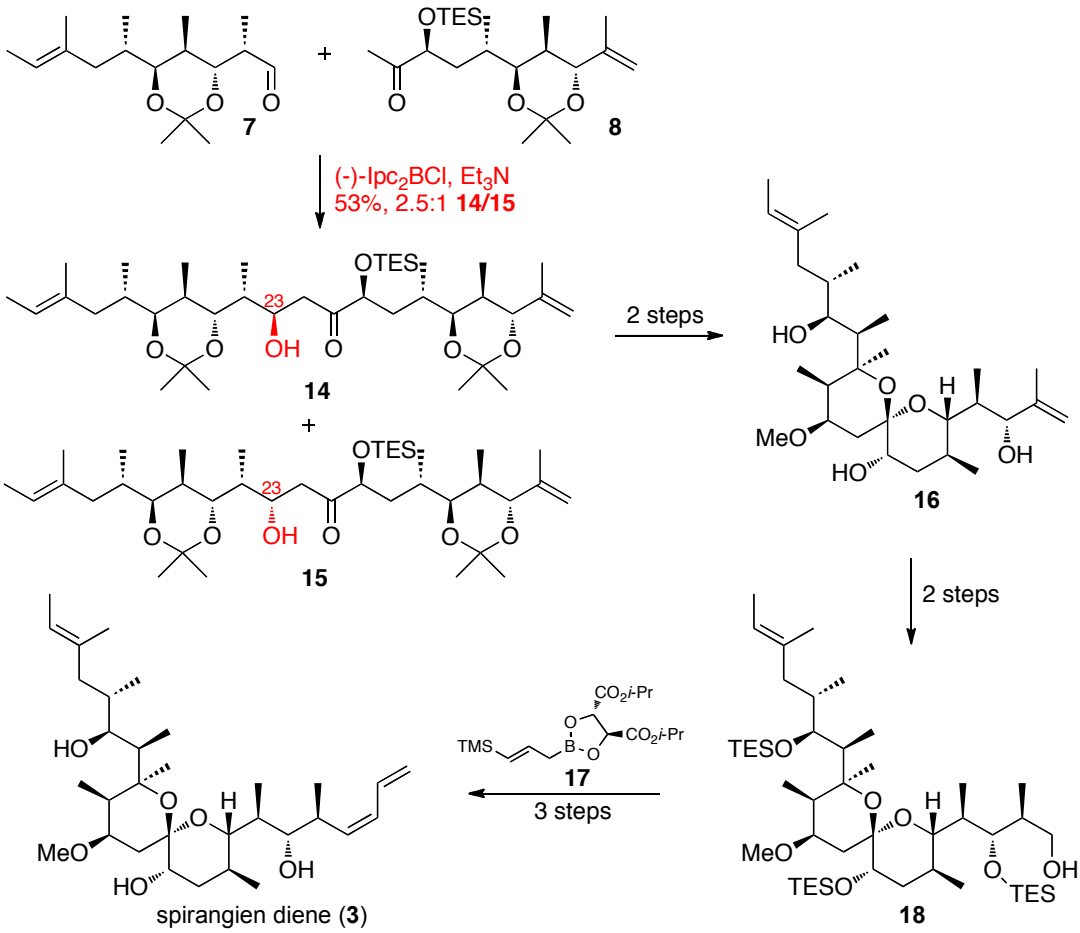
The most significant efforts to date towards the synthesis of spirangiens A and B were achieved by the Paterson group of Cambridge University, England. They completed the synthesis of spirangien diene (**3**) in 2007,[10] followed by the total synthesis of spirangien A (**1**) and its methyl ester in 2008.[11,12]

The strategy employed by the Paterson group towards the spiroacetal core exploited the obvious aldol disconnection at C22-23, recognising that the two coupling partners contained a common stereotetrad. Their approach was to synthesise the two aldol coupling partners **7** and **8** (scheme 2.2) *via* two parallel sequences from common precursor **9**. The absolute stereochemistry of the stereotetrad was readily achieved through coupling of dipropionate equivalent **(*S*)-10** with methacrolein under standard conditions ($(c\text{-Hex})_2BCl/Et_3N$) previously developed by Paterson,[13,14] with subsequent *anti*-selective reduction of the ketone. Elaboration of aldehyde precursor fragment **11** was achieved by a Cu mediated alkylation using alkyllithium **12**. A Myers alkylation was cleverly utilised to elaborate ketone precursor fragment **13** to install the unusual α-hydroxyketone functionality.



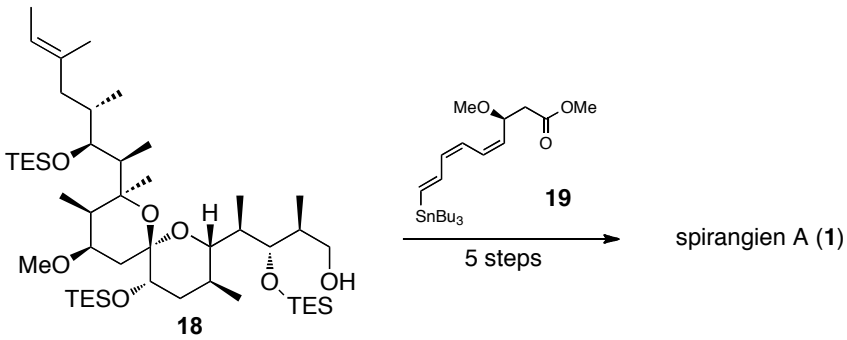
Scheme 2.2: Aldol coupling partner synthesis by Paterson *et al*.[10,11]

Aldol coupling of ketone **8** and aldehyde **7** was achieved with only moderate diastereoselectivity using (-)-Ipc_2BCl/Et_3N to give the desired aldol adduct **14** in 53% yield and 2.5:1 dr (scheme 2.3). The chiral boron reagent was required to overcome the inherent facial preference of coupling partners **7** and **8** which gave rise to the incorrect isomer **15** using LDA (3.5:1 dr) or $(c\text{-}Hex)_2BCl/Et_3N$ (5:1 dr). Paterson did not report any further optimisation of the aldol reaction conditions. The stereochemistry of the two aldol adducts was determined by spirocyclisation of the *O*-methylated aldol adducts to spiroacetal **16** and its C23-epimer. Diagnostic nOe enhancements enabled differentiation between the two isomers.



Scheme 2.3: Synthesis of spirangien diene (**3**) by Paterson *et al.*[10]

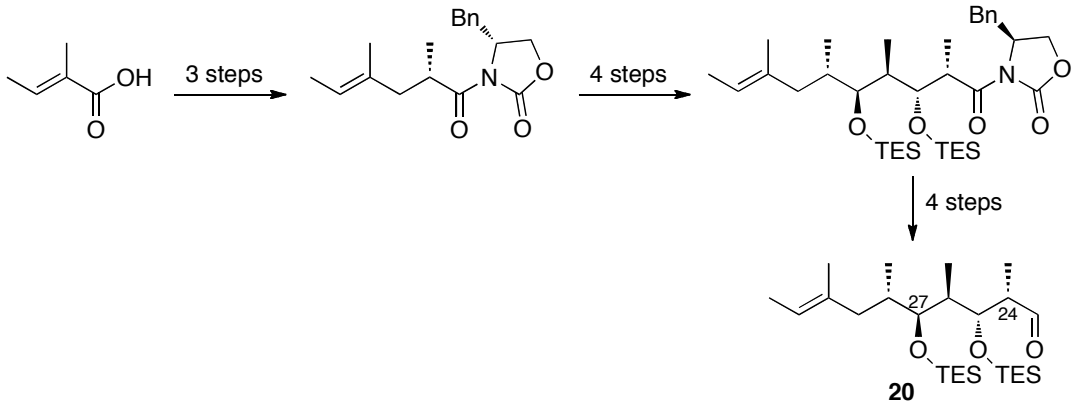
The correct diastereomer (C23-*R*) of the spiroacetal core was then appended with the appropriate side chain fragment to give spirangien diene (**3**)[10] (scheme 2.3) and spirangien A (**1**)[11,12] (scheme 2.4). Allyl borinate **17** was employed to furnish compound **3** (*via* advanced intermediate **18**) while the natural product side-chain would need to be synthesised separately. This was a delicate process as the pentaene fragment is highly susceptible to photoisomerisation and degradation under acidic conditions.[15] This synthesis of side chain fragment **19** for spirangien A remains the only published[11,12] synthesis of this fragment and was attached to advanced intermediate **18** by a Stork-Wittig elimination reaction.



Scheme 2.4: Total synthesis of spirangien A (**1**) by Paterson *et al*.[11,12]

2.2.2 Kalesse's Studies Towards spirangien diene (3)

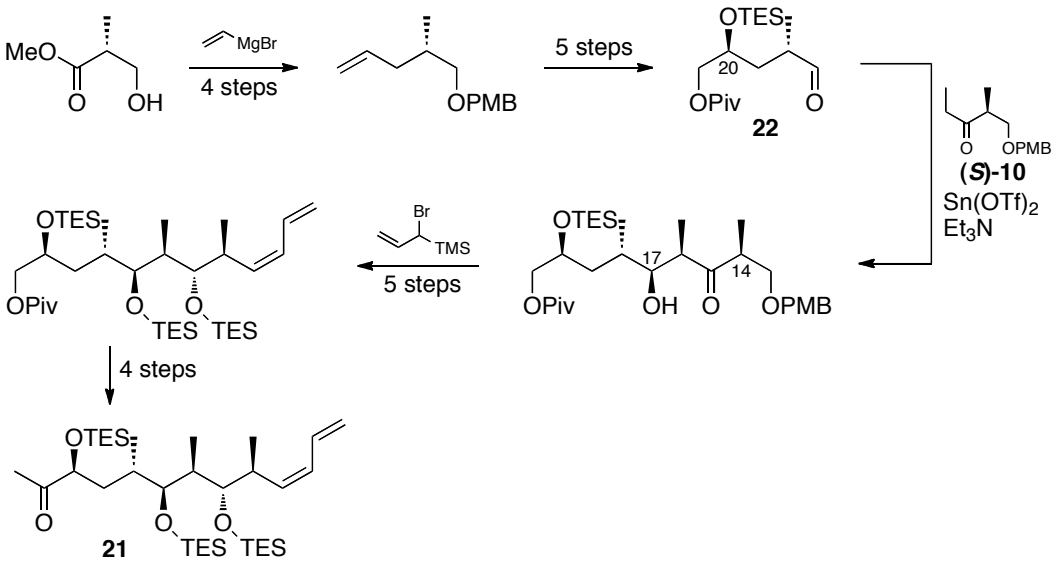
Another major contributor to the synthesis of the spirangiens is the Kalesse group from the University of Hannover, Germany. Kalesse also employed an aldol approach to the spiroacetal linear precursor, shown in scheme 2.7. Kalesse and Lorenz published the synthesis of aldehyde fragment **20** in 2007,[16] utilising a tin triflate mediated Evans dipropionate aldol reaction to install the desired stereochemistry of C24-27 (scheme 2.5).



Scheme 2.5: Synthesis of aldehyde fragment **20** by Kalesse and Lorenz.[16]

In 2008 the synthesis of ketone fragment **21** was published, along with preliminary results for the aldol coupling.[17] In this approach, Kalesse and Lorenz employed a

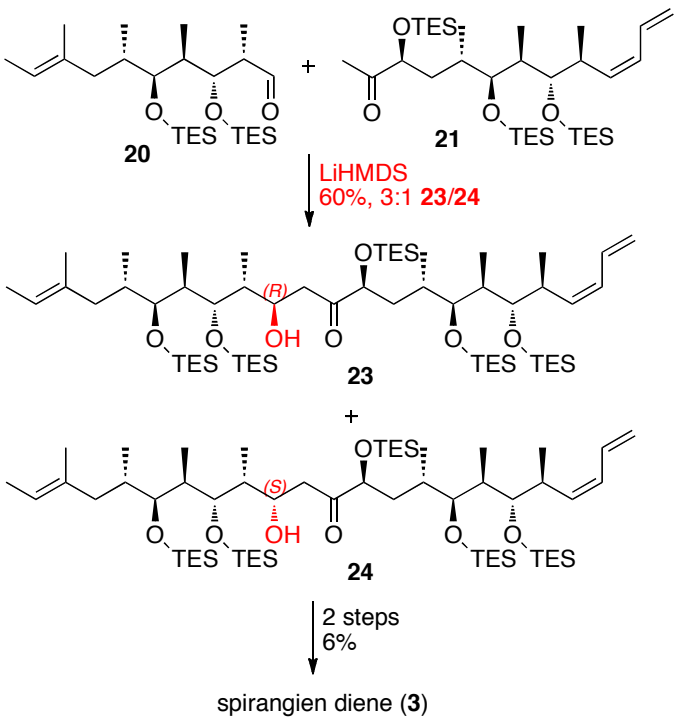
Sharpless asymmetric dihydroxylation to afford the protected 1,2-diol in **22** with the correct stereochemistry at C20 (the minor isomer was able to be removed at a later step). Interestingly, Kalesse uses tin triflate once again in the dipropionate aldol of **(*S*)-10** with aldehyde **22** and subsequent *anti*-reduction to install the C14-17 stereochemistry. This was followed by installation of the 1,3-diene moiety (which Paterson installed after cyclisation) and an oxidation-methylation sequence to establish the methyl ketone **21** (scheme 2.6).



Scheme 2.6: Synthesis of methyl ketone **21** by Kalesse and Lorenz.[17]

While the approach taken by Kalesse to synthesise the aldehyde and ketone fragments required for the main aldol coupling is significantly different from that of Paterson,[10-12] the only key difference between the final two pairs is the protecting groups chosen for the 1,3-diols. Paterson chose to use the acetonide group for both fragments, which evidently showed the unfavoured Felkin-Anh preference in the aldol adduct under achiral enolising conditions. With this knowledge in hand, Kalesse chose to protect the 1,3-diol in both fragments as the *di*-TES ethers.[17] This difference, particularly in the aldehyde fragment, was expected to play an important role in the selectivity of the aldol reaction. Indeed, Kalesse reported that

the reaction with LiHMDS gave 60% yield and 3:1 ds in favour of the desired isomer **23** (scheme 2.7) (LDA, KHMDS and Mukaiyama-type aldols were also trialled but resulted in poor yields in all cases).[17] Unfortunately, the diastereomers were unable to be separated at any stage and were carried through to the final product. The 1,3-diene product was produced in only 6% yield over 3 steps, however the major product was able to be isolated by HPLC and the spectroscopic data of the product supported its identity as spirangien diene (**3**) (ie. the correct diastereomer for the natural product).[17] However, spirangien diene (**3**) was obtained in only 6% yield (0.2 mg), therefore it is possible that the ratio of 1,3-diene products may not accurately represent the ratio of aldol adducts **23**/**24**.



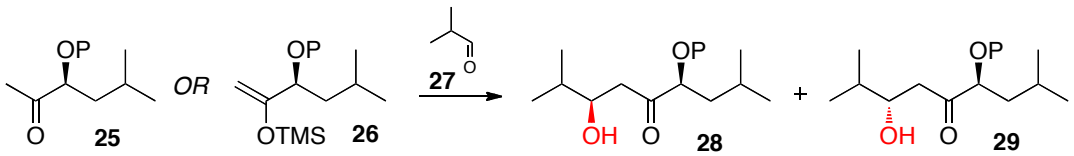
Scheme 2.7: Synthesis of spirangien diene (**3**) by Kalesse as a 3:1 mixture of diastereomers.[17]

The Kalesse group also published a paper on their investigations into the C22-23 aldol coupling.[18] In this report Kalesse *et al*.[18] focus on the effects of base and counterions on the aldol reaction, as well the effects of changing the reaction

conditions from enolate activation to Lewis acid activation (ie. Mukaiyama conditions).

Kalesse and coworkers showed that the Felkin opposing effects of the β-substituent on aldehyde **20** consistently overrides the Felkin preference of the α-substituent when reacted with an achiral methyl ketone (methyl isopropyl ketone).[18] Diastereoselectivities of >95% ds were observed with both LiHMDS and KHMDS in THF and CH_2Cl_2. In other words, aldehyde **20** directed the aldol reaction to the desired *anti*-Felkin isomer.

The directing effects of the ketone were studied using the simplified models **25** and **26**, reacted with achiral aldehyde **27** (isobutyraldehyde). These ketones incorporated only the α-sterechemistry, and differ only in the choice of α-alkoxy protecting group, P. Table 2.1 shows the diastereomeric ratio (dr) of aldol products **28** and **29** obtained. Na, Li and K counterions were tested and Li gave the best selectivity and Na the worst, however diastereoselectivities were consistently in favour of the unwanted isomer **29**. Diastereoselectivity was also consistently higher when P = PMB due to chelation of the PMB oxygen to the metal cation. Boron enolates were also investigated, but 72-93% ds in favour of the unwanted isomer **29** was observed, depending on the conditions employed.[18] Mukayaima conditions ($BF_3.OEt_2$/toluene)[19] on the other hand resulted in complete reversal of selectivity, with 98% ds in favour of the desired isomer **28** observed for the reaction of methyl ketone **26** (P = TES) with aldehyde **27**.



Ketone equivalent	Protecting group (P)	Conditions	dr 28/29
25	P = PMB	LiHMDS/THF	13:87
		NaHMDS/THF	32:68
		KHMDS/THF	19:81
		(*c*-Hex)$_2$BCl/Et$_3$N/Et$_2$O	23:77
		Bu$_2$BOTf/*i*-Pr$_2$NEt/CH$_2$Cl$_2$	7:93
		Bu$_2$BOTf/*i*-Pr$_2$NEt/toluene	20:80
	P = TES	LiHMDS/THF	32:68
		NaHMDS/THF	50:50
		KHMDS/THF	47:53
		(*c*-Hex)$_2$BCl/Et$_3$N/Et$_2$O	16:84
	P = TBS	LiHMDS/THF	38:62
		NaHMDS/THF	42:58
		KHMDS/THF	41:59
26	P = PMB	BF$_3$.OEt$_2$ (0.3 eq)/toluene	96:4
		BF$_3$.OEt$_2$ (1 eq)/toluene	94:6
	P = TES	BF$_3$.OEt$_2$ (0.3 eq)/toluene	98:2

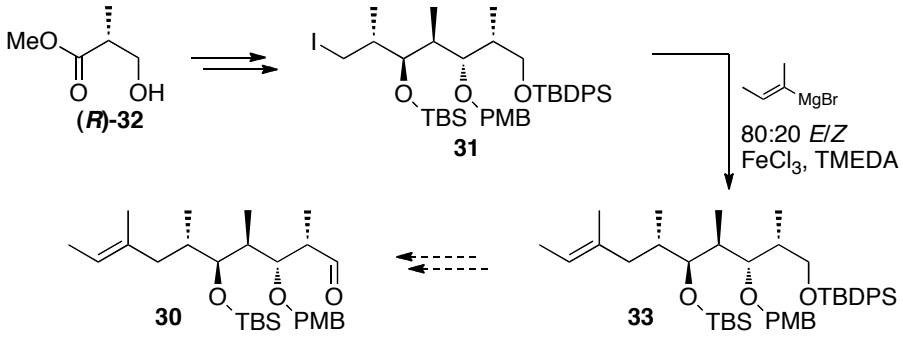
Table 2.1: Summary of the directing effects of model ketones **25** and **26** observed by Kalesse *et al.*[18]

It should be noted that this system is not necessarily an accurate model for the major ketone fragment as it does not take into account the 1,6- and 1,7-induction effects of the ketone, nor does it consider the combined effects of the facial preference of both coupling partners.

2.2.3 Other Synthetic Studies Towards Spirangien A

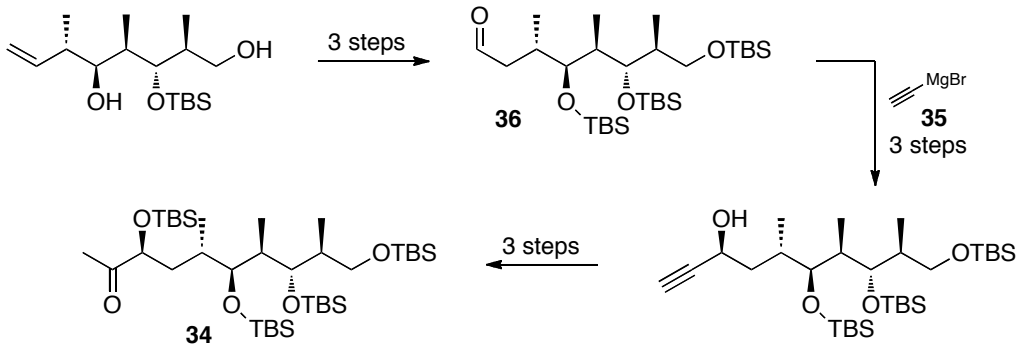
Cossy and co-workers published some preliminary studies towards spirangien A in 2008 in which they achieved the synthesis of a precursor to aldehyde **30** (scheme 2.8).[20] Cossy *et al*.[20] synthesised alkyliodide **31** from (*R*)-Roche ester [**(*R*)-32**], with the intention of performing a palladium-catalysed cross-coupling with either a vinyl metal or vinyl halide. This initial approach was unsuccessful, however it led the authors to develop novel methodology for the cross-coupling reaction between alkyl halides and alkenyl Grignard reagents, catalysed by iron salts. Applied to the

current system, they were able to produce precursor fragment **33** to aldehyde **30** as shown in scheme 2.8.



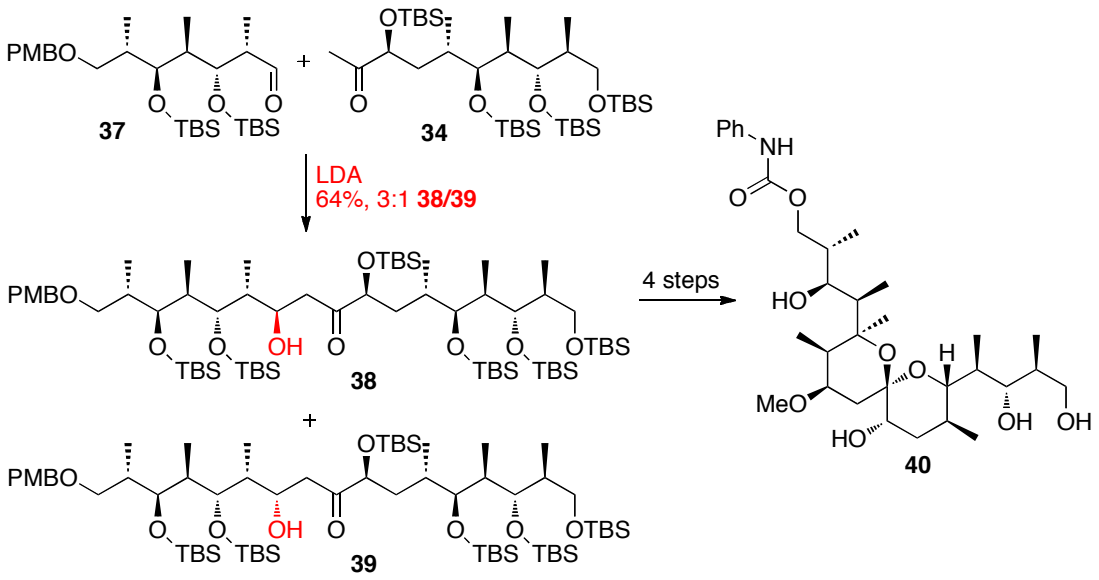
Scheme 2.8: Synthesis of a precursor to aldehyde **30** *via* an Fe catalysed cross-couling by Cossy *et al*.[20]

Further results from Cossy and co-workers were published in 2010, highlighting their synthetic efforts towards the spiroketal core of spirangien A.[21] Ketone **34** was synthesised according to the process outlined in scheme 2.9, by addition of ethynylmagnesium bromide (**35**) to aldehyde **36**, followed by a selective oxidation-reduction sequence to install the C20 stereochemistry. The methyl ketone moiety was introduced by mercury-catalysed hydration of the triple bond (scheme 2.9).



Scheme 2.9: Synthesis of methyl ketone **34** by Cossy *et al*.[21]

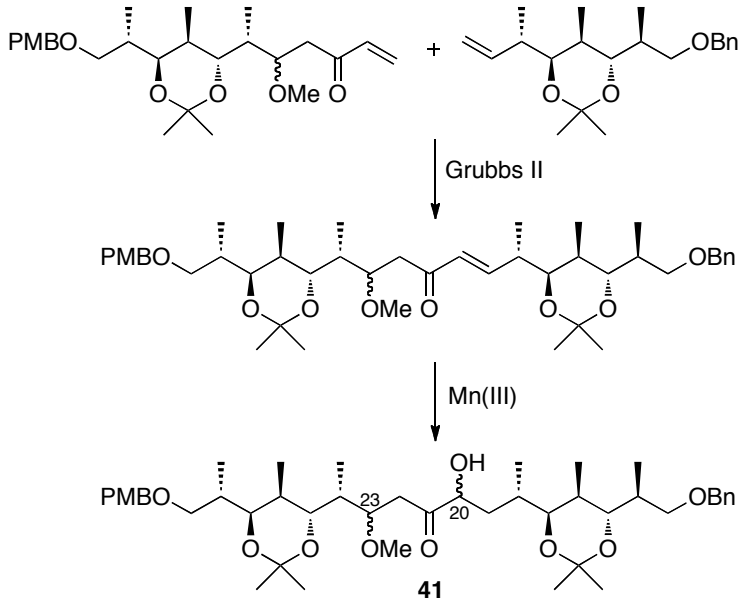
Coupling of major aldehyde **37** (the alkenyl group was omitted as it was thought to interfere with the later spirocycliation) and ketone **34** was attempted using (-)Ipc_2BCl/Et_3N for enolisation, identical to the procedure Paterson *et al.*,[10-13,22] however no reaction was observed. The reaction was then attempted using LDA as the enolising reagent, producing aldol adducts **38** and **39** in a 3:1 ratio in favour of the desired isomer **38**, consistent with the results of Kalesse.[17] This also suggests a high level of substrate control is present in this reaction, as Paterson performed the LDA aldol with his acetonide protected aldehyde and observed selectivity of 3.5:1 in favour of the undesired isomer **39**.[10] Cossy and co-workers were able to separate the two aldol adducts by flash chromatography and the major isomer **38** was converted to spiroketal analogue **40**, leading to confirmation of the C23 stereochemistry by nOe analysis (scheme 2.10).



Scheme 2.10: Aldol coupling of ketone **34** with aldehyde **37** and subsequent spiroketalisation by Cossy *et al.*[21]

In unpublished efforts presented at a conference in 2008,[22] the Rizzacasa group from the University of Melbourne, Australia have completed a synthesis of linear precursor **41** that adopts an alternative approach to those seen thus far. Instead of

utilising C22-23 as the major bond disconnection in a retro-aldol fashion, Rizzacasa chose to construct the linear precursor *via* cross-metathesis at C19-20. This was followed by an Mn(III) catalysed conjugate reduction/oxidation for the synthesis of linear precursor **41**. The major drawback of this synthesis is the poor selectivity observed at both C20 and C23.



41

Scheme 2.11: Synthesis of linear precursor **41** to spirangien A by Rizzacasa *et al*.[22]

2.3 The Synthetic Approach to Spirangien A

Spirangien A (**1**) was chosen as the initial target over spirangien B (**2**) as it is the more biologically active of the two compounds and it was also proposed to share an advanced common intermediate with its 1,3-diene analogue **3**, which could be used to determine the absolute configuration of the natural products. Therefore, a stereocontrolled, convergent synthesis would be required that takes advantage of the close structural relationship between spirangien A (**1**) and spirangien diene (**3**).

It was obvious that attachment of the pentaene side-chain would be the final stage in the synthesis of spirangien A as it is a highly sensitive and unstable structural element, and can be substituted with a simpler diene side-chain as a final divergent

step to complete spirangien diene (**3**). Cyclisation of the spiroacetal core from a linear precursor would be the penultimate stage in the synthesis, giving rise to the advanced common intermediate for the two targets. Construction of the linear precursor was predicted to take advantage of the C22-23 aldol disconnection, a fundamental process in polyketide synthesis, as depicted in the retro-synthetic analysis below (section 2.3.1).

As previously mentioned, there were no synthetic studies towards spirangiens A and B reported at the outset of these studies. However, as new publications towards the synthesis of spirangien A (**1**) emerged it became apparent that the goals of this project would need to be altered in light of the emerging research. As such, the aim of the project was amended to be a formal synthesis, with particular emphasis on improving the selectivity of the key aldol reaction to form the linear precursor to spirangien A (**1**) and spirangien diene (**3**) and providing an alternative and potentially improved pathway to the natural products.

For ease of comparison, all compounds to follow will be numbered according to the natural product, spirangien A (**1**).

2.3.1 Retrosynthetic Analysis

As previously mentioned, the synthesis and attachment of the delicate pentaene side-chain was to be attempted as the final synthetic step towards spirangien A (**1**). However, as the total synthesis of spirangien A was completed by Paterson *et al.*[11,12] before this step was reached, the original goal of total synthesis was amended to a formal synthesis. This would involve synthesis of spiroacetal **18**, an advanced intermediate in Paterson's total synthesis of spirangien A (section 2.3), which would not require synthesis of the pentaene side-chain. As such, the side-chain will not be discussed further in this account.

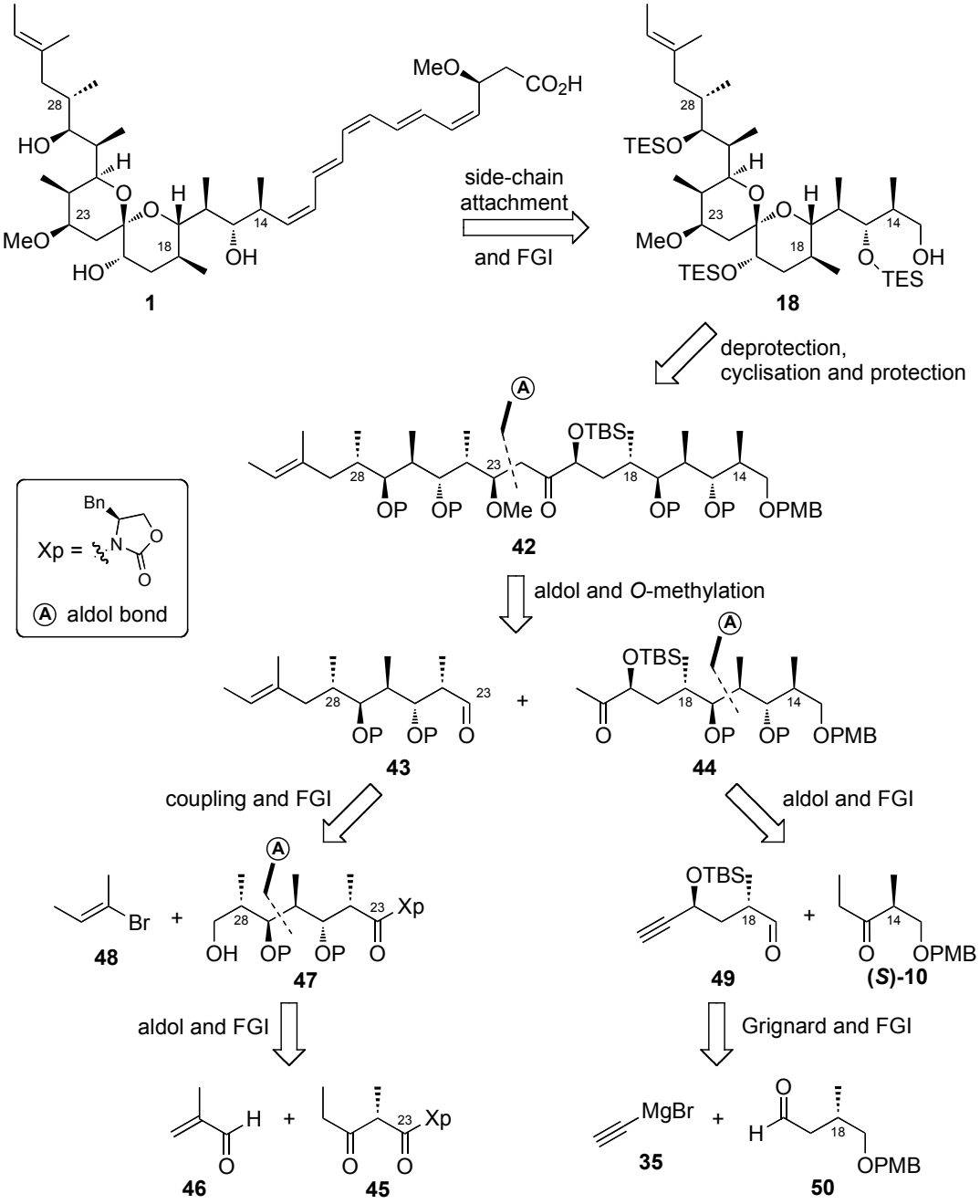
Synthesis of the spiroacetal core **18** was anticipated to arise from the spirocyclisation of a linear precursor in the form of **42**. This would result from liberation of the hydroxyl groups at C17 and 25 and subsequent cyclisation under

mild conditions. The protecting group strategy for four of the hydroxyl groups in **42** (C15, 17, 25 and 27) will form part of the focus of model studies to follow. To complete a formal synthesis, the resulting hydroxyl groups at C15, 20 and 27 in **42** would ultimately need to be protected as the corresponding TES ethers as in Paterson's synthesis,[10] and deprotection of the PMB ether to afford the terminal alcohol **18**.

Formation of linear precursor **42** forms the pivotal focus of this project. This is because it was imagined to arise from the aldol coupling of a ketone and aldehyde fragment, the outcome of which had, at the outset of this project, no literate precedent. As outlined in section 2.2, there have since been attempts towards this union, however it was hoped that the selectivity of this reaction could be improved upon by employing a different protecting group strategy and/or alternative enolisation conditions. The new hydroxyl group would subsequently be *O*-methylated to give the required C23 functionality and linear precursor **42**.

Synthesis of the aldol coupling partners aldehyde **43** and ketone **44** form a major component of these studies. Both partners were envisioned to arise from a dipropionate aldol coupling to install the requisite stereochemistry. Synthesis of aldehyde **43** was proposed from coupling of Evans'[23] dipropionate equivalent **45** with methacrolein (**46**), followed by *anti*-reduction and protection of the resultant 1,3-diol with a suitable protecting group. The terminal olefin would then need to be elaborated using a hydroboration reaction to give the desired C28 stereochemistry in alcohol **47** and alkylated with alkyl bromide **48**, followed by removal of the auxiliary to give aldehyde **43**.

Ketone **44** on the other hand was proposed to arise from union of dipropionate equivalent **(*S*)-10** with aldehyde **49**, which would provide an interesting synthetic challenge of its own. Reaction of commercially available (Sigma-Aldrich Chemical Co.) Grignard reagent ethynylmagnesium bromide (**35**) with known[24,25] aldehyde **50** was envisioned to give rise to an epimeric alcohol which, upon appropriate functional group manipulation would give aldehyde **49** with the correct C20 stereochemistry.

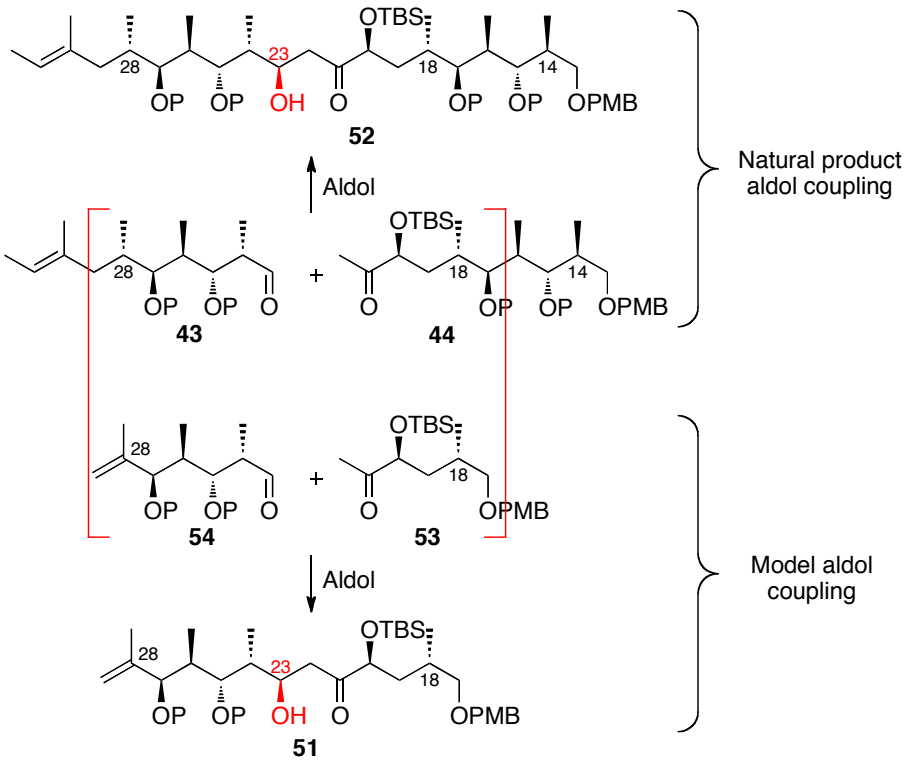


Scheme 2.12: Retrosynthetic analysis of spirangien A (**1**).

2.4 Model Studies

A model system was employed that was anticipated to mimic the reactivity of major coupling partners ketone **44** and aldehyde **43** in the key C22-23 aldol reaction, to provide a more efficient way of optimising the stereochemical outcome of this novel coupling. This approach has the added benefit of testing the efficacy of a significant portion of the synthetic pathway towards the natural product aldol coupling partners and potentially generate useful intermediates for the natural product synthesis.

Scheme 2.13 illustrates the chosen model system, in which simplified aldol coupling partners will be united to give **51**, in order to determine the appropriate conditions to produce aldol adduct **52**. Model ketone **53** incorporates the α-hydroxy stereocentre, which would undoubtedly exhibit some control over aldol stereochemistry (as later confirmed by Kalesse *et al.*[18]). The model ketone also lacks the C14-17 stereopentad seen in ketone **44**, and consequently the 1,3-diol protecting group(s), which are all sufficiently remote from the reaction site that they were expected to exert little or no control over the diastereoselectivity of the aldol reaction. The model aldehyde **54** on the other hand would feature the 1,3-diol, as the more remote β- and γ-stereocentres on chiral aldehydes can exert significant control over the diastereoselectivity of aldol couplings and can override the Felkin preference imparted by the α-stereocentre.[26] The model system also affords the opportunity to attach different protecting groups to aldehyde **54** as the protecting group chosen could also significantly influence the stereochemistry of the aldol adduct.



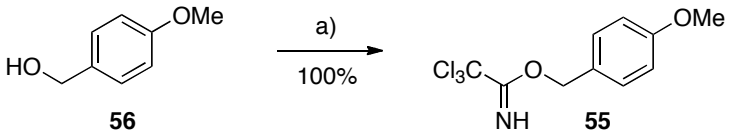
Scheme 2.13: Comparison of the model aldol coupling to that required for the natural product.

2.4.1 Synthesis of Model Ketone 53

Synthesis of model ketone **53** (scheme 2.13) was envisaged to occur from elaboration of the commercially available (TCI Chemical Co.) chiral starting material (*R*)-Roche ester (**[*R*)-32**]. The sequence began by protecting the free hydroxyl as the *para*-methoxybenzyl (PMB) ether. The PMB protecting group was chosen because it was required to survive a lengthy sequence of reactions and be removed selectively at a later stage.

In the original method for preparation of PMB imidate,[27,28] PMB alcohol is treated with NaH and trichloroacetonitrile, requiring the careful washing and handling of NaH under a nitrogen atmosphere. The modified procedure of Patil[29] however, can be applied to a wide range of benzyl-acetimidates and can be carried out under aqueous conditions and was therefore the chosen method for the synthesis of PMB imidate **55**. Accordingly, PMB alcohol (**56**) was treated with trichloroacetonitrile

(Cl_3CCN) in a biphasic solvent (1:1 50% aqueous KOH:CH_2Cl_2), in the presence of a phase transfer catalyst (tetrabutylammonium hydrogen sulphate) (scheme 2.14). The reaction mixture was stirred vigoriously for 1 hour to ensure sufficient mixing of the phases to react all of the PMB alcohol (**56**). Unreacted PMB alcohol was undesirable as it was difficult to separate and competed for PMB protection in the following step. This reaction gave high yields of PMB imidate, which could be used without purification if pure by NMR, or distilled under reduced pressure to remove impurities.

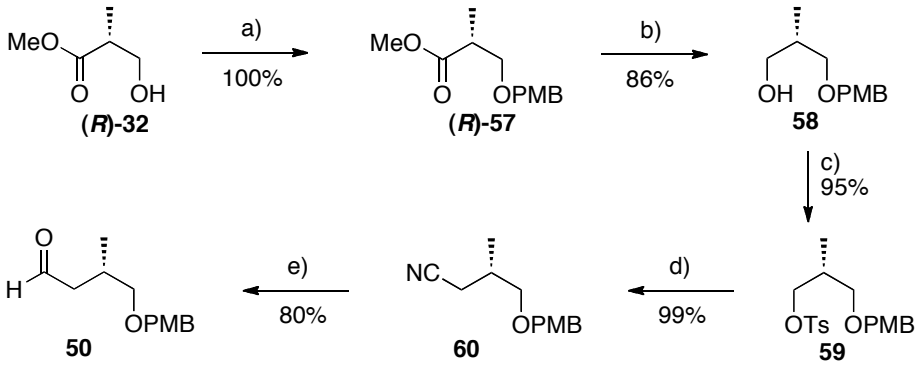


56 **55**

Reagents and conditions: a. i. KOH (50% aq), *n*-$Bu_4N{\cdot}HSO_4$ (cat.), CH_2Cl_2, −15 °C, 5 min; ii. Cl_3CCN (1.2 eq), −15 °C, 30 min to rt, 30 min.

Scheme 2.14: Preparation of PMB imidate **55**.

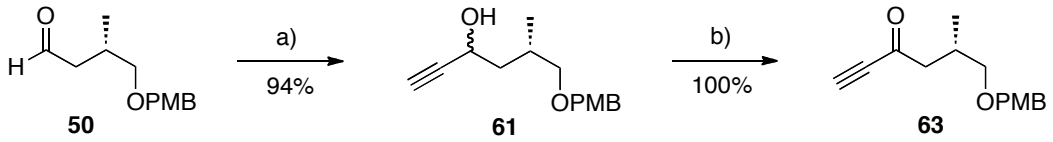
(*R*)-Roche ester [**(*R*)-32**] was protected as PMB ether **(*R*)-57** in quantitative yield using the prepared PMB-imidate (**55**) and catalytic TfOH in Et_2O.[30] Ester **57** underwent complete reduction with $LiAlH_4$ to give alcohol **58**, followed by tosylation of the resulting hydroxyl group using tosyl chloride in a solution of pyridine to furnish **59**.[31] The tosyl group was used to activate **59** towards nucleophilic substitution by a cyanide anion, so that addition of sodium cyanide in warm DMSO gave nitrile **60**.[32] Nitrile **60** was then reduced using DIBAL to provide known aldehyde **50** in 65% yield over 5 steps from **(*R*)-32**, in preparation for further functionalisation (scheme 2.15).[32] Purification of all intermediates in this sequence was achieved by flash column chromatography of single component crude residues.



Reagents and conditions: a. PMB imidate (**55**) (1.5 eq), TfOH (10 mol%), Et_2O, rt, 18 h; **b.** $LiAlH_4$ (2.4 eq), THF, 0 ^oC to rt, 30 min; **c.** *p*-TsCl (1.4 eq), pyridine, 0 ^oC, 9 h; **d.** NaCN (2.1 eq), DMSO, 60 ^oC, 18 h; **e.** DIBAL (3 eq), CH_2Cl_2, -78 ^oC, 2 h.

Scheme 2.15: Synthesis of aldehyde **50** from commercially available (*R*)-Roche ester [**(*R*)-32**].

Aldehyde **50** was purified by column chromatography using buffered silica and prepared immediately prior to use to prevent decomposition. A simple Grignard addition of ethynylmagnesium bromide (**35**) to aldehyde **50** gave epimeric alcohol **61** in good yield (94%) (scheme 2.16). Two isomers of alcohol **61** were evident from double resonances for diagnostic peaks in the ^1H and ^{13}C NMR. The Grignard reaction gave the required carbon chain length for the model ketone, however only one epimer of alcohol **61** was required for the remainder of the synthesis. Separation of the isomers was not only difficult, but would result in an undesirable 50% loss of material. Therefore, a two-step oxidation/selective reduction sequence was proposed to convert the epimeric mixture to a single diastereomer of alcohol **62**. First, the mixture of epimers **61** was oxidised under modified Dess-Martin conditions[33-35] with DMP and a catalytic amount of H_2O to furnish ketone **63** in quantitative yield (scheme 2.16).

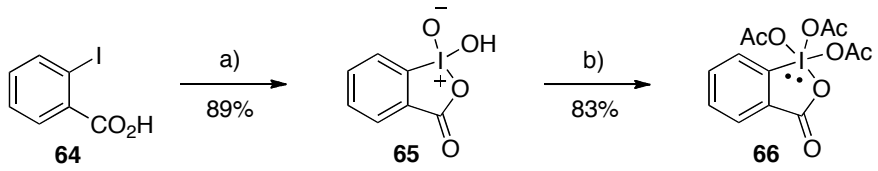


Reagents and conditions: a. Ethynylmagnesium bromide (**35**) (1.5 eq), THF, rt, 2 h; **b.** DMP (1.5 eq), H_2O (1 eq), CH_2Cl_2, rt, 4h.

Scheme 2.16: Synthesis of ketone **63** from aldehyde **50**.

Dess-Martin periodinane was prepared according to the procedure of Dess and Martin[33,34], modified by Ireland and Liu[36] (scheme 2.17). Iodobenzoic acid (**64**) was first treated with $KBrO_3$ in a solution of H_2SO_4 to produce the stable intermediate IBX (**65**).[33,34] IBX is also a good oxidising agent, but is less soluble in organic solvents than DMP. Dess and Martin's original procedure then required acetylation of IBX (**65**) by treatment with acetic acid (AcOH) and acetic anhydride at 100 ^{o}C.[33,34] This procedure has since been superseded by Ireland and Liu's acetylation,[36] which calls for treatment of intermediate **65** with *p*-TsOH (in place of AcOH) and acetic anhydride. This method is more reliable, requires shorter reaction times, simpler workup and higher yields. As a result, the air and moisture sensitive Dess-Martin reagent **66** was produced in 74% yield in 2 steps from iodobenzoic acid (**64**).

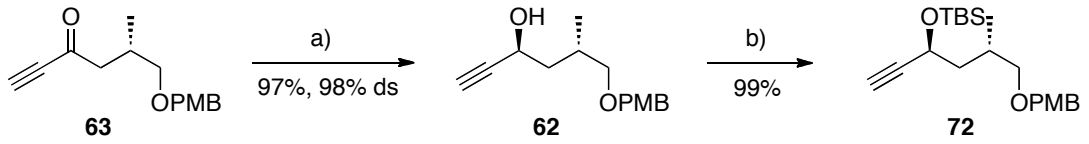
Oxidation of secondary alcohols using DMP alone can be sluggish, but Meyer and Schreiber[35] found that the addition of H_2O accelerates the reaction rate. This is because ligand exchange occurs between the H_2O and one of the acetate ligands on the iodine. The resulting hydroxyl group donates electrons to the iodine, causing the I-OAc bond to weaken, accelerating dissociation of the final acetate ligand to complete the oxidation.[35,34]



Reagents and conditions: a. $KBrO_3$ (1.3 eq), H_2SO_4 (0.7 M, 1.57 eq), 68 ^oC, 3.6 h; **b.** *p*-TsOH (cat.), Ac_2O, 80 ^oC, 2 h.

Scheme 2.17: Preparation of Dess-Martin periodinane (**66**).

Next, the required C20 stereochemistry was established by a highly diastereoselective (>98%) reduction of ketone **63** using stoichiometric amounts of (*S*)-2-methyl-CBS-oxazaborolidine (CBS catalyst, **67**) and $BH_3.Me_2S$, according to the procedure of Trost *et al.*[37], modified from the original procedure developed by Corey *et al.*[38,39] Alcohol **62** was readily separated from excess catalyst by column chromatography, which could be recycled if necessary. The reaction proceeded in 97% yield and 98% ds (scheme 2.18). This was an excellent result, giving almost exclusively the desired isomer of alcohol **62** in high yield from compound **61** (a 1:1 mixture of diastereomers).

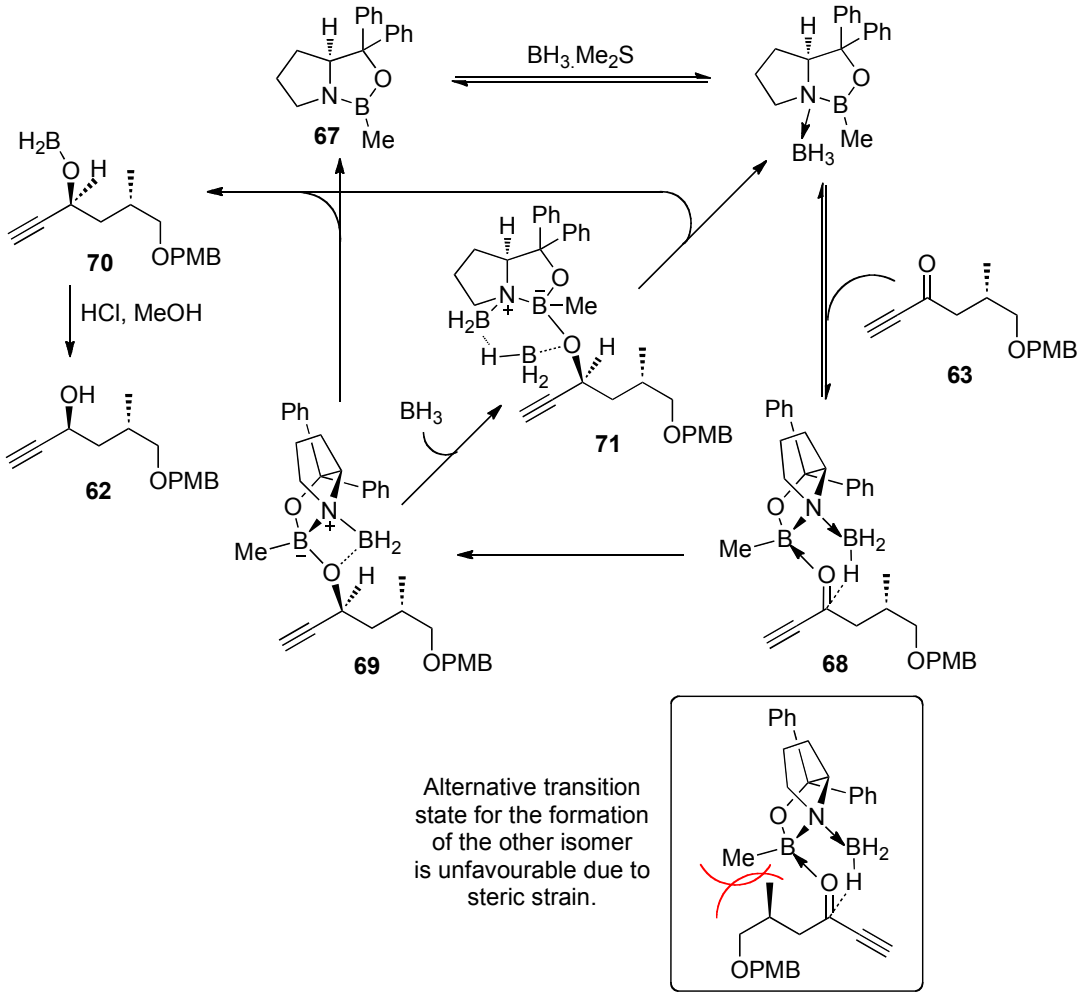


Reagent and conditions: a. (*S*)-2-methyl-CBS-oxazaborolidine (**67**) (1.1 eq), $BH_3.Me_2S$ (5 eq), THF, -30 ^oC, 2 h; **b.** 2,6-lutidine (2 eq), TBSOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 7.5 h.

Scheme 2.18: Synthesis of alkyne **72** from ketone **63**.

The CBS catalyst (**67**) is a chiral catalyst derived from proline and is a versatile reagent that can be used for the stereoselective reduction of prochiral ketones as

well as Diels-Alder reactions and [3+2] cycloadditions.[38,39] This reagent is ideal for the reduction of ketones that bear two substituents of significantly different steric bulk. This causes steric strain in the transition states leading to the two possible stereoisomers to be considerably greater for one isomer, leading almost exclusively to the formation of the other. The catalytic CBS cycle[40] for the generation of chiral alcohol **62** is shown in scheme 2.19.



Scheme 2.19: The CBS catalytic cycle for the formation of alcohol **62**.[40]

The excellent stereochemical outcome of the CBS reduction was rationalised by Corey (one of the namesakes of the CBS – Corey-Bakshi-Shibata – reaction) in a review paper on the usefulness of this method.[40] The first step in the cycle is the

reversible coordination of BH_3 to the Lewis basic nitrogen of oxazaborolidine **67** to form a *cis*-fused complex, activating the BH_3 as a hydride donor. The Lewis acidity of the endocyclic boron atom is also considerably increased so that it readily binds to the ketone *via* the more sterically accessible lone pair. The ketone binds in such a way that it minimises steric interaction with the oxazolidinone and is aligned with the vicinal BH_3 ready for hydride delivery *via* six-membered transition state **68**. The reduction product is then liberated either by cycloelimination of intermediate **69** to regenerate the catalyst and give boronate **70**, or by addition of BH_3 to form intermediate **69** which decomposes to reproduce the catalyst and borinate **71**. Alcohol **62** is finally produced under acidic workup conditions.

The newly generated hydroxyl group of compound **62** was protected as the *tert*-butyldimethylsilyl (TBS) ether **72** (scheme 2.18) using 2,6-lutidine and TBSOTf (99% yield).[41] The TBS group is sufficiently robust that it will remain attached throughout the desired transformations, while it can also be removed under mild conditions to preserve the sensitive substrate. Thus it was chosen in favour of bulkier silyl groups such as triisopropylsilyl (TIPS) or triphenylsilyl (TPS), which would require harsher conditions for removal, and there is a risk of not being able to remove them at all.

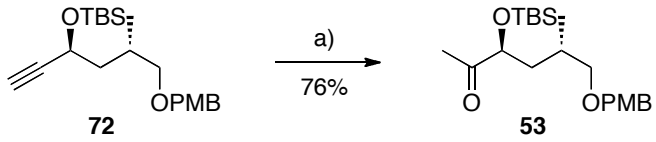
Alkyne **72** was chosen as an advanced intermediate in the synthesis of the model ketone **53** as it is also an intermediate in the proposed synthesis of ketone fragment **44**, required for the formal synthesis of spirangien A (**1**). Alkyne **72** was therefore produced in multi-gram quantities so that, upon optimisation of the model pathway, it could also be utilised in the total (or formal) synthesis of spirangien A (**1**).

Completion of the model ketone would require conversion of terminal alkyne **72** to the corresponding methyl ketone **53**. Initial attempts involved a direct conversion by means of a mercury-catalysed hydration of the alkyne. This approach was desired as it is a one-step procedure during which the oxidation state of the carbon at the reaction site does not change (ie. the alkyne and ketone are in the same oxidation state). The procedure involves the Hg catalysed Markovnikov addition of H_2O across the alkyne in the presence of acid to produce the enol, with subsequent

tautomerisation to the ketone. Alternative procedures would require a two-step process of reduction to the alkene, followed by oxidation to the ketone.

Typically Hg-catalysed hydration of alkynes is achieved using strong acid (H_2SO_4) and can require high temperatures. With an acid-sensitive substrate such as **72**, these conditions cause decomposition by cleavage of the silyl and/or PMB protecting groups. According to a procedure recently utilised by Paterson and Tudge,[42] which also employed an acid-sensitive substrate, the use of PPTS was sufficiently acidic to catalyse the reaction, whilst also being mild enough to prevent starting material or product decomposition. This method used $Hg(OAc)_2$, H_2O and PPTS in THF at 45 ^{o}C, however yields for this reaction when applied to the present substrate **72** were poor (≤39%) and it was apparent from the ^{1}H NMR that the PMB ether was being cleaved. Cossy *et al.*[21] also experienced a poor yield (41%) for a similar reaction in their studies towards spirangien A, observing decomposition by cleavage of their TBS ethers.

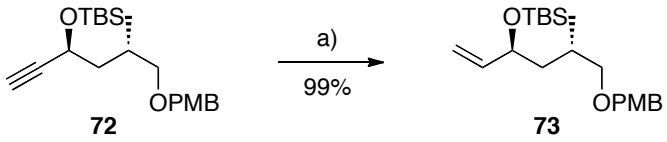
It was clear that optimisation of the yield would be required if this method were to be applied to the natural product system. To this effect, H_2O was substituted with pH 7 phosphate buffer solution, and the reaction time was shortened to 5 h (as dictated by TLC monitoring) from the initial 60 h, resulting in improved yields of methyl ketone **53** of up to 76% (scheme 2.20). It was also found that the reaction proceeded readily at rt. The appearance of decomposition products due to cleavage of the TBS and/or PMB ether was visible upon monitoring of the reaction by TLC, indicating when to cease the reaction. These minor by-products were separable from methyl ketone **53** upon column chromatography. The ^{1}H and ^{13}C NMR spectra of model ketone **53** can be seen in appendix A (figures A1 and A2).



Reagent and conditions: a. PPTS (1.5 eq), pH 7 buffer (2 eq), $Hg(OAc)_2$ (0.3 eq), THF, 45 ^{o}C, 5 h.

Scheme 2.20: Successful conversion of alkyne **72** to methyl ketone **53**.

Concurrent to investigations into the direct conversion of alkyne **72** to methyl ketone **53**, an alternative reduction-oxidation pathway was explored, as the potential for higher yields could outweigh the benefits of a one-step approach. As such, alkyne **72** was reduced under Lindlar conditions[43,44] at rt for 1 h, affording pure alkene **73** in 99% yield (scheme 2.21). Reaction times exceeding 1 h caused over-reduction to produce the corresponding alkane.

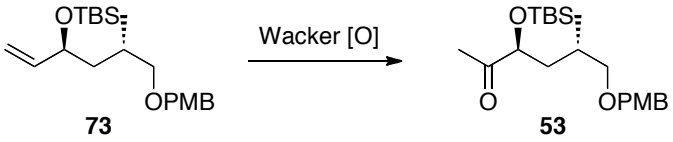


Reagent and conditions: a. H_2 (1 atm), quinoline (0.03 eq), Lindlar cat. (10% w/w), MeOH, rt, 1 h.

Scheme 2.21: Lindlar reduction of alkyne **72**.

A Wacker oxidation was envisioned to achieve the conversion of alkene **73** to methyl ketone **53**. Initially, modified Wacker oxidation conditions were employed, which used O_2 and $PdCl_2$ as the sole catalyst in DMA under an atmosphere of O_2.[45] However, in the mixture of products that ensued, neither methyl ketone **53** nor alkene **73** could be identified in the ^{1}H NMR of the crude mixture. More traditional conditions were then trialled, which used stoichiometric amounts of $PdCl_2$, $CuCl_2$ and LiCl as co-catalysts,[46-48] however this only resulted in partial conversion to

methyl ketone **53** (around 50%), as did $Pd(OAc)_2$, with pyridine and propan-2-ol, according to the modified procedure of Nishimura *et al*.[49] (table 2.2).



73 **53**

Conditions	Yield
$PdCl_2$, O_2, DMA, 80 ^oC, 4 h	Decomposition
i) $Hg(OAc)_2$, MeOH, rt, 12 h ii) $PdCl_2$, LiCl, $CuCl_2$, MeOH, 55 ^oC, 3 h	52%
$Pd(OAc)_2$, pyridine, O_2, propan-2-ol, toluene, 60 ^oC, 6 h	43%

Table 2.2: Conditions trialled for the Wacker oxidation of alkene **73**.

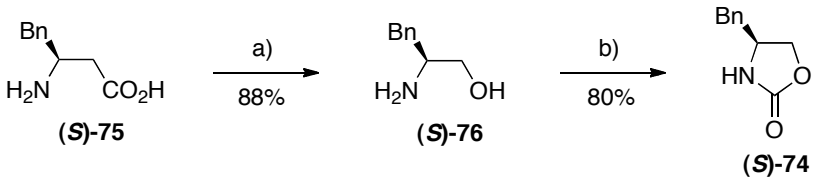
Investigations into the Wacker oxidation were not pursued any further at this stage, as the direct hydration approach gave higher yields in a single step and was easier to purify. This approach was however revisited later in a more complicated system towards the natural product synthesis.

2.4.2 Synthesis of Model Aldehydes 85 and 107

To increase the efficiency of the overall synthesis in terms of both time and economic viabilty, the initial approach to model aldehydes with the general structure of **54** was to employ the same procedure proposed for the natural product aldehyde **43**, omitting the alkenyl functionality and the C28 stereocentre (scheme 2.13). As such, the synthetic pathway to the model aldehyde would need to proceed *via* an intermediate that could be elaborated upon to furnish the natural product aldehyde fragment.

The initial strategy for this synthesis of aldehyde **54** would require large quantities of β-ketoimide **45**, a suitable dipropionate equivalent for installing the C24-27 stereotetrad. Evans' auxiliary **(*S*)-74** was synthesised according to the modified two-

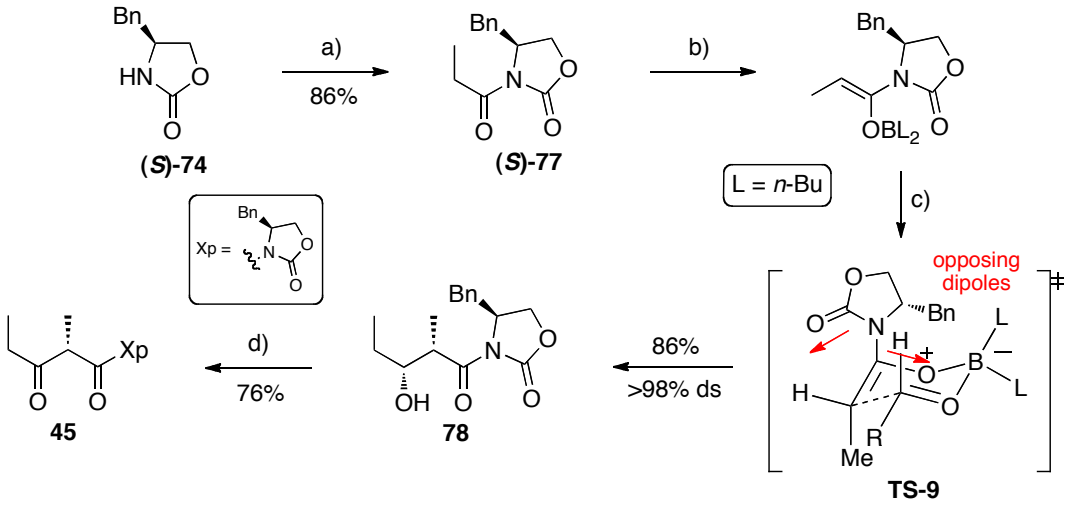
step procedure of Gage and Evans[50] from (*S*)-phenylalanine [**(*S*)-75**] (70% over 2 steps). (*S*)-phenylalanine was first reduced to (*S*)-phenylalanol [**(*S*)-76**] using $NaBH_4$ and I_2,[51] a more effective reduction than the traditional approach of Gage and Evans[50] using $BF_3.OEt_2/BH_3.Me_2S$. The amino alcohol was then reacted with diethyl carbonate ($(EtO)_2CO$) to form the oxazolidinone ring **(*S*)-74** (scheme 2.22).[50]



Reagent and conditions: a. $NaBH_4$ (2.4 eq), I_2 (1 eq), THF, 0 ^oC to reflux, 18 h;
b. $(EtO)_2CO$ (2 eq), K_2CO_3 (0.1 eq), 135 ^oC, 3 h.

Scheme 2.22: Synthesis of Evans auxiliary **(*S*)-74**.

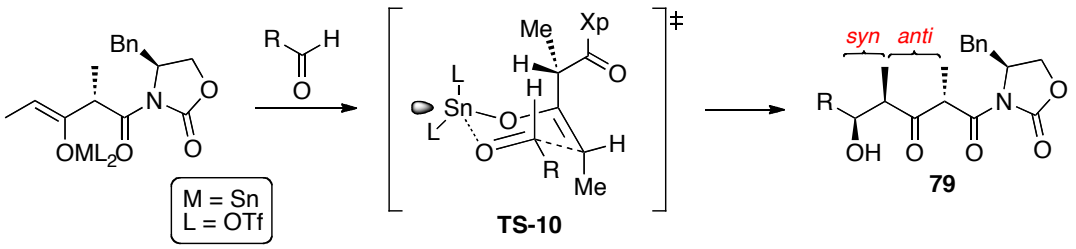
N-acylation of **(*S*)-74** to *N*-acyl (*S*)-oxazolidine **(*S*)-77** was readily achieved using propionyl chloride (EtCOCl) and *n*-butyllithium (86% yield).[50] This compound underwent a standard Evans aldol[23] using dibutylboron triflate (Bu_2BOTf) and triethylamine (Et_3N) to form the (*Z*)-enol borinate, with addition of an excess of freshly distilled propanal to give exclusively the *syn* aldol adduct **78**, *via* **TS-9** (86% yield; >98% ds). The rationale for the *syn* selectivity of this reaction is outlined in chapter one (section 1.3.1.3). Oxidation of the new hydroxyl group in **78** was achieved *via* a Parikh-Doering oxidation,[52,23] using DMSO as the oxidant, activated by sulfur trioxide-pyridine complex in the presence of Et_3N, allowing for access to multi-gram quantities of β-ketoimide **45** in good yield (76%) (scheme 2.23).



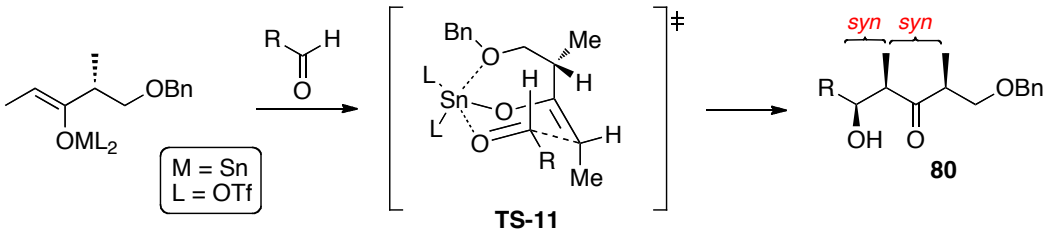
Reagent and conditions: a. i. *n*-BuLi (1.02 eq), THF, −78 °C; ii. propionyl chloride (1.1 eq), −78 °C, 30 min to rt, 1 h; **b.** i. Bu_2BOTf (1.2 eq), 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; **c.** propanal (2 eq), -78 °C, 30 min to 0 °C, 4 h; **d.** SO_3.pyr (3 eq), Et_3N (3 eq), DMSO/CH_2Cl_2, rt, 3 h.

Scheme 2.23: Synthesis of β-ketoimide **45**.

Tin triflate/Et_3N is used to enolise β-ketoimide **45** (or its enantiomer) in order to produce *syn,anti* aldol adducts such as **79** (scheme 2.24) in high diastereoselectivity (>95% for achiral aldehydes).[23] This outcome was justified by Evans and co-workers by invoking a transition state (**TS-10**) for the reaction in which the carbonyl oxygen of the enolate does not coordinate to the tin, positioning itself in such a way that it minimises steric strain over the ring system (scheme 2.24).[23] This argument is not however consistent with that presented by Paterson,[53] who attributed the high selectivity observed for the aldol reaction of his dipropionate equivalent to the coordination of the benzyl ether oxygen to the tin (**TS-11**) to produce *syn,syn* adduct **80** (scheme 2.25).[54] No consistent rationale exists to date that can explain the outcome of both reactions.



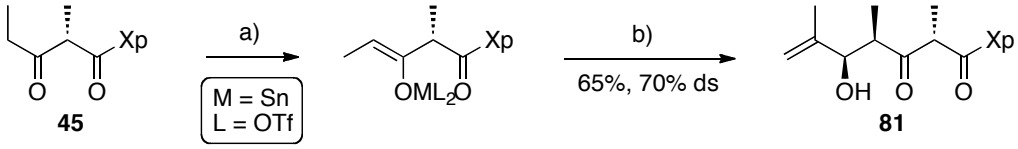
Scheme 2.24: Transition state rationale for the *syn,anti* outcome of the tin-aldol reaction by Evans.



Scheme 2.25: Transition state rationale for the *syn,syn* outcome of the tin-aldol reaction by Paterson.

Tin triflate is a particularly sensitive reagent that decomposes readily upon exposure to air or moisture. It is commercially available (Sigma Aldrich Chemical Co.), or it can be synthesised from tin(II) chloride and triflic acid in a lengthy and very sensitive reaction that is carried out (and the product isolated) under an atmosphere of argon.[55,56] To prepare this reagent, tin(II) chloride was dried under high vacuum at 120 ^{o}C for 2 h, then treated with an excess of TfOH and heated to 80 ^{o}C under argon for 12 h. The product was isolated *via* Schlenk techniques and washed with copious amounts of dry Et_2O to remove excess TfOH and the HCl by-product (ie. until neutral to litmus). The resultant white powder was then dried under high vacuum, ideally for 24-48 h, and it is necessary to handle the reagent in an argon glove bag to prevent decomposition. The product cannot be characterised due to its sensitive nature and therefore the outcome of the subsequent aldol reaction is the only test for its quality.

Several attempts were made to synthesise tin triflate, but these were all ineffective. All possible sources of contamination were probed, with fresh reagents purchased and $SnCl_2$ ground to a fine powder and washed several times with dry Et_2O to remove impurities. However, the source of error for this reaction was never discovered as time restraints led to abandoning this process in favour of the commercially available (Sigma Aldrich Chemical Co.) reagent. The reaction of β-ketoimide **45** with methacrolein (**46**) was carried out in 65% yield with reasonable diastereoselectivity (75% ds) to produce known[23] aldol adduct **81** (scheme 2.26). The two products could be separated by column chromatography and the ^1H and ^{13}C NMR spectra of pure **81** can be found in appendix A (figures A3 and A4). The identical reaction has previously been achieved in >95% ds, indicating that the quality of $Sn(OTf)_2$ purchased was not as expected. The poor quality of the $Sn(OTf)_2$ also meant that the reaction could not be reliably reproduced and as such a sufficient quantity of **81** could not be obtained by this method. This approach was eventually concluded to be impractical, however it was pursued to the model aldehyde (below) to show that it *could* be a feasible pathway if time permitted optimisation of the $Sn(OTf)_2$ synthesis.

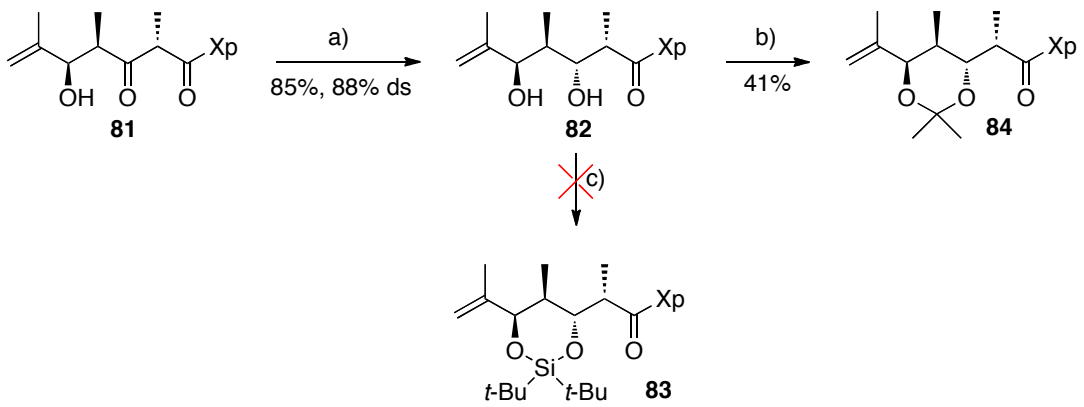


Reagent and conditions: a. i. $Sn(OTf)_2$ (1.3 eq), CH_2Cl_2, 0 ^oC; ii. Et_3N (1.3 eq), 10 min; iii. β-ketoimide **45**, CH_2Cl_2, −20 ^oC, 1 h; **b.** methacrolein (**46**) (1.5 eq); −78 ^oC, 30 min.

Scheme 2.26: Tin triflate mediated aldol reaction of β-ketoimide **45** with methacrolein (**46**).

Aldol adduct **81** was reduced using sodium triacetoxyborohydride in acetic acid to *anti*-1,3-diol **82** in 85% yield and 88% ds as white foam upon purification by column

chromatography (scheme 2.27).[57] It was originally anticipated that the 1,3-diol would be protected as the di-*tert*-butylsilylene **83**,[58-60] however attempts at this protection were unsuccessful. To determine whether the sterically bulky nature of this protecting group was impeding the reaction, protection as the less bulky diisopropylsilylene was also attempted, however the same problems were encountered, suggesting that it was the *anti* relationship of the 1,3-diol rather than steric issues that was impeding the reaction. Due to the difficulty of attaching a bridging silyl group, the acetonide protecting group was chosen instead, which was readily appended using 2,2-dimethoxypropane in the presence of PPTS to provide acetonide **84** (scheme 2.27).

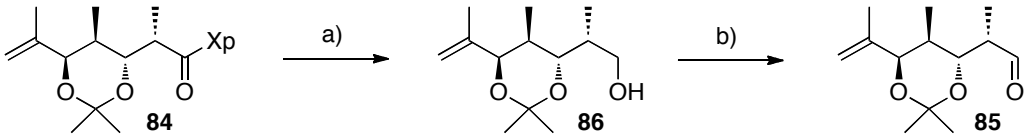


Reagent and conditions: a. $NaBH(OAc)_3$ (5 eq), AcOH, 5 ^oC, 3 h; **b.** PPTS (cat.), 1:1 $(MeO)_2C(CH_3)_2/CH_2Cl_2$, rt, 3 h; **c.** 2,6-lutidine (3 eq), *t*-$Bu_2Si(OTf)_2$ (2 eq), CH_2Cl_2, rt, 5 h.

Scheme 2.27: Generation and protection of 1,3-diol **82**.

It was anticipated that aldehyde **85** - the acetonide protected variant of model aldehyde **54** - would be obtained by reductive cleavage of the auxiliary using $LiBH_4/EtOH$[61] to afford alcohol **86**. Complete recovery of the chiral auxiliary **(*S*)-74** could be achieved by column chromatography. This was followed by a Swern[62] oxidation to give aldehyde **85**. As a consequence of the small quantities of aldol adduct **81** obtained *via* the $Sn(OTf)_2$ method, model aldehyde **85** could only be

produced on a small scale (scheme 2.28). Thus, although it is possible to produce model aldehyde **85** *via* this pathway, it was not pursued due to the problems associated with obtaining high quality $Sn(OTf)_2$.

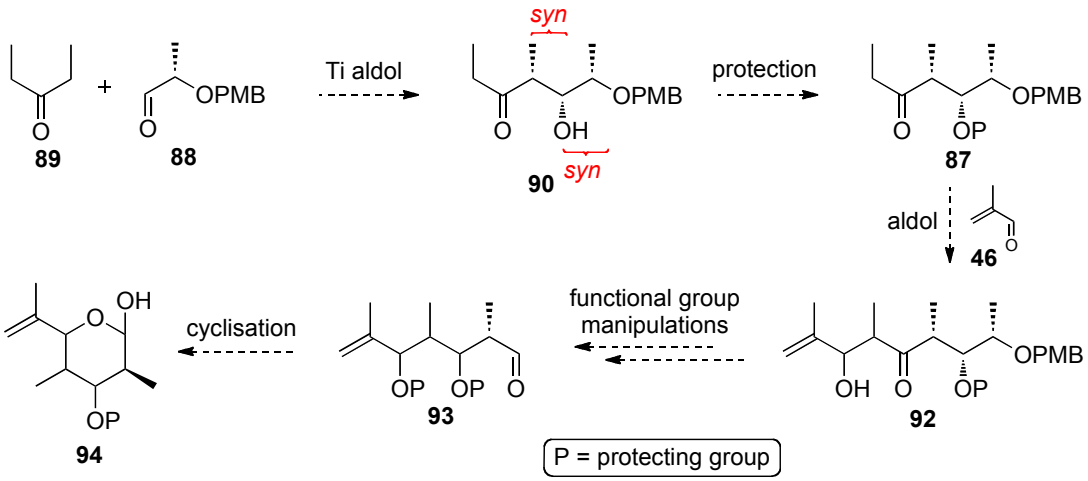


Reagent and conditions: a. EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^oC, 4 h; **b.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **86**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.28: Synthesis of model aldehyde **85** *via* an Evans dipropionate aldol pathway.

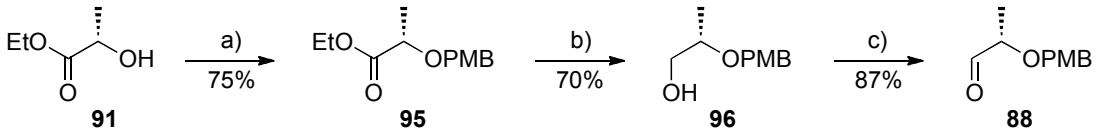
While $Sn(OTf)_2$ is the only known reagent available for the highly diastereoselective synthesis of *syn,anti* dipropionate aldol adducts like **81**, an alternative pathway would need to be explored which would avoid the need for this reagent. This shortfall prompted investigations into a new potential dipropionate equivalent for aldol reactions. This compound would take the form of **87** (scheme 2.29) and was envisioned to arise from the aldol coupling of chiral aldehyde **88** (which could be readily prepared from inexpensive commercially available starting materials) and diethyl ketone (**89**) to give aldol adduct **90**, followed by protection of the free hydroxyl. According to literature precedent from Solsona *et al*,[63] the facial preference of aldehydes derived from ethyl (*S*)-lactate (**91**) is towards the Felkin product using $TiCl_4$/*i*-Pr_2NEt. It was anticipated that the same selectivity would be observed with the α-chiral aldehyde **88**, which differs only by the hydroxyl protecting group. The resulting dipropionate equivalent would then be reacted with methacrolein (**46**) under various enolising conditions to give different isomers of aldol adduct **92**. Various functional group manipulations could then give rise to aldehydes in the form of **93**, as required for the model system. Cyclisation of these

aldehydes to the corresponding hemicetal **94** would provide a means of complete stereochemical assignment by examination of the nOe correlations with the known stereocentre.



Scheme 2.29: Proposed pathway to novel dipropionate equivalent **87** and transformation to aldehyde **92**.

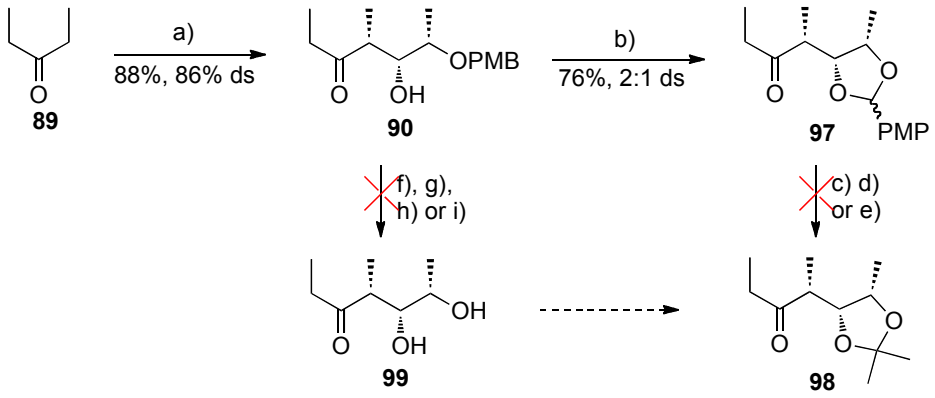
First, the free hydroxyl of commercially available (Sigma Aldrich Chemical Co.) ethyl (*S*)-lactate (**91**) was protected as the PMB ether **95**. Protection of alcohols of this type work best using catalytic CSA,[64,65] rather than the more acidic TfOH. The PMB protection proceeded in reasonable yield (75%), followed by $LiAlH_4$ reduction of the ester and subsequent Swern[62] oxidation to afford chiral aldehyde **88** *via* alcohol **96** in 46 % yield over 3 steps (scheme 2.30).



Reagent and conditions: a. PMB imidate (**55**) (1.3 eq), CSA (0.1 eq), CH_2Cl_2, rt, 4 days; **b.** $LiAlH_4$ (1.13 eq), THF, 0 ^oC to rt, 30 min; **c.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **96**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.30: Synthesis of aldehyde **88** from ethyl (*S*)-lactate (**91**).

A standard $TiCl_4$/*i*-Pr_2NEt aldol[23] between diethyl ketone (**89**) and chiral aldehyde **88** furnished aldol adduct **90** in 88% yield, 86% ds. These conditions drive the formation of the *Z*-(O)-enolate, giving predominantly the *syn* relationship of the two new stereocentres, and the Felkin relationship with the pre-existing stereocentre (ie. *syn*), as shown in scheme 2.29. The minor aldol isomer was removed by column chromatography to deliver pure **90**. To convert aldol adduct **90** to an appropriate dipropionate equivalent, the free hydroxyl would need to be protected. Several protecting group options were available, however it seemed logical to utilise the existing PMB group to create a PMP acetal, thus avoiding the need for additional protecting groups and extra steps to remove them at a later stage. As such, oxidative conditions were employed (DDQ/4 Å sieves)[66], which resulted in cyclisation to form PMP acetal **97**. Unfortunately, PMP acetal **97** existed as a 2:1 mixture of isomers that could not be separated, as a result of the new acetal stereocentre. While the stereochemistry at this centre is largely inconsequential as the protecting group is designed to be removed at a later stage, the presence of two isomers made characterisation and stereochemical assignment of any further aldol adducts more difficult and could potentially effect the diastereoselectivity of subsequent aldol reactions.



Reagent and conditions: a. i. $TiCl_4$ (1.2 eq), CH_2Cl_2, -78 ^oC, 30 min; ii. *i*-Pr_2NEt (1.4 eq), -78 ^oC, 1.5 h; iii. **88**, -90 ^oC, 1.5 h; **b.** 4 Å sieves, DDQ (1.2 eq), CH_2Cl_2, 0 ^oC, 5 h; **c.** PPTS (0.2 eq), $(MeO)_2C(CH_3)_2$, 60 ^oC, 20 h; **d.** CSA (0.1 eq), $(MeO)_2C(CH_3)_2$, rt, 1 h; **e.** i. PPTS (0.25 eq), MeOH, 70 ^oC, 30 min; ii. PPTS (cat.), $(MeO)_2C(CH_3)_2$, CH_2Cl_2, rt, 15 h; **f.** DDQ (1.5 eq), pH 7 buffer, CH_2Cl_2, 0 ^oC, 3 h; **g.** Me_2S (0.1 eq), $MgBr_2.OEt_2$ (3 eq), CH_2Cl_2, rt, 24 h; **h.** CAN (3 eq), H_2O, CH_3CN, rt, 12 h; **i.** H_2, 10% Pd/C (10% w/w), MeOH, rt, 12 h.

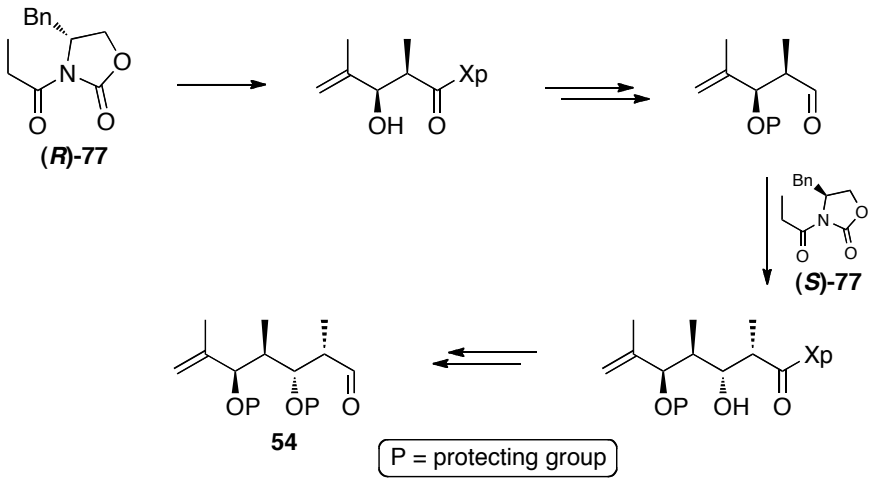
Scheme 2.31: Aldol coupling of diethyl ketone (**89**) with aldehyde **88** and attempted transformations.

Differential protection with a silyl group (TES or TBS) was undesirable, as these groups are often used to protect the subsequent aldol adduct (in this case **92**) and would make differential deprotection difficult at a later stage. Exchange of the PMP acetal for an acetonide group was attempted using both PPTS and CSA in a solution of 2,2-dimethoxypropane [$(MeO)_2C(CH_3)_2$] (scheme 2.31). While no acetonide **98** was produced, PMB aldehyde could be identified in the crude residue (by ^1H NMR), indicating that the PMP acetal was being cleaved, but acetonide protection of the ensuing diol was not occurring and the diol was thought to be remaining in the aqueous phase. Intramolecular hemiacetalisation may have occurred, however no hemiacetal was detected in the crude residue. Deprotection was also tried using PPTS in MeOH, with isolation of the diol by evaporation of the solvent and subsequent acetonide protection using PPTS/$(MeO)_2C(CH_3)_2$ in CH_2Cl_2. Once again,

only PMB aldehyde was recovered, and it was thought that acetonide protection was not occurring due to the insolubility of diol intermediate **99** in organic solvents.

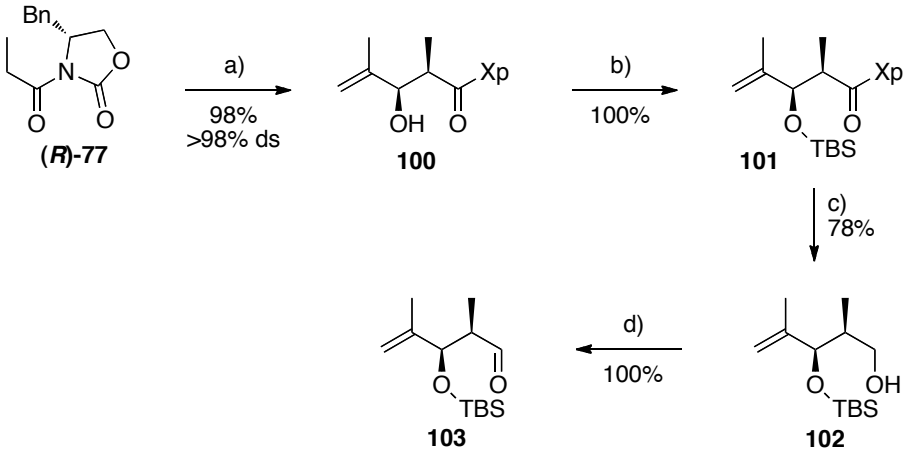
Cleavage of the PMB ether from **90** was also trialled under various conditions in the hope that diol **99** could be isolated (scheme 2.31). Standard DDQ deprotection, using DDQ in the presence of pH 7 phosphate buffer to oxidatively cleave PMB aldehyde,[67] did not result in deprotection, but gave the cyclic PMP acetal **97**. This shows that PMP acetal formation is a highly favourable process, as it usually requires anhydrous conditions to proceed. PMB cleavage was also attempted using $MgBr_2.OEt_2/Me_2S$[68], CAN[69] and hydrogenation, but these conditions did not invoke a reaction. As neither the PMB ether nor PMP acetal could be cleaved successfully, the investigations into the use of **97** as a dipropionate equivalent were ceased, as the removal of this group was essential to produce aldehyde **93**.

It was thought that the most reliable alternative, though it involved more steps, would involve two separate monopropionate Evans aldol reactions using both enantiomers of *N*-acylated oxazolidinone **77** (scheme 2.32). This strategy would also provide the opportunity for differential protection of the 1,3-diol, which could offer a further handle for optimising the model aldol reaction. This pathway could also be readily applied to the synthesis of aldehyde **43**, required for the formal synthesis.



Scheme 2.32: Proposed pathway for the synthesis of aldehyde **54**.

The initial aldol employed (*R*)-oxazolidinone **(*R*)-77** (synthesised as per **(*S*)-77** from (*R*)-phenylalanine) in a Bu_2BOTf/Et_3N mediated *syn*-selective reaction with methacrolein (**46**) to produce aldol adduct **100** in high yield and selectivity (98% yield; >98% ds) according to the popular procedure of Evans and co-workers.[70] Aldol adduct **100** was then protected as the TBS ether **101** in quantitative yield under standard conditions (2,6-lutidine/TBSOTf),[41] followed by reductive cleavage of the auxiliary using $LiBH_4$/EtOH,[61] affording alcohol **102** (78% yield). Swern[62] oxidation readily oxidised alcohol **102** to aldehyde **103** (shceme 2.33). Purification of these components was achieved using column chromatography.

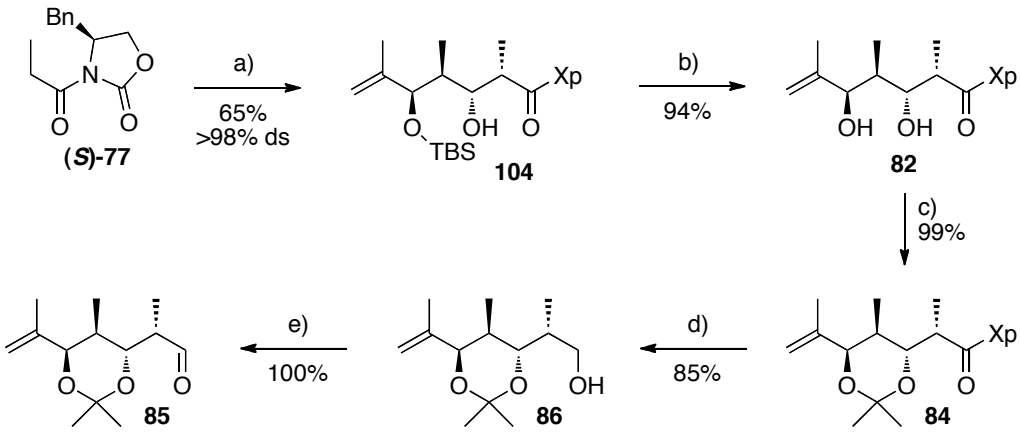


Reagent and conditions: a. i. Bu_2BOTf (1.2 eq), 0 ^oC, 30 min; ii. Et_3N (1.3 eq), 0 ^oC, 30 min; iii. methacrolein (**46**) (2 eq), -78 ^oC, 30 min to 0 ^oC, 4 h; **b.** 2,6-lutidine (2 eq), TBSOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 5 h, **c.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^oC, 4 h; **d.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **102**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.33: Synthesis of aldehyde **103** from **(*R*)-77**.

A second dibutylboron triflate mediated aldol reaction of (*S)*-oxazolidinone **(*S*)-77** with aldehyde **103** provided *syn* aldol adduct **104** (65% yield) in >98% ds (scheme 2.34). The TBS group was then cleaved using buffered hydrogen fluoride/pyridine (HF/pyr/pyr) and a catalytic amount of H_2O at rt for 5 days (HF/acetonitrile or

HF/pyridine not surprisingly resulted in decomposition of the acid-sensitive substrate).[71-73] This sequence gave rise to 1,3-diol **82** in good overall yield with >98% ds, as compared with the initial approach (ie. $Sn(OTf)_2$ followed by hydride reduction of the β-hydroxy ketone **81**) which gave the 1,3-diol **82** in moderate yield and moderate diastereoselectivity.



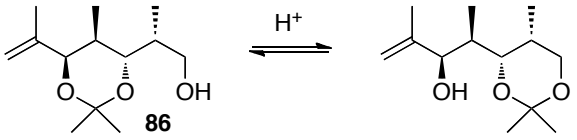
Reagent and conditions: a. i. Bu_2BOTf (1.2 eq), 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; iii. aldehyde **103** (1 eq), -78 °C, 30 min to 0 °C, 4 h; **b.** HF/pyr/pyr, THF, H_2O (cat.), rt, 5 days; **c.** PPTS (cat.), 1:1 $(MeO)_2C(CH_3)_2/CH_2Cl_2$, rt, 3 h; **d.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 °C, 4 h; **e.** i. DMSO (3 eq), CH_2Cl_2, -78 °C; ii. $(COCl)_2$ (1.5 eq), -78 °C, 30 min; iii. alcohol **86**, -78 °C, 45 min; iv. Et_3N (6 eq), -78 °C, 30 min to 0 °C, 30 min.

Scheme 2.34: Synthesis of aldehyde **85** *via* a sequential Evans *syn* aldol pathway.

The acetonide protecting group was readily appended in near quantitative yield to give compound **84** (scheme 2.34). The ^{13}C NMR shifts for the acetonide methyls (δ 25.3 and 24.0) confirmed the *anti* relationship of the 1,3-diol. This is because *anti* 1,3-diol acetonides adopt a twist boat conformation to avoid the *syn* pentane interactions associated with a chair conformation, causing the acetonide methyls to have near identical chemical shifts.[74] *Syn* 1,3-diol acetonides on the other hand do not experience such interactions in the chair conformation and a significant

difference in chemical shift is seen (~10 ppm) for the acetonide methyls as one adopts an axial position while the other is equatorial.[74]

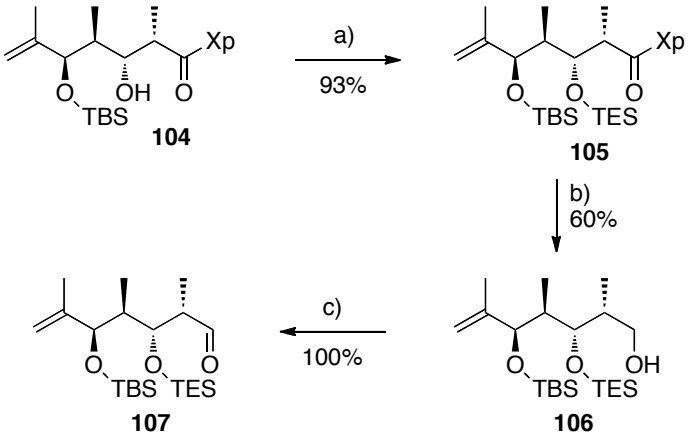
Upon reductive cleavage of the chiral auxiliary it was apparent by ^{1}H NMR and ^{13}C NMR analysis that some migration of the acetonide group was occurring to give a 2:1 ratio of the structural isomers of alcohol **86** shown in scheme 2.35. There was no evidence in the literature of such a migration occurring under the conditions employed; therefore it seemed likely that the migration was occurring either upon purification or characterisation. Buffered silica was used for purification of this alcohol (as with all potentially acid-sensitive compounds), therefore it seemed likely that the deuterated chloroform ($CDCl_3$) used for NMR characterisation was causing the migration as it can become acidic due to decomposition upon exposure to air and moisture. Indeed, when $CDCl_3$ was filtered through basic alumina prior to use, no migration of the acetonide was observed. As such, $CDCl_3$ was subsequently filtered through basic alumina prior to use with any potentially acid-sensitive substrates. Model aldehyde **85** was then produced in high yield (85% over 2 steps) from oxazolidinone **84** (scheme 2.34) (see appendix A for NMR spectra, figures A5 and A6).



Scheme 2.35: The two structural isomers seen by NMR analysis of **86** in acidic $CDCl_3$.

To provide access to an alternative model aldehyde, compound **104** was protected with a second silyl protecting group, the triethylsilyl (TES) group, to give the *di*-silyl protected species **105**. Reductive cleavage of the auxiliary with $LiBH_4$/EtOH[61] gave alcohol **106** and subsequent Swern[62] oxidation (as before) delivered model aldehyde **107** in 56% over 3 steps from compound **104** (scheme 2.36) (see appendix A for NMR spectra of aldehyde **107**, figures A7 and A8). The opportunity also existed

at this point to attach a range of other protecting groups, but this option was not pursued at this stage.



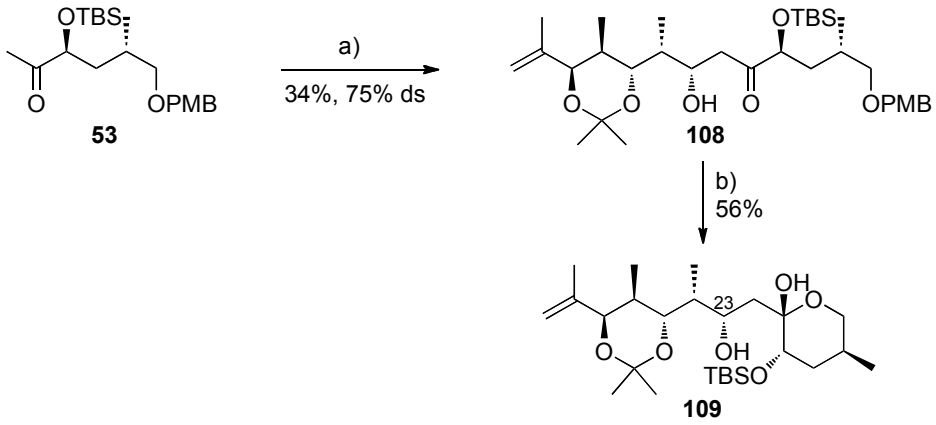
Reagent and conditions: a. 2,6-lutidine (2 eq), TESOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 7 h, **c.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^oC, 4 h; **d.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **106**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78 ^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.36: Synthesis of model aldehyde **107**.

2.4.3 Model Aldol Coupling

With model ketone **53** and two model aldehydes **85** and **107** in hand, the fragment union could be attempted. As a starting point, a Li aldol was chosen as the enolate is readily formed in 1 step and the inherent facial preference of both coupling partners could be observed. This was to be achieved by separately coupling the model ketone **53** with both aldehydes (**85** and **107**) using an enolising agent that would not significantly influence the selectivity of the reaction. LiHMDS was chosen because it is an achiral reagent and is readily commercially available (Sigma Aldrich Chemical Co.) as a solution in THF. As the ketone is a methyl ketone, enolate geometry was not a consideration.

The reaction between acetonide protected aldehyde **85** and model ketone **53** was achieved by first treating a solution of ketone **53** in THF with 1.5 equivalents of LiHMDS in THF at -78 ^{o}C, with stirring for 30 min to ensure complete enolisation (scheme 2.37).[75-77] Aldehyde **85** was then added at -78 ^{o}C, followed by stirring at this temperature for 5 h to give 34% yield of aldol adduct **108** and its C23 epimer. This mixture, consisting of a 3:1 ratio of products, was unable to be separated by column chromatography (^{1}H NMR spectrum, figure 2.4).



Reagent and conditions: a. i. LiHMDS (1.5 eq), THF, -78 ^{o}C, 30 min; ii. aldehyde **85** (1 eq), -78 ^{o}C, 5 h; **b.** DDQ (1.5 eq), pH 7 buffer, CH_2Cl_2, 0 ^{o}C, 3 h.

Scheme 2.37: Aldol reaction between model aldehyde **85** and model ketone **53** and subsequent PMB deprotection to produce hemiacetal **109**.

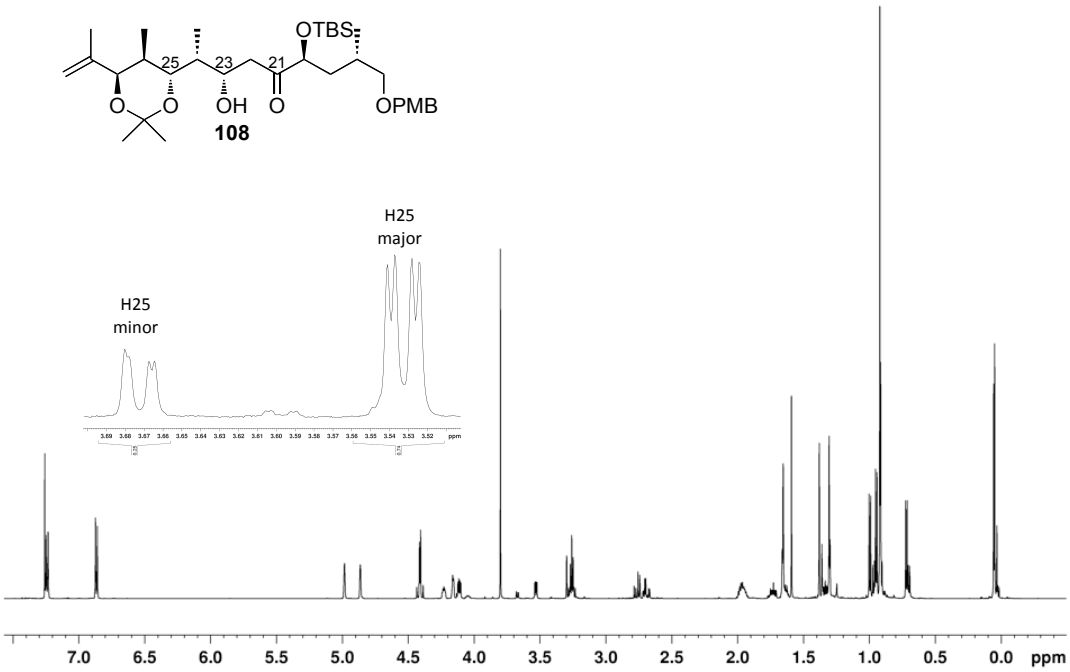


Figure 2.4: 600 MHz ^{1}H NMR spectrum of aldol adduct **108** in $CDCl_3$.

The results published by Paterson[10] around the same time as these studies were being conducted, showed a preference for the unwanted isomer in the C22-23 aldol. It was thus important to perform further transformations that would allow for conclusive stereochemical assignment of aldol adduct **108**. First, the mixture of products was treated with aqueous DDQ to reveal the terminal hydroxyl, which spontaneously cyclised onto the carbonyl to give hemiacetal **109** (and its C23 epimer) (scheme 2.37). The structure of hemiacetal **109** was assigned on the basis of 1D and 2D NMR, with hemiacetal formation apparent from the characteristic acetal OH singlet at δ 5.51 in the ^{1}H NMR (figure 2.5). Peaks corresponding to the cleaved PMB aldehyde are visible in figure 2.5 also as they were unable to be separated by column chromatography. A singlet at δ 9.89 (not shown in figure 2.5) indicates the presence of PMB aldehyde, and the absence of the methylene AB quartet at δ 4.41 shows that it has been completely oxidatively cleaved.

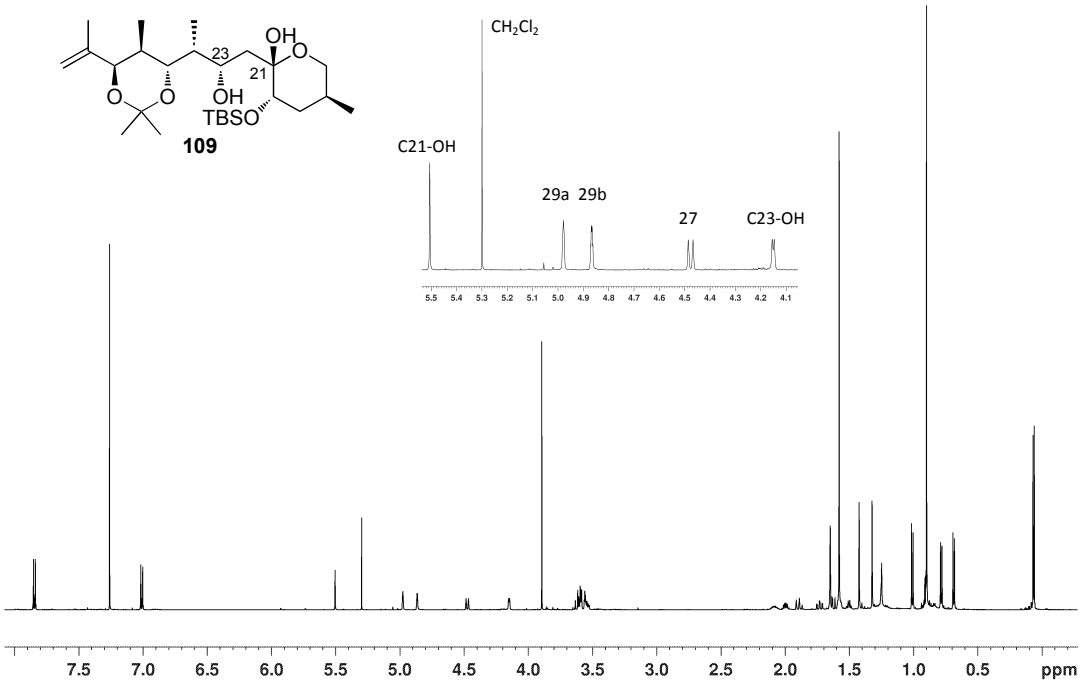
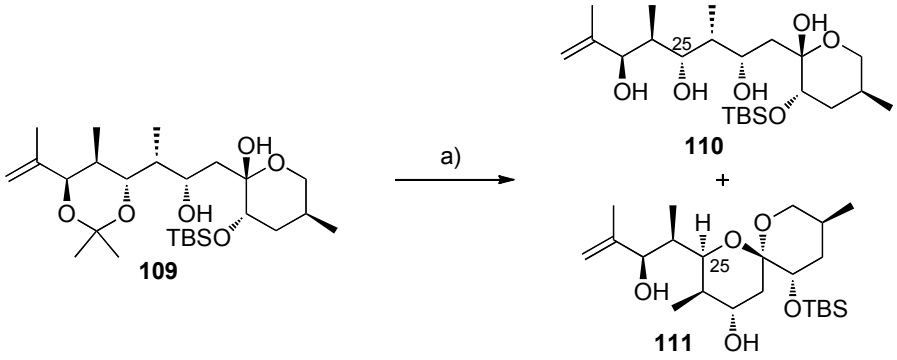


Figure 2.5: 600MHz ^{1}H NMR spectrum of mixture of hemiacetal **109** in $CDCl_3$.

Following this, the acetonide group was removed from compound **109** under mildly acidic conditions (PPTS/MeOH), revealing the deprotected hemiacetal **110**, some of which cyclised further to furnish spiroacetal **111** (hemiacetal **110**/spiroacetal **111** = 1:1). From the limited amount of this material obtained (2.9 mg), ^{1}H NMR assignments could be made based on COSY correlations. Hemiacetal **110** was identified on the basis of its characteristic acetal OH singlet at δ 5.09. H23 resonates at δ 4.06 (ddd, J = 9.6, 1.8, 1.2 Hz) in spiroacetal **111**, while in hemiacetal **110** H23 resonates further downfield at δ 4.64 (ddd, J = 10.8, 1.8, 1.8 Hz). The diagnostic nOe correlations observed for the spiroacetal, as depicted in figure 2.7, confirmed the undesired (*S*) configuration at C23 for the major product.



Reagent and conditions: a. PPTS (cat.), MeOH, rt, 14 h.

Scheme 2.38: Acetone deprotection of acetonide **109** to furnish hemiacetal **110** and spiroacetal **111**.

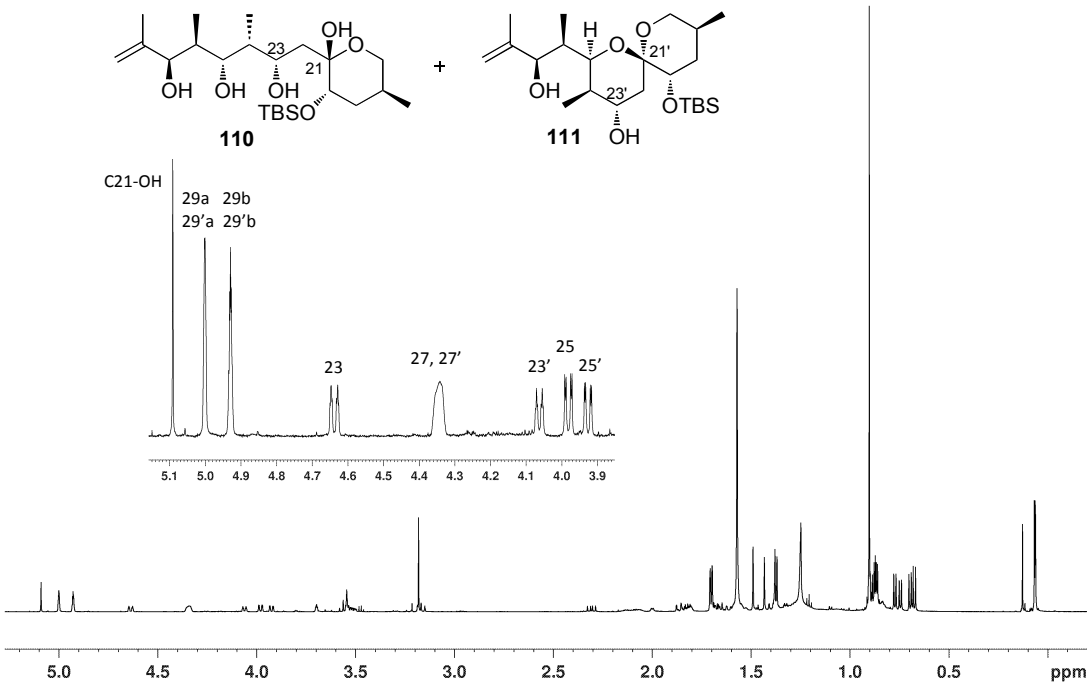


Figure 2.6: 600 MHz ^{1}H NMR spectrum of the mixture of hemiacetal **110** and spiroacetal **111** in $CDCl_3$.

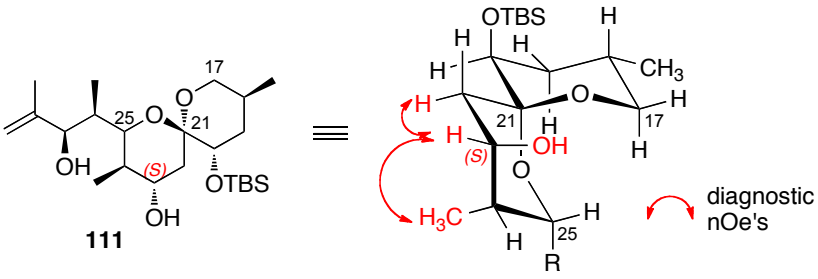
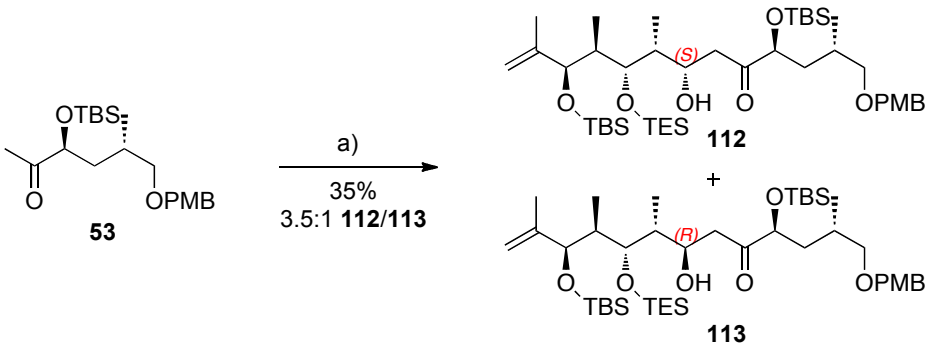


Figure 2.7: Diagnostic nOe correlations observed for spiroacetal **111**.

The reaction of silyl protected aldehyde **107** and methyl ketone **53** was also carried out using LiHMDS (1.5 eq) in THF at -78 ^{o}C for 5 h. This gave rise to a mixture of the two possible aldol adducts **112** and **113** in a 3.5:1 ratio (35 % yield) (scheme 2.39). Fortunately, these two compounds could be separated by column chromatography, meaning that each epimer could be analysed independently for the determination of stereochemistry.



Reagent and conditions: a. i. LiHMDS (1.5 eq), THF, -78 ^{o}C, 30 min; ii. aldehyde **107** (1 eq), -78 ^{o}C, 5 h.

Scheme 2.39: Aldol coupling of model aldehyde **107** with model ketone **53**.

The ^{1}H NMR spectra of major isomer **112** and minor isomer **113** are shown in figures 2.8 and 2.9 respectively. It can be seen that there are significant differences in the

chemical shifts of the protons close to the reaction site, particularly H22a, H22b and H23. For the major isomer **112**, H23 appears as a multiplet at δ 4.05, while in the minor isomer **113**, it is shifted significantly upfield at δ 3.77 (ddd, J = 8.4, 4.8, 1.8 Hz). H22a and H22b appear very close together as a multiplet at δ 2.65-2.64 in major isomer **112**, while minor isomer **113** shows H22a as a dd at δ 2.75 with AB distortion towards H22b at δ 2.59 (dd). This implies that H-bonding (which occurs between the C23 hydroxyl and C21 carbonyl) causes the H22 protons to be in significantly different environments by restricting rotation about the C22-23 bond.

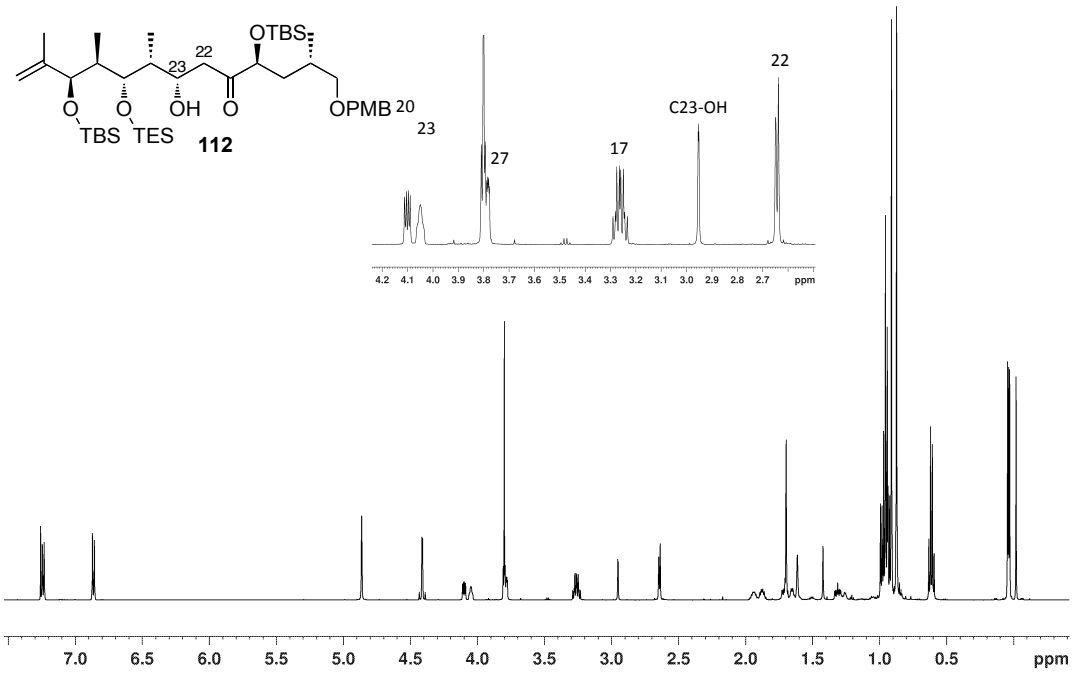


Figure 2.8: 600 MHz ^{1}H NMR spectrum of major aldol isomer **112** in $CDCl_3$.

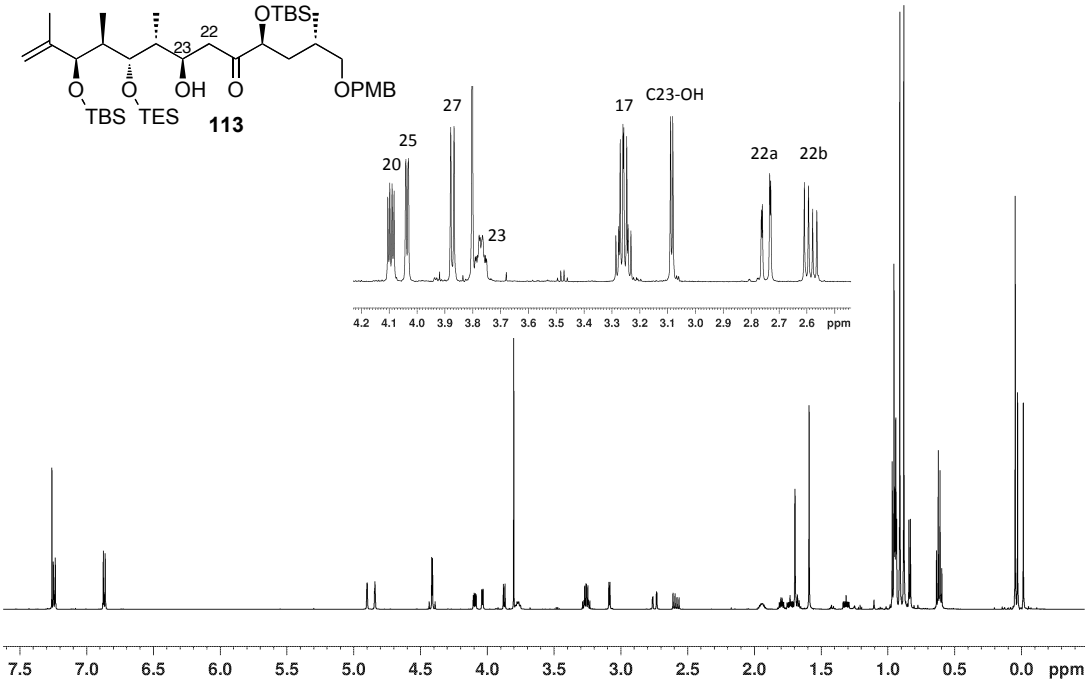
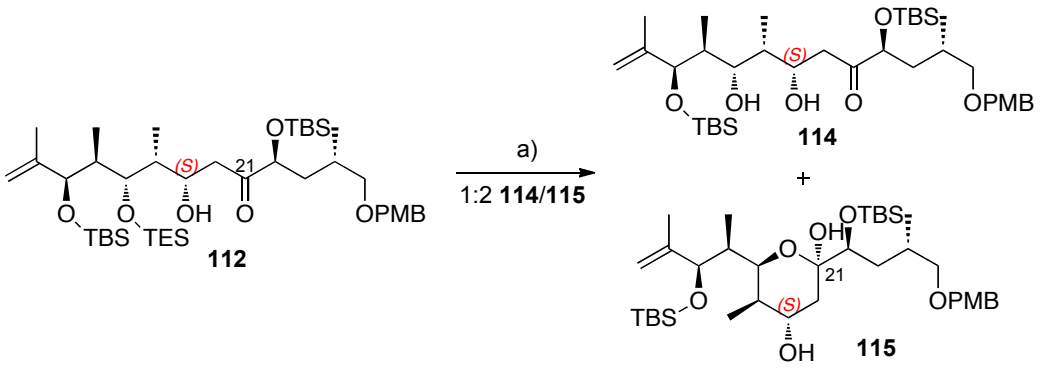


Figure 2.9: 600 MHz ^{1}H NMR spectrum of minor aldol isomer **113** in $CDCl_3$.

To determine the stereochemistry of aldol adducts **112** and **113**, both compounds were independently subjected to standard HF/pyr/pyr deprotection conditions[71-73] (approx. 4 h), with monitoring by TLC to remove only the more labile TES group, leaving the two TBS ethers intact. The TES-deprotection of the major aldol adduct **112** resulted in two products – linear diol **114** and cyclic hemiacetal **115** (resulting from cyclisation of the newly liberated hydroxyl onto the carbonyl at C21) (scheme 2.49). The ratio of products was 2:1 in favour of hemiacetal **115** and the two products were unable to be separated by column chromatography as they existed in equilibrium with one another. Hemiacetal **115** could be identified by the characteristic acetal OH peak at δ 4.41 in the ^{1}H NMR spectrum, and the hemiacetal peaks were distinguishable from the diol peaks by their integration, as these were approximately twice as large as the diol peaks (figure 2.10).



Reagent and conditions: a. HF/pyr/pyr, THF, H_2O (cat.), rt, 4 h.

Scheme 2.49: TES deprotection of major aldol adduct **112** to afford diol **114** and hemiacetal **115**.

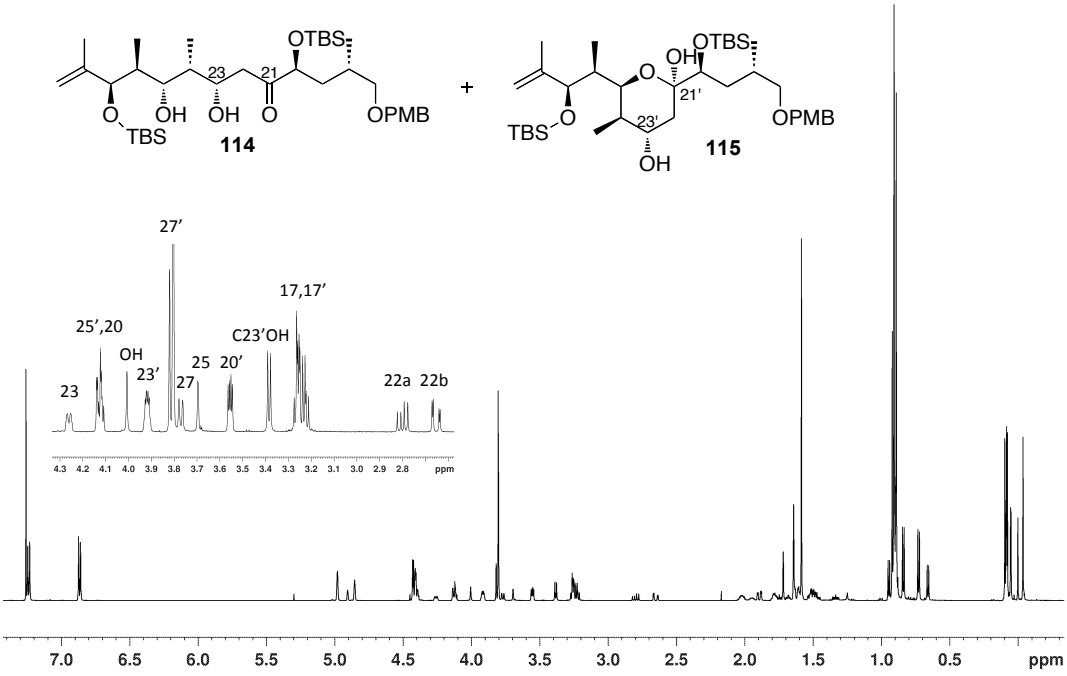


Figure 2.10: 600 MHz ^{1}H NMR spectrum of the mixture of diol **114** and hemiacetal **115** in $CDCl_3$.

Comprehensive NMR analysis and examination of the diagnostic nOe correlations in hemiacetal **115** suggested that the major isomer was the unwanted isomer [C23-(*S*)]

(as denoted in figure 2.11). This was evident from correlations between H23 and C24-Me and the C23-OH and C25, which are only present if C23 is (*S*) (the unwanted isomer). This result is contrary to the reports by Kalesse[17] who observed that the Li aldol of similar fragments favoured C23-(*R*), discussed in more detail later. Analysis of the minor product was therefore crucial to confirm or dispute the validity of these results.

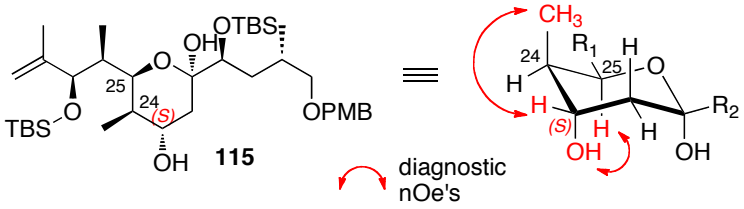
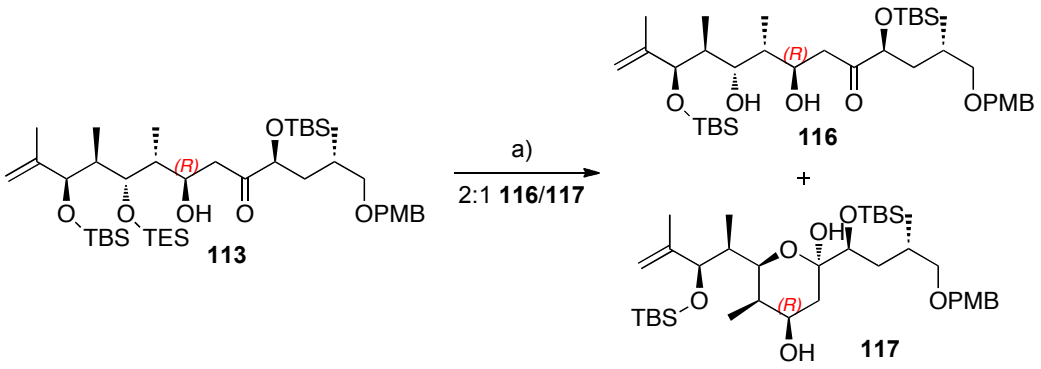


Figure 2.11: Diagnostic nOe correlations observed for hemiacetal **115**.

Similarly, treatment of minor aldol adduct **113** with HF/pyr/pyr[71-73] resulted in a mixture of diol **116** and hemiacetal **117** products. This time however, the ratio of products was 2:1 in favour of diol **116**, the reverse of that seen for the major isomer (scheme 2.49). The ^{1}H NMR spectrum of this mixture is shown in figure 2.12. Analysis of the nOe correlations observed for hemiacetal **117** (figure 2.13) strongly suggested that, in agreement with the results presented above, the minor product was C23-(*R*) (as per adduct **113**), the correct stereochemistry for the natural product. This was due to nOe correlations observed between C23-OH and C24-Me, as well as between H23 and H25, which only occur in the C23-(*R*) (desired) isomer.



Reagent and conditions: a. HF/pyr/pyr, THF, H_2O (cat.), rt, 4 h.

Scheme 2.50: TES deprotection of minor aldol isomer **113**.

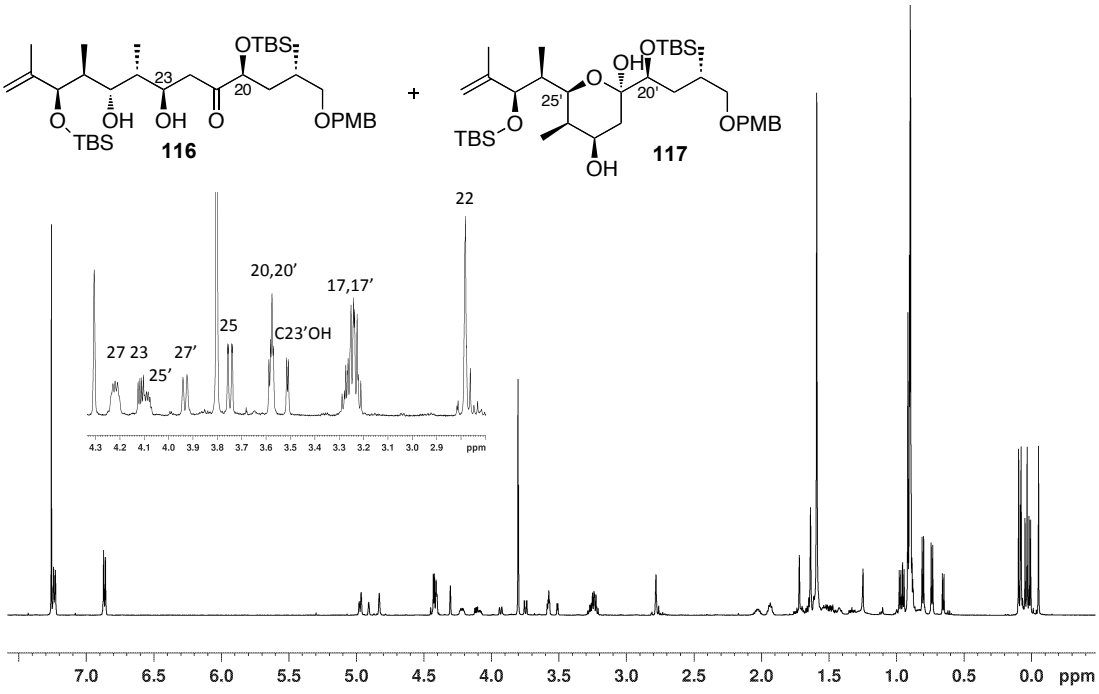


Figure 2.12: 600 MHz ^{1}H NMR spectrum of the mixture of diol **116** and hemiacetal **117** in $CDCl_3$.

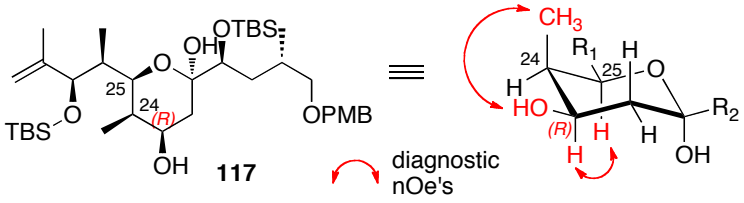


Figure 2.13: Diagnostic nOe interactions observed for hemiacetal **117**.

As reported above, the products of TES deprotection of the major isomer gave a ratio of products approx. 2:1 in favour of the hemiacetal product **115**, while the minor isomer gave 2:1 in favour of the diol product **116**. It is thought that cyclisation is favoured in the major isomer due to hydrogen bonding between C23-OH and C21-OH, as shown in the lowest energy chair conformations for both structures in figure 2.14, making the hemiacetal more stable as it is less susceptible to ring-opening. This also lends support to the assignment of stereochemistry, as hydrogen bonding can only occur when the C23 hydroxyl is (*S*) (ie. axial as illustrated).

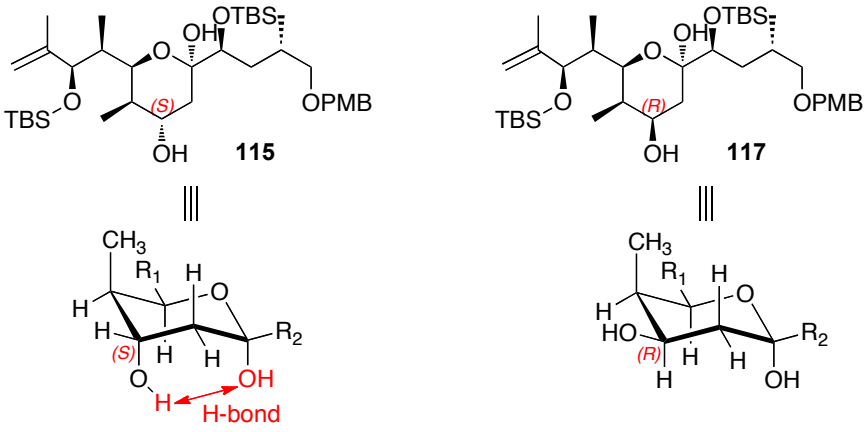
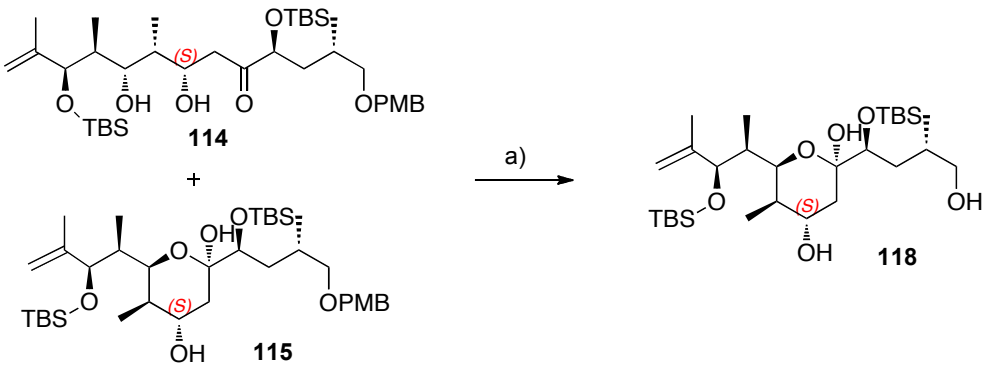


Figure 2.14: Lowest energy chair conformations for hemiacetals **115** and **117**.

To further confirm the stereochemical assignment, the two separate mixtures of diol/hemiacetal were treated with pH 7 buffer and DDQ in CH_2Cl_2 at 0 ^{o}C for 3 h, in

order to remove the PMB protecting group and induce cyclisation of the free hydroxyl onto the carbonyl to produce a spiroacetal.

Upon treating with these conditions, the mixture of compounds derived from the major aldol isomer (**114** and **115**) gave rise to a single component product, which appeared from close NMR examination to be the hemiacetal-triol **118**, resulting from simple PMB deprotection and complete hemiacetal formation (scheme 2.51). This compound was apparently not susceptible to spontaneous spirocyclisation, probably due to the strong hydrogen bonding once again observed in the hemiacetal. This result was confirmed by obtaining an accurate mass, which was consistent with a molecular formula of $C_{29}H_{60}O_6Si_2$. The ^1H NMR of this product is shown in figure 2.15. Due to overlapping peaks for H23 and the C23 hydroxyl proton, nOe analysis of this compound could not provide further confirmation of the C23 stereochemistry.



Reagent and conditions: a. DDQ (1.5 eq), pH 7 buffer, CH_2Cl_2, 0°C, 3 h.

Scheme 2.51: PMB deprotection of major component mixture diol **114** and hemiacetal **115**.

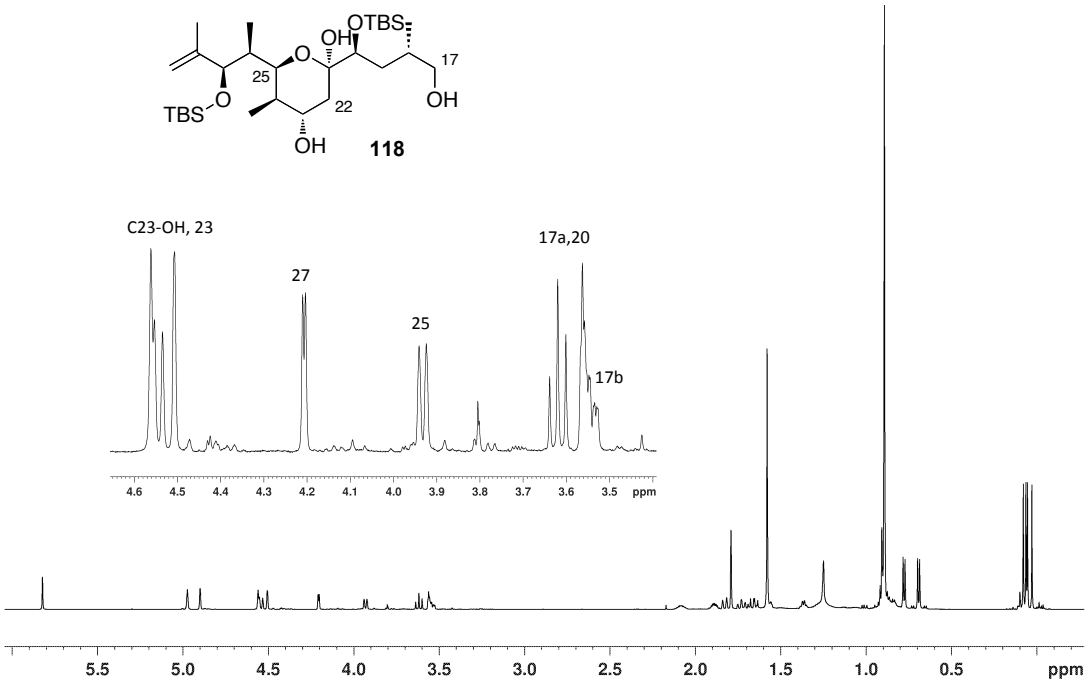
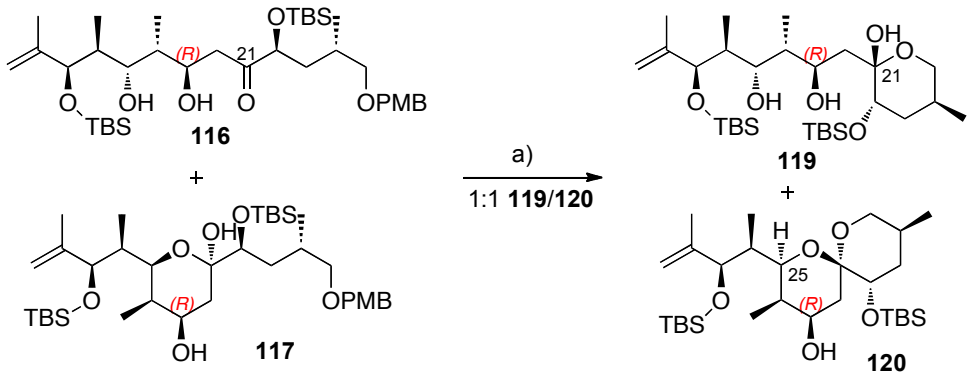


Figure 2.15: 600 MHz ^{1}H NMR spectrum of hemiacetal-triol **118** in $CDCl_3$.

The minor isomer mixture of diol **116** and hemiacetal **117**, when subjected to the same conditions, gave rise to a ~1:1 mixture of alternative hemiacetal **119** (resulting from cyclisation of the newly liberated hydroxyl in the linear system onto the C21 carbonyl) and spiroacetal **120** (scheme 2.52). The ^{1}H NMR spectrum of this mixture can be seen in figure 2.16, showing the characteristic acetal OH peak for hemicetal **119** at δ 5.21 and the C25 proton of spiroacetal **120** at δ 3.96. These two compounds were unable to be separated and once again overlapping peaks in the ^{1}H NMR spectrum complicated stereochemical confirmation based on NOESY correlations.



Reagent and conditions: a. DDQ (1.5 eq), pH 7 buffer, CH_2Cl_2, 0 ^{o}C, 3 h.

Scheme 2.52: PMB deprotection of minor component mixture **116** and **117**.

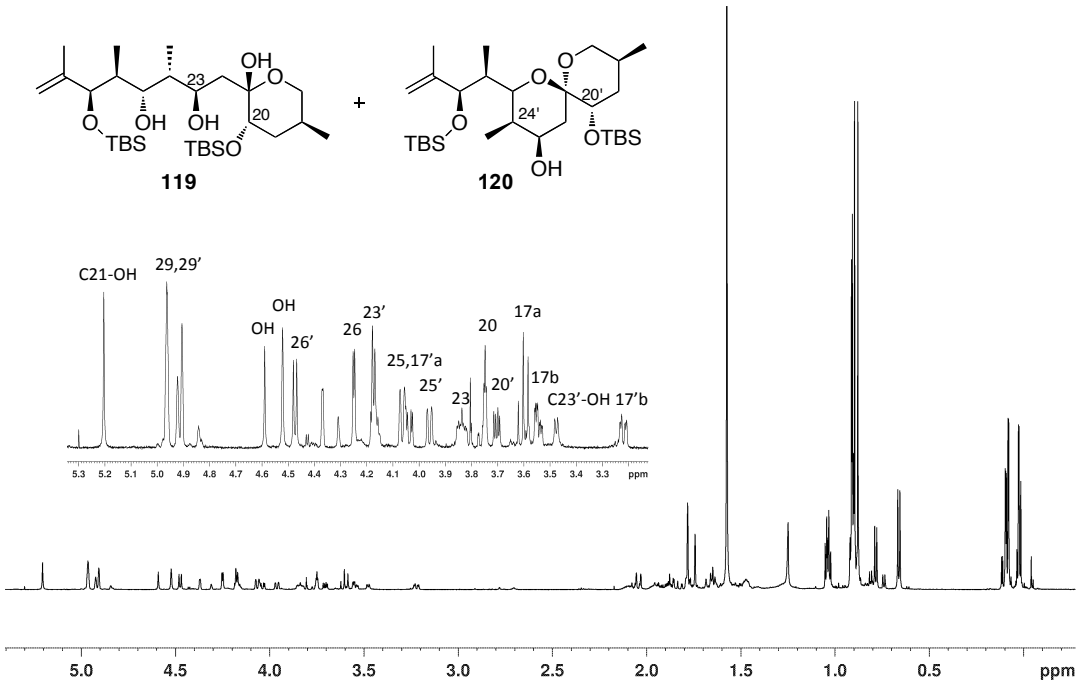
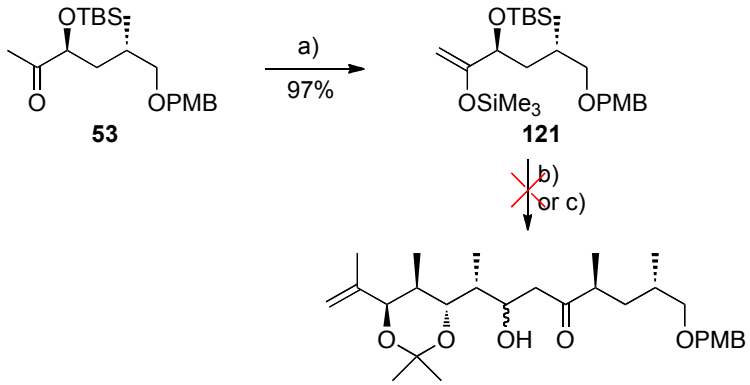


Figure 2.16: 600 MHz ^{1}H NMR spectrum of the mixture of hemiacetal **119** and spiroactal **120** in $CDCl_3$.

The Mukaiyama aldol involves the reaction of a silyl enol ether with an aldehyde in the presence of a Lewis acid catalyst.[78,19] Different selectivity is often observed compared with traditional aldol methods as they do not go *via* a metal enolate (and

thus a well-defined metal bound closed transition state), but rather are activated by the interaction of a Lewis acid with the aldehyde carbonyl oxygen and formation of open transition states.[79] It is not unusual for selectivity to be completely reversed by employing a Mukaiyama protocol.[80] The outcome of these reactions can be difficult to predict due to a number of competing open transition states,[81,82] however they typically give high levels of selectivity and in propionate aldols give predominantly the Felkin product. Predicting the outcome of traditional acetate aldols on the other hand is not straightforward as there are a multitude of factors that can influence the stereochemical outcome, making transition state modelling complicated.

The silyl enol ether of the model ketone **53** was readily generated in high yield by treatment with LiHMDS to invoke enolisation and a mixture of TMSCl/Et_3N to capture the enolate as the silyl ether.[83,84] Silyl enol ether **121** was then reacted with model aldehyde **85**, under the two different sets of conditions outlined in scheme 2.53. Unforunately, the $BF_3.OEt_2$ catalysed reaction[83] was too acidic and resulted in decomposition of the starting materials, while Ti(O*i*-Pr)Cl_3 (a milder Lewis acid substitute for the more widely utilised $TiCl_4$)[19] did not produce any product, returning only starting materials.



Reagent and conditions: a. i. 1:1 TMSCl/Et_3N (10 eq), LiHMDS (2 eq); **b.** Aldehyde **85** (5 eq), $BF_3.OEt_2$ (5 eq), CH_2Cl_2, -78 ^oC, 1.5 h; **c.** i. Ti(O*i*-Pr)$_4$ (0.28 eq), $TiCl_4$ (0.84 eq), CH_2Cl_2, 0 ^oC, 10 min to rt, 10 min; ii. aldehyde **85** (1 eq), -78 ^oC, 2 min; iii. ketone **53** (1 eq), -78 ^oC, 3 h.

Scheme 2.53: Attempted Mukaiyama reactions of model aldehye **85** with the silyl enol ether of model ketone **53**.

The model studies presented above show that the lithium aldol of model ketone **53** with both the acetonide and silyl protected aldehydes **85** and **107** respectively significantly favour the unwanted isomer [C23-(*S*)] of the aldol adduct (**108** and **112** respectively). During the investigations into this model system, results were published by Paterson and co-workers[10] that also showed that the reaction was highly substrate controlled, and that the inherent facial selectivity of the coupling partners could be overcome by utilising the asymmetric control induced by chiral ligands on the Lewis acid metal, in this case (-)-Ipc_2BCl.

Paterson *et al.*[10] used both an aldehyde and ketone for the coupling that was protected as the acetonide at the 1,3-diol positions. This gave the desired aldol adduct **14** [C23-(*R*)] in 3.5:1 ds using (-)-Ipc_2BCl/Et_3N. They also attempted the same reaction using LDA and found that it gave 3:1 ds in favour of the unwanted isomer **15** [C23-(*S*)]. A comparison of Paterson's aldol adduct **15** and model aldol adduct **108** are shown in figure 2.17. The results of Paterson were confirmed by extensive

nOe analysis of the spiroacetals derived from the aldol adducts, and eventual total synthesis of the natural product.[10,12]

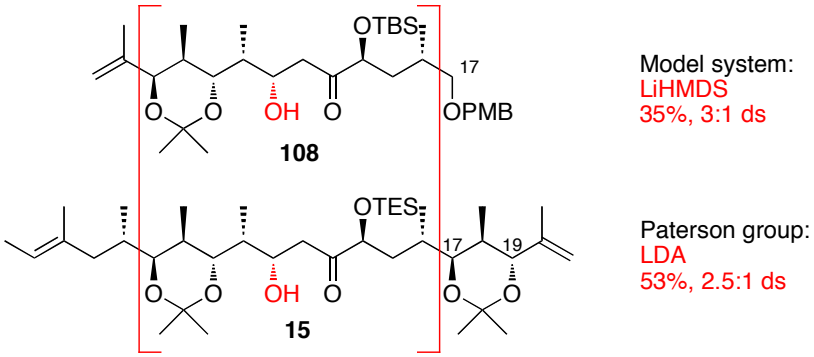
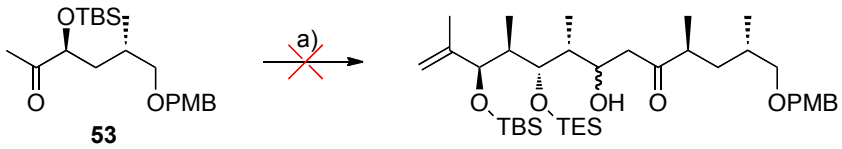


Figure 2.17: Comparison of model aldol adduct **108** with Paterson's aldol adduct **15**.

Paterson did not investigate the use of alternative protecting groups on either fragment, so it was not apparent whether the same selectivity would be achieved by coupling silyl protected aldehyde **107** with the chiral enol borinate of ketone **53**. However, Kalesse *et al.*[18] reported that the α-hydroxy stereocentre on the ketone exerts the overriding control of facial selectivity [1,4-induction of this nature (ie. by an α-alkoxy methyl ketone) is not uncommon in the literature].[85-89] As such, the same facial preference should be observed for the reaction of silyl protected model aldehyde **107** with model ketone **53** using (-)-Ipc_2BCl. To test this, the aldol coupling betweeon silyl protected aldehyde **107** and model ketone **53** was attempted under the same conditions employed by Paterson.[10,12,22] Model ketone **53** was added to a solution of (-)-Ipc_2BCl at 0 ^oC, followed by addition of Et_3N and stirring at 0 ^oC for 1.5 to complete enolisation. Aldehyde **107** was then added at -78 ^oC, followed by stirring at -78^o C, with monitoring by TLC. Unfortunately, after several hours, no reaction had occurred (scheme 2.54). Despite careful handling of (-)-Ipc_2BCl in an argon glove bag, it was thought that the commercial reagent was not of sufficient quality to promote enolisation.



Reagent and conditions: a. i. (-)-Ipc_2BCl (1 eq), Et_3N (1.1 eq), Et_2O, 1 h, 0 ^oC;
ii. aldehyde **107** (1.2 eq), -78 ^oC, 3 h to -20 ^oC, 12 h.

Scheme 2.54: Attemted aldol coupling of model ketone **53** and model aldehyde **107** under chiral enolising conditions.

The research groups of both Kalesse[17] and Cossy[21] employed aldehyde and ketone coupling partners which both had the 1,3-diol protected as silyl ethers. Both groups observed that the Li aldol (achiral reagents) gave the desired stereochemistry for the natural product [ie. C23-(*R*)]. This strongly implies that the stereochemistry and/or protecting group of the C17 hydroxyl also play a significant role in the stereochemical outcome of the aldol reaction (ie. there is significant 1,7-induction). In Paterson's study,[10] the 1,3-diol on both coupling partners was protected as the acetonide and was thus confined to a 6-membered ring. As previously mentioned, Paterson attempted the Li aldol with this compound and found that it gave 3.5:1 ds in favour of the unwanted isomer [C23-(*S*)].[10] This seemingly occurs due to the more rigid conformation of the acetonide protected compounds.

In the model system presented here, C17 is a simplified methylene unit and the C17 hydroxyl is protected as the PMB ether. As shown in figure 2.18, the only significant differences between the major model aldol adduct **112** and the major aldol adducts of Kalesse[17] – aldol adduct **23** - and Cossy[21] – aldol adduct **38** - is the C17 functionality, yet a complete reversal of selectivity is observed. This strongly suggests that the more remote centres play an important role in the diastereoselectivity of the aldol reaction. This was not necessarily expected, but methyl ketone aldols can be very difficult to predict, particularly when the coupling partners exhibit such complex stereochemistry. Also notable here are the results of Cossy which showed that the inclusion of the olefinic moiety on the aldehyde

fragment did not effect the stereochemistry of the product, though its exclusion resulted in a higher aldol yield and fewer decomposition products in the spirocyclisation step.[21]

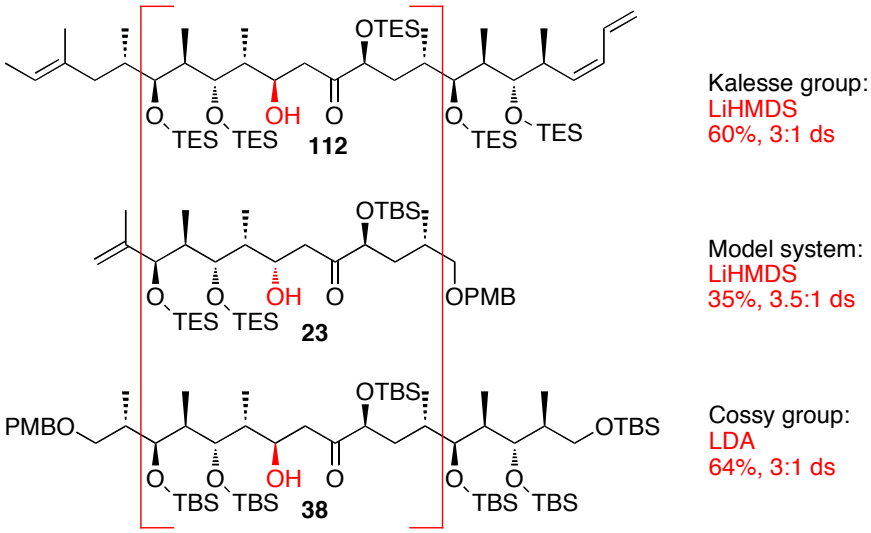


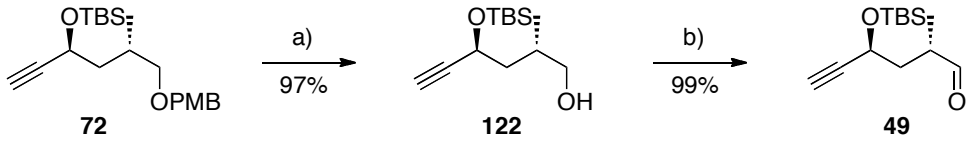
Figure 2.18: Comparison of major model aldol adduct **112** with Kalesse's major aldol adduct **23** and Cossy's major aldol adduct **38**.

It is apparent that there are a number of complex factors that control the aldol selectivity and as such obtaining high selectivity for this reaction would be difficult. Evidently, the model system employed here, which was initially thought to contain all of the key functionality and stereochemistry close to the reaction site, does not represent an accurate model for the natural product system as 1,7-asymmteric induction appears to be a significant factor in controlling the aldol selectivity. As such, the aldol coupling partners required for the synthesis of the natural product were pursued and the lithium aldol would be explored further on this more complex system.

2.5 Towards a Formal Synthesis of Spirangien A

2.5.1 Synthesis of Major Ketone Fragments 130 and 133

PMB ether **72**, used in the synthesis of the model ketone, serves as a common intermediate that can be elaborated upon for the synthesis of the natural product ketone. In the model system the terminal alkyne of **72** was converted directly to the methyl ketone to afford model ketone **53**. However, for the natural product ketone synthesis, the alkynyl moiety would remain intact until the final step, while the other end of the molecule would be manipulated first. Accordingly, deprotection of PMB ether **72** was carried out using buffered aqueous DDQ to afford primary alcohol **122** in high yield (97%), followed by Swern[62] oxidation to give aldehyde **49**, also in excellent yield (scheme 2.55).



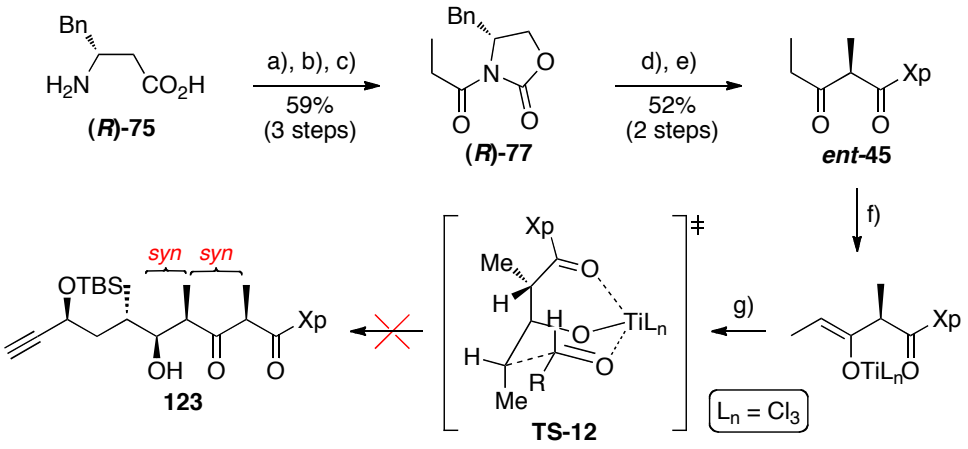
72 **122** **49**

Reagent and conditions: a. DDQ (1.5 eq), pH 7 buffer, CH_2Cl_2, 0 ^oC, 3 h; **b.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **122**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78 ^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.55: Synthesis of aldehyde **49**.

Aldehyde **49** was required to undergo aldol coupling with some sort of dipropionate equivalent to give the correct stereochemistry of the C14-17 stereotetrad. Initially, the enantiomer of β-ketoimide **45** (***ent*-45**) was employed as the dipropionate equivalent (synthesised according to the procedure outlined in section 2.4.2 from (*R*)-phenylalanine **(*R*)-75** *via* oxaxolidinone **(*R*)-77**), however this time the product required *syn-syn* stereochemistry (as opposed to the *syn-anti* outcome of the $Sn(OTf)_2$ mediated aldol coupling of β-ketoimide **45**. β-Ketoimide ***ent*-45** was treated with $TiCl_4$/*i*-Pr_2NEt, according to the procedure of Evans and coworkers[23] to

give the *Z*-(O)-enolate. The reaction of the Ti enolate with aldehyde **49**, which ought to proceed *via* transition state **TS-12** to the *syn,syn* adduct (scheme 2.56), did not furnish aldol adduct **123** as expected (scheme 2.56). Only β-ketoimide ***ent*-45** was retrieved from the reaction, inidicating that the conditions were too acidic ($TiCl_4$ is a Lewis acid) and resulted in decomposition of aldehyde **49**.

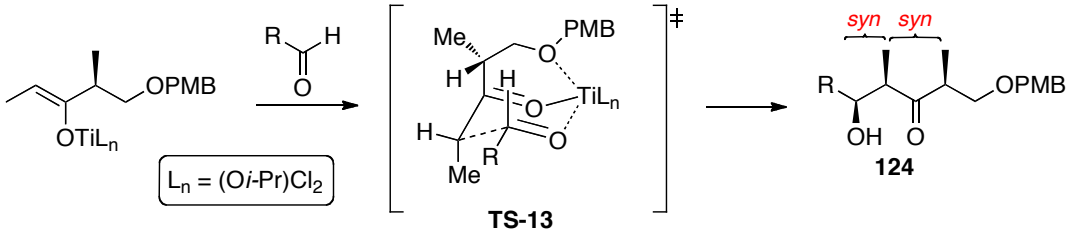


Reagent and conditions: a. $NaBH_4$ (2.4 eq), I_2 (1 eq), THF, 0 °C to reflux, 18 h; **b.** $(EtO)_2CO$ (2 eq), K_2CO_3 (0.1 eq), 135 °C, 3 h; **c.** i. *n*-BuLi (1.02 eq), THF, −78 °C; ii. EtCOCl (1.1 eq), −78 °C, 30 min to rt, 1 h; **d.** i. Bu_2BOTf (1.2 eq), 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; iii. propanal (2 eq), -78 °C, 30 min to 0 °C, 4 h; **e.** SO_3.pyr (3 eq), Et_3N (3 eq), DMSO/CH_2Cl_2, rt, 3 h; **f.** i. $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), CH_2Cl_2, -5 °C, 1 h; **g.** aldehyde **49** (1 eq), -78 °C, 1.5 h to -20 °C, 12 h.

Scheme 2.56: Attempted synthesis of aldol adduct **123** using β-ketoimide ***ent*-45** in a *syn,syn* selective dipropionate aldol.

An alternative dipropionate aldol was then investigated, based on Paterson's dipropionate equivalent bearing a benzyl protecting group,[53] but modified by Solsona and coworkers[63] to avoid the use of the cumbersome reagent $Sn(OTf)_2$. Solsona *et al.*[63] showed that using the less robust PMB protecting group on chiral ketone **(*S*)-10** and the mild Lewis acid Ti(O*i*-Pr)Cl_3, the aldol reaction proceeded *via* the transition state model depicted in scheme 2.57 to give the *syn,syn*- aldol adduct

in high diastereoselectivity (95% ds with an achiral aldehyde). The reaction proceeds *via* **TS-13** (scheme 2.57) in which the PMB ether oxygen coordinates to the titanium to give *syn,syn*-adduct **124**.

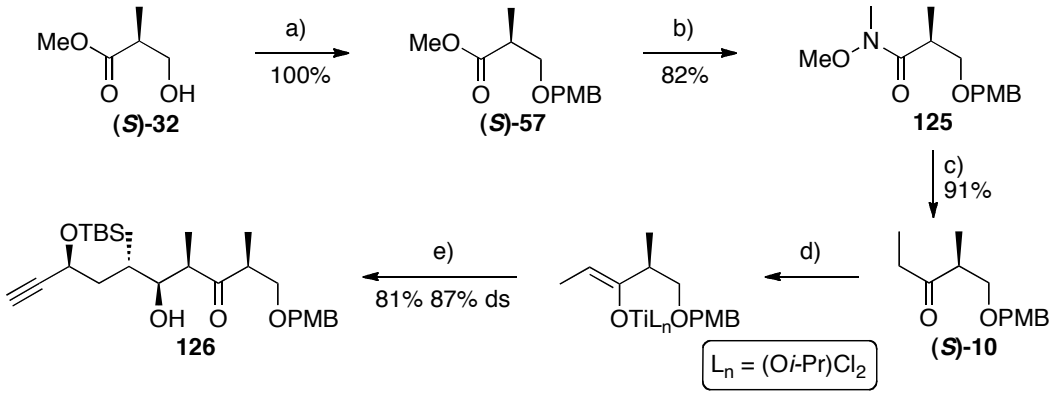


Scheme 2.57: Rationale for the *syn,syn*- selectivity of the Ti(O*i*-Pr)Cl_3 mediated aldol reactions of chiral ketone **(*S*)-10**.

Chiral ketone **(*S*)-10** was synthesised in 3 steps from (*S*)-Roche ester [**(*S*)-32**] *via* Weinreb amide intermediate **125**. First, PMB proection of **(*S*)-32** was carried out according to the procedure of Patil[29] to furnish PMB ether **(*S*)-57**, which was converted to Weinreb amide **125** by treatment with MeN(OMe)H.HCl/*i*-PrMgCl.[90] The Weinreb amide prevented over-addition of EtMgBr in the following step, resulting exclusively in ketone **(*S*)-10** in 75% over 3 steps (scheme 2.58).

Application of Solsona and coworkers' modified conditions (Ti(O*i*-Pr)Cl_3/*i*-Pr_2NEt)[63] to the reaction of ketone **(*S*)-10** with chiral aldehyde **49** gave the desired *syn-syn* product **126** in 87% ds and 81% yield (scheme 2.58). Ti(O*i*-Pr)Cl_3 is produced *via* a ligand exchange reaction between Ti(Oi-Pr)$_4$ and $TiCl_4$, reducing the Lewis acidity of the Ti and thus preventing decomposition of the sensitive substrates. This reaction was carried out at 0 ^oC (lower temperatures caused an insoluble titanium aggregate to form), and subsequently added to a solution of ketone **(*S*)-10** in CH_2Cl_2 at -78 ^oC, followed by addition of base (*i*-Pr_2NEt). After 30 min the aldehyde was added *via* cannula and the reaction was complete after 3 h at -78 ^oC. The minor aldol isomer could be separated by column chromatography to give exclusively the major isomer **126** for use in the following steps. The structure was confirmed on the basis of 1D

and 2D NMR and HRESIMS confirmed the molecular formula to be $C_{27}H_{44}O_5Si$ (calc. for $C_{27}H_{44}O_5SiCl^-$: 511.2652; found: 511.2655). The ^1H and ^{13}C NMR spectra for pure aldol adduct **126** can be found in appendix A (figures A17 and A18).

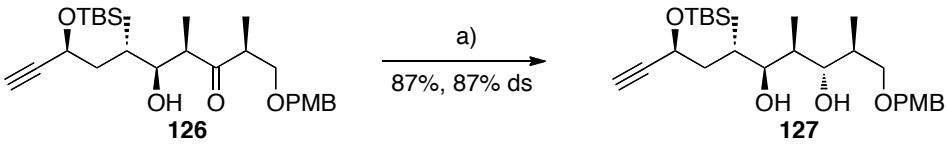


Reagents and conditions: a. PMB imidate (**55**) (1.5 eq), TfOH (10 mol%), Et_2O, rt, 18 h; **b.** MeN(OMe)H.HCl (1.5 eq), *i*-PrMgCl (3 eq), THF, -15 ^oC, 30 min; **c.** EtMgBr (1.9 eq), THF, 0 ^oC, 2 h; **d.** i. Ti(O*i*-Pr)$_4$ (0.28 eq), $TiCl_4$ (0.84 eq), CH_2Cl_2, 0 ^oC, 10 min to rt, 10 min; ii. ketone **(*S*)-10**, -78 ^oC, 2 min; iii. *i*-Pr_2NEt (1.1 eq), -78 ^oC, 30 min; **e.** aldehyde **49** (0.9 eq), -78 ^oC, 3 h.

Scheme 2.58: Diastereoselective synthesis of aldol adduct **126**.

With aldol adduct 1**26** in hand, efforts were directed to accomplishing the *anti*-reduction of the β-hydroxyketone. As a first attempt, $NaBH(OAc)_3$ (5 eq) was used in AcOH, under conditions identical to those used in the model aldehyde synthesis (section 2.4.2). However, this procedure resulted in decomposition of the aldol starting material **126**. As an alternative to $NaBH(OAc)_3$, the milder *anti*-reducing reagent $Me_4NBH(OAc)_3$ was used. This reagent was developed by Evans and co-workers[91] as a milder and more selective reducing agent than $NaBH(OAc)_3$ for the *anti*-reduction of β-hydroxyketones. Evans *et al.*[91] discovered that diastereoselectivity in the *anti*-reduction of β-hydroxyketones was optimised with a 50% concentration of acetic acid in acetonitrile, and at temperatures below the freezing point of acetic acid.[91] Indeed, the use of $Me_4NBH(OAc)_3$ in a 1:1 mixture of

AcOH/CH_3CN achieved reduction of aldol **126** to *anti*-diol **127**, with optimum conditions employing 5 equivalents of reducing agent, added at 0 ^oC, with subsequent warming to rt for 5 days. The resultant diol was readily purified by column chromatography to afford the *anti*-1,3-diol product in 87% yield and 87% ds. The minor isomer was able to separated by column chromatography to deliver a single diastereomer of diol **127** for use in further steps.



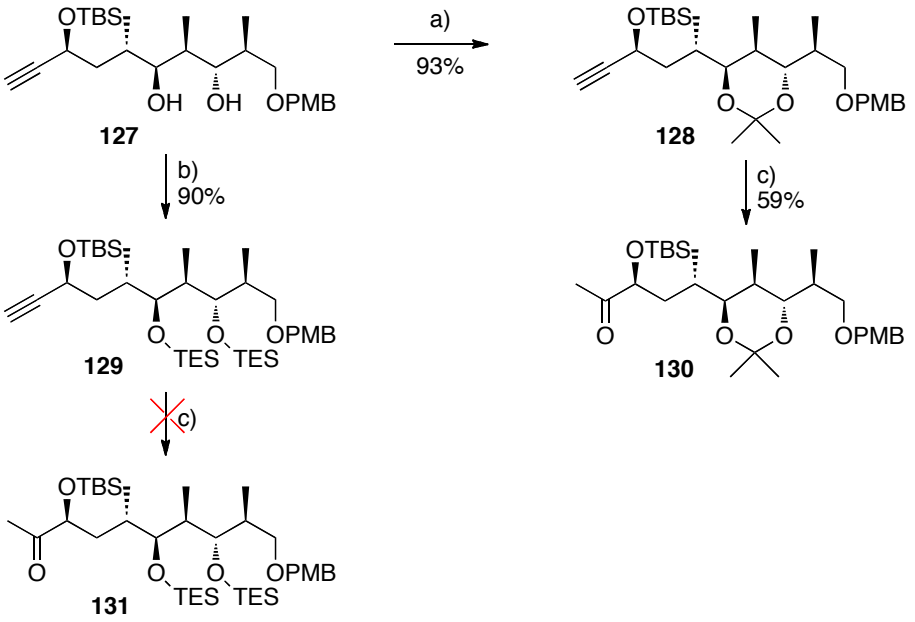
Reagent and conditions: a. $Me_4NBH(OAc)_3$ (5 eq), AcOH/CH_3CN, 0 ^oC to rt, 5 days.

Scheme 2.59: Synthesis of 1,3-diol **127**.

Anti-1,3-diol **127** was readily protected as the acetonide **128** and as the *di*-TES ether **129** in 93 and 90% yields respectively, with the aim of producing two different forms of ketone **44** (scheme 2.12; 1,3-diol protecting groups undetermined). A bridging silylene protecting group was not used here as they presented some difficulty in attaching to hindered *anti*-1,3-diols, as seen in section 2.4.2. Both compounds **128** and **129** were treated with PPTS/pH 7 buffer/$Hg(OAc)_2$ as per the conditions optimised for the model ketone for the conversion of the terminal alkyne to a methyl ketone. Acetonide protected **128** was converted to ketone **130** in modest yield (≤56%), while the *di*-TES compound did not produce methyl ketone **131**, but rather underwent TES-deprotection with ensuing decomposition (scheme 2.60).

The ^1H NMR spectrum of methyl ketone **130** confirms the formation of a methyl ketone with a 3H singlet at δ 2.16 and the absence of the alkynyl doublet at δ 2.37 (appendix A, figure A19). The ^{13}C NMR and IR also indicate the presence of a ketone due to a signals at δ 212.8 and 1715 cm^{-1} respectively. HRESIMS confirmed the

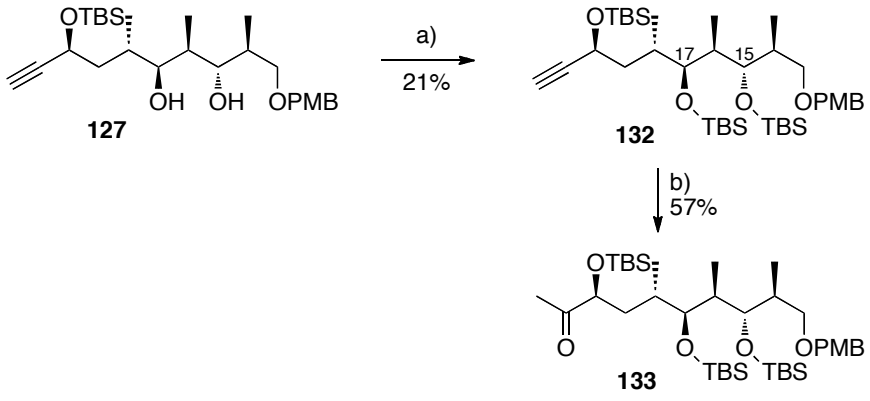
molecular formula to be $C_{30}H_{52}O_6Si$ (calc. for $C_{30}H_{52}O_6SiNa^+$: 559.3425; found: 559.3427).



Reagent and conditions: a. PPTS (cat.), 1:1 $(MeO)_2C(CH_3)_2/CH_2Cl_2$, rt, 3 h; **b.** 2,6-lutidine (4 eq), TESOTf (3 eq), CH_2Cl_2, -78 ^oC, 7 h; **c.** PPTS (1.5 eq), pH 7 buffer (2 eq), $Hg(OAc)_2$ (0.3 eq), THF, 45 ^oC, 5 h.

Scheme 2.60: Synthesis of methyl ketone **130** and attempted synthesis of methyl ketone **131**.

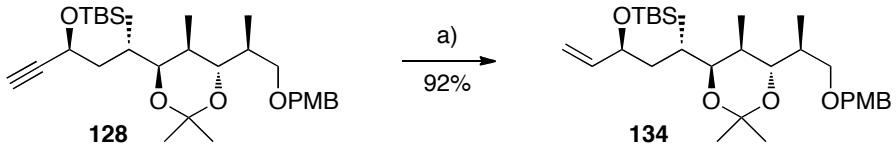
Owing to the instability of the TES ether under the chosen hydrating conditions, two TBS groups were trialled as an alternative. Treatment of 1,3-diol **127** with TBSOTf/2,6-lutidine[41] readily protected the C17 hydroxyl, but the C15 hydroxyl was then relatively hindered and protection here was much more difficult. Extended reaction time and warming to 0 ^oC still gave only 21% of the desired *tri*-TBS compound **132**. This material was treated under the same mercury-catalysed hydration conditions as above, and after 4 days resulted in ketone **133** (57% yield) without removal of the more robust silyl protecting groups. Comprehensive NMR, IR and HRESIMS confirmed the structure of methyl ketone **133**.



Reagent and conditions: a. 2,6-lutidine (4 eq), TBSOTf (3 eq), CH_2Cl_2, -78 ^oC, 5 h to 0 ^oC, 5 h; **b.** PPTS (1.5 eq), pH 7 buffer (2 eq), $Hg(OAc)_2$ (0.3 eq), THF, 45 ^oC, 4 days.

Scheme 2.70: Synthesis of *tri*-TBS protected methyl ketone **133**.

The yields observed for the hydration of both the acetone and silyl protected alkynes **128** and **132** respectively were consistently lower than those obtained for the model system. This prompted further investigation into the Lindlar reduction – Wacker oxidation sequence that found limited success in the model system, in the hope that a higher yielding sequence could be developed.

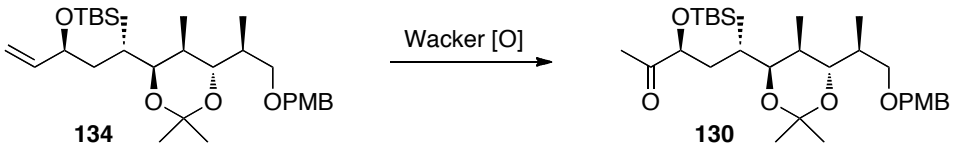


Reagent and conditions: a. H_2 (1 atm), quinoline (0.03 eq), Lindlar cat. (10% w/w), MeOH, rt, 1 h.

Scheme 2.71: Lindlar reduction of alkyne **128**.

Lindlar reduction[43,44] of alkyne **128** proceeded in good yield (92%) to give exclusively alkene **134** in 1 h without over-reduction (scheme 2.71). As with the model ketone, Wacker oxidation[46-48] using $PdCl_2$, LiCl and $CuCl_2$ gave moderate yield (approx. 50%),

however the product was unable to be isolated from residual starting material. Alternative Wacker oxidation conditions were trialled, as summarised in table 2.3, but none were able to produce a high yield or isolable product to warrant application to the natural product synthesis. Further attempts to optimise the Wacker oxidation conditions were thus abandoned and synthesis pursued with ketones **130** and **133** produced *via* the direct hydration approach.



Conditions	Yield
i) $Hg(OAc)_2$, MeOH, rt, 12 h ii) $PdCl_2$, LiCl, $CuCl_2$, MeOH, 55 ^oC, 3 h	2:1 **134/130** (inseparable)
$PdCl_2$, O_2, DMA, 80 ^oC, 6 h	**134** only
$PdCl_2$, $CuCl_2$, O_2, 1:1 DMF/H_2O, rt, 5 h	**134** only
Pd[(-)-sparteine]Cl_2, O_2, 4:1 DMA/H_2O, 70 ^oC, 18 h	**134** only
$Pd(OAc)_2$, pyridine, O_2, propan-2-ol, toluene, 60 ^oC, 6 h	1:1 **134/130** (inseparable)

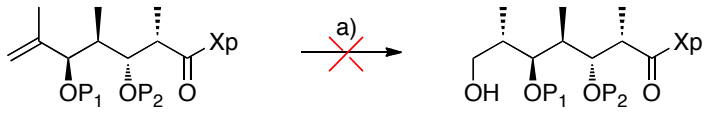
Table 2.3: Conditions trialled for the Wacker oxidation of alkene **134**.

2.5.2 Synthesis of Major Aldehyde Fragment 150

It was originally proposed that aldehydes of general structure **43** (scheme 2.12; 1,3-diol protecting groups undetermined) could be obtained by elaboration of intermediate **47**. This would require hydroboration-oxidation of the acetonide and silyl protected terminal alkene intermediates **84** and **105** to provide a handle for alkylation *via* cross-coupling with an alkyl metal or alkyl halide. Typically, hydroboration-oxidation is stereoselective in favour of the *anti* isomer (as required here) due to steric considerations, though regioselectivity and stereoselectivity varies with the choice of reagent.[92] Also, *syn* selectivity can be achieved or asymmetry induced using alternative boron reagents such as catecholborane or diisopinocampheylboranes.[93-96] Literature precedent for hydroboration of closely

related substrates to **84** and **105** suggested the use of the versatile reagent 9-BBN[97] for both compounds.[93,98] Bulky alkyl groups on the borane are necessary for greater regioselectivity[92] and to prevent addition to other π-bonds in the molecule,[99,100] therefore $(Sia)_2BH$[101] or $(Thex)BH_2$[102] would also be appropriate choices.

As it could be readily purchased (Sigma Aldrich Chemical Co.), is air stable, and can hydroborate relatively hindered alkenes, a solution of 9-BBN (0.5M in THF) was first used to try to produce terminal alcohols **135** and **136** (variants of alcohol **47**). Unfortunately, several attempts at this procedure[93] (using two different batches of reagent) did not give any hydroboration-oxidation product, returning only starting material (scheme 2.72).



84: $P_1 = P_2 = C(CH_3)_2$
105: P_1 = TBS, P_2 = TES

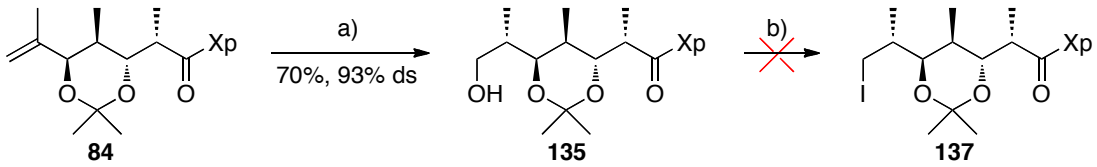
135: $P_1 = P_2 = C(CH_3)_2$
136: P_1 = TBS, P_2 = TES

Reagent and conditions: a. i. 9-BBN (1.5 eq), THF, rt, 0 °C, 15 min to rt, 24 h; ii. 1:1 EtOH/THF, pH 7 buffer, 30% aq. H_2O_2, 0 °C, 15 min to rt, 3 h.

Scheme 2.72: Attempted hydroboration-oxidation of alkenes **84** and **107** using 9-BBN.

Alternatively, $(Sia)_2BH$ and $(Thex)BH_2$, which are not stable for long-term storage, were both synthesised *in situ* by treating a solution of BH_3.THF in THF with 2-methyl-2-butene or 2,3-dimethyl-2-butene respectively. The use of $(Sia)_2BH$ for hydroboration of alkene **84** under standard conditions with oxidation using $H_2O_2/NaHCO_3$[101] caused the chiral auxiliary to be cleaved and consequent decomposition. This result was attributed to the harsh oxidative conditions and indeed the use of milder oxidative conditions (pH 7 buffer/MeOH/30% aq. H_2O_2) resulted in the generation of the desired hydroboration-oxidation product **135** (scheme 2.73). Unfortunately, the yield and diastereoselectivity observed for this

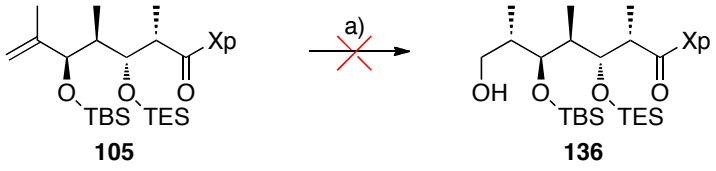
reaction (70%, 93% ds) could not be reproduced on a large scale. Conversion to iodide **137** was attempted on the small amount of material produced, but the conditions[103] employed resulted in partial decomposition of the substrate.



Reagent and conditions: a. i. BH_3.THF (12.4 eq), THF, 0 ^oC; ii. 2-methyl-2-butene (24.8 eq), 0 ^oC, 3 h; iii. alkene **84**, 0 ^oC, 3 h to rt, 12 h; iv. pH 7 buffer, MeOH, 30% aq H_2O_2, THF, 0 ^oC to rt 1 h; **b. i.** imidazole (3 eq), PPh_3 (1.1 eq), 0 ^oC; ii. I_2 (1.1 eq), 0 ^oC, 10 min; iii. alcohol **135**, 0 ^oC, 15 min to rt, 12 h.

Scheme 2.73: Hydroboration of alkene **84** using disiamyl borane and attempted conversion to iodide **137**.

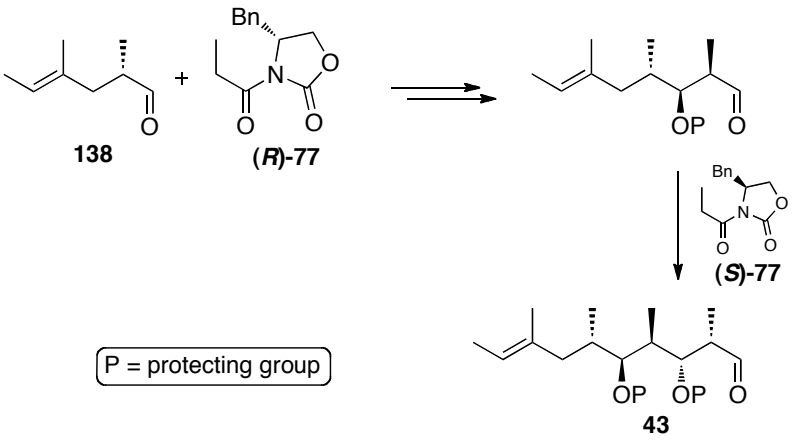
The attempted hydroboration of silyl protected alkene **105** using (Thex)BH_2[102] gave no reaction and returned only starting material (scheme 2.74). Therefore it was decided that an alternative synthesis of the major aldehyde fragment would be pursued.



Reagent and conditions: a. i. 2,3-dimethyl-2-butene (8 eq), THF, 0 ^oC; ii. BH_3.THF (7.3 eq), 0 ^oC, 2 h to rt, 1 h; iii. alkene **105**, 0 ^oC, 2 h to rt, 18 h; iv. pH 7 buffer, MeOH, 30% aq H_2O_2, THF, 0 ^oC to rt, 1 h.

Scheme 2.74: Attempted hydroboration of **105** using thexyl borane.

It was proposed that instead of using iodide **137** (derived from the hydroboration of alkene **84**) to provide a handle for alkylation, aldehyde **138** could be used instead of methacrolein in the dipropionate aldol (or double aldol sequence) (scheme 2.75). This would avoid the potentially difficult metal-catalysed alkylation reaction of iodide **137**, as the *trans*-substituted olefinic bond would already be built into the aldehyde fragment, as well as the C28 stereochemistry which would by-pass the need for hydroboration. Attention was therefore turned to the synthesis of aldehyde **138**.



Scheme 2.75: Alternative strategy towards aldehyde **43**.

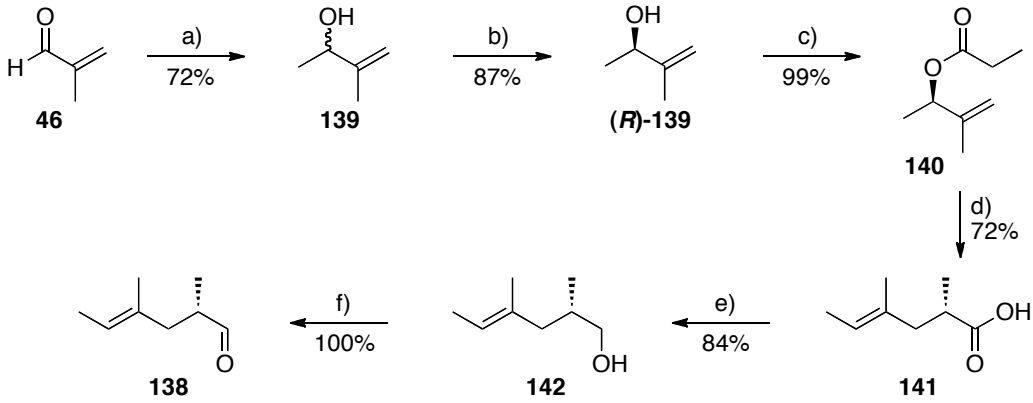
The strategy employed by Paterson and Perkins[73] for synthesis of a related aldehyde was chosen to achieve the synthesis of aldehyde **138**, which utilises a Sharpless kinetic resolution[104,105] to impart enantioselectivity, followed by an Ireland-Claisen rearrangement[106] to produce the required carbon skeleton and desired configuration at C28. This approach began with methacrolein (**46**), which underwent Grignard addition with methylmagnesium bromide to give racemic alcohol **139**, distilled to purity in 72% yield (scheme 2.76). A Sharpless kinetic resolution[104,105] using diispropyl L-(+)-tartrate was anticipated to give the (*R*)-enantiomer of alcohol **139** in high enantiomeric excess (ee) (typically >90%).

The epoxidation of chiral allylic alcohols was developed by Katsuki and Sharpless,[104] and in the case of secondary allylic alcohols such as **139**, can result in the resolution of enantiomeric pairs.[105] Epoxidation was achieved using *tert*-butylhydroperoxide (*t*-BuOOH), in the presence of catalytic Ti(O*i*-Pr)$_4$ and L-(+)-diisopropyl tartrate. The reaction proceeds *via* a mechanism that is not well understood, but mutual kinetic enantioselection allows one enantiomer to react much faster than the other. As a result, the unwanted enantiomer **(*S*)-139** is almost completely converted to the epoxide, making separation of the two compounds achievable by column chromatography.

The hygroscopic nature of the tartrate reagent called for a large quantity of 4 Å molecular sieves to be present in order to produce the epoxide, and hence for kinetic resolution to be achieved. This could be confirmed by the yield of epoxide obtained, optical rotation analysis of the resultant allylic alcohol, or Mosher ester[107] derivatisation. In this case, the presence of epoxide (approx. 50%) was sufficient to determine that the reaction had occurred, giving **(*R*)-139** upon chromatographic separation. An optical rotation of $[\alpha]^{20}_{D}$ = +1.57 (c 2.55, CH_2Cl_2) also showed that the alcohol was no longer racemic (though it was not expected to have a large optical rotation). The determination of % ee would be carried out at a later step.

Acylation of **(*R*)-139** with propionyl chloride and pyridine in CH_2Cl_2 gave ester **140** in excellent yield (99%) and could be purified by distillation under reduced pressure or column chromatography. Chromatography was found to be consistently more efficient for purification in the presence of other impurities. Ester **140** underwent Ireland-Claisen rearrangement[106] by treatment of the ester with a TMSCl/Et_3N mixture (centrifuged to remove the gelatinous white precipitate) in THF, followed by treatment with LDA at -78 ^{o}C to convert the ester to its corresponding silyl ketene acetal.[83] Once enolisation was complete the reaction was heated to reflux for 4 h to provoke rearrangement to the carboxylic acid silyl ester, which upon acidic workup resulted in carboxylic acid **141** (scheme 2.76). The purity of the ester starting material and the efficiency of LDA formation strongly influenced the outcome of this reaction, however when successful the reaction produced a good yield of acid **141** (72% crude), which was used crude in the following step.

Carboxylic acid **141** was reduced to the corresponding alcohol **142** using a standard $LiAlH_4$ reduction[108] followed by a Swern[62] oxidation to give aldehyde **138**. This volatile aldehyde was retained in a small quantity of solvent (CH_2Cl_2) to avoid loss of product under reduced pressure and used in the subsequent aldol reaction immediately after preparation to prevent decomposition and potential polymerisation.

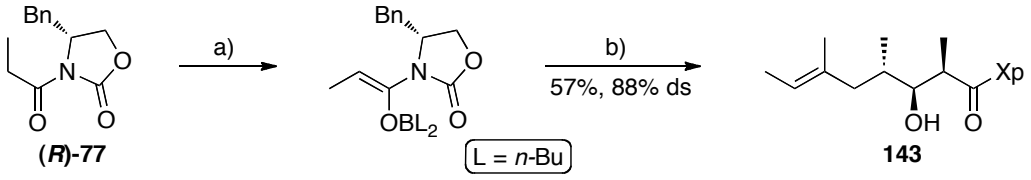


Reagent and conditions: a. MeMgBr (1 eq), Et_2O, -78 ^oC, 30 min; **b. i.** diisopropyl (*L*)-(+)-tartrate (0.15 eq), 4 Å sieves, CH_2Cl_2, -20 ^oC; ii. Ti(O*i*-Pr)$_4$ (0.1 eq), -20 ^oC, 30 min; iii. *t*-BuOOH (0.58 eq), -20 ^oC, 48 h; **c.** i. pyridine (1.4 eq), CH_2Cl_2, rt; ii. EtCOCl (1.4 eq), rt, 4 h; **d.** i. TMSCl/Et_3N (12 eq), THF, -78 ^oC, ii. LDA (1.3 eq), -78 ^oC, 1 h to rt, 1 h, to reflux 4 h; **e.** $LiAlH_4$ (4 eq), Et_2O, -78 ^oC to 0 ^oC, 30 min; **f.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **142**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.76: Synthesis of aldehyde **138** *via* an Ireland-Claisen rearrangement.

Aldehyde **138** was then to be reacted as per the model system, *via* two highly selective *syn* Evans aldol reactions (section 2.4.2). The product of the aldol reaction between aldehyde **138** and oxazolidinone **(*R*)-77** provided aldol adduct **143** in 88% ds (57% yield in 2 steps from alcohol **142**) (scheme 2.77). As the Evans aldol reaction typically produces products in >98% ds, this implies that the % ee of aldehyde **138**, as a result of the kinetic resolution, was >86%. Fortunately, the two diastereomers

of aldol adduct produced here could be separated by column chromatography, which would enable pursuit of diastereomerically pure aldehyde fragment **138**.



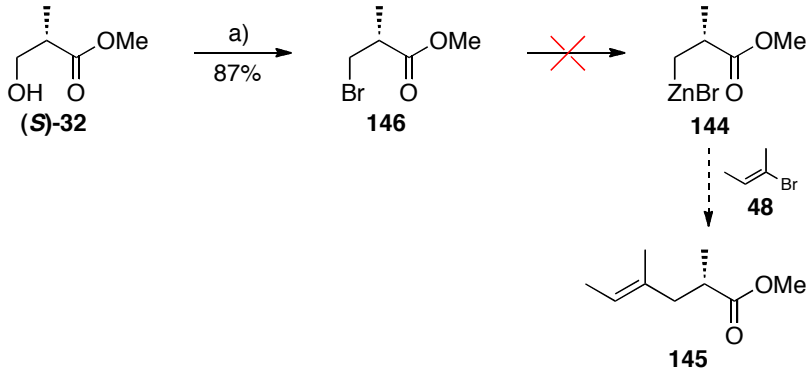
Reagent and conditions: a. i. Bu_2BOTf (1.2 eq), 0 ^oC, 30 min; ii. Et_3N (1.3 eq), 0 ^oC, 30 min; iii. aldehyde **138** (1 eq), -78 ^oC, 30 min to 0 ^oC, 4 h.

Scheme 2.77: Aldol reaction of aldehyde **138** with oxazolidinone **(*S*)-77**.

Due to the inherent inefficiency of the Sharpless kinetic resolution (ie. 50% loss of starting material as the enantiomeric epoxide) and the moderate 86% ee of aldehyde **138** (making separation of diastereomers crucial at a later step), an alternative and more efficient pathway to aldehyde **138** was also investigated. This would require the palladium-catalysed coupling of zinc homoenolate **144** with (*E*)-2-bromo-2-butene (**48**) to produce exclusively the (*S*)- configuration of ester **145** (scheme 2.78).[109,110] A homoenolate is a compound that contains an ionic carbon β- to a carbonyl group or a moiety that can be converted into a carbonyl group.[111] Zinc, titanium and metal-free homoenolates have been synthesised for use in homoaldol reactions, but zinc homoenolates are particularly useful as they can undergo Pd coupling reactions and conjugate additions as well as homoaldols.

Synthesis of the zinc homoenolate **144** was attempted by zinc insertion into the alkyl bromide of (*S*)-Roche ester **146** (produced by a simple bromination of (*S*)-Roche ester [**(*S*)-32**])[112] (scheme 2.78). Zinc powder was washed successively with 2M HCl, H_2O, EtOH and Et_2O according to standard purification techniques,[113] and activation was attempted using 1,2-dibromoethane, TMSCl and I_2. It was evident however that the zinc was not being sufficiently activated by this method.

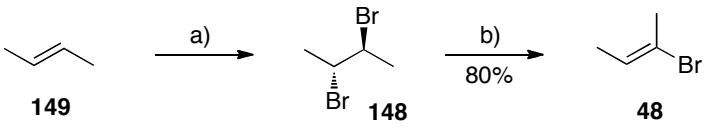
Fortunately, zinc homoenolate **144** was commercially available (Sigma Aldrich Chemical Co.) as a 0.5 M solution in THF.



Reagent and conditions: a. i. PPh_3 (1 eq), imidazole (1 eq), Br_2 (1.06 eq), 0 ^{o}C, 10 min; ii. alcohol **(*S*)-32**, rt, o/n.

Scheme 2.78: Bromination of (*S*)-Roche ester **(*S*)-32** and attempted conversion to zinc homenolate **144**.

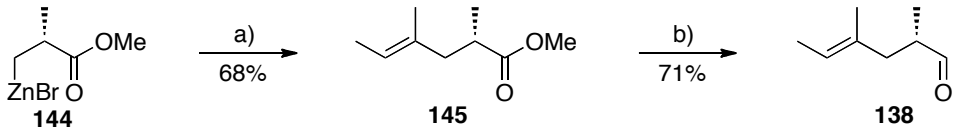
(*E*)-2-bromo-2-butene (**48**) was produced in 2 steps from *trans*-2-butene (**147**) *via* bromination and subsequent elimination (scheme 2.79). First, in a procedure adapted from Cochran *et al*.,[114] gaseous *trans*-2-butene (**147**) was condensed using a cold finger (-78 ^{o}C) into CH_2Cl_2 at -15 ^{o}C, followed by addition of a 1 M solution of Br_2 until the first persistent colour change indicated the reaction was complete. Distillation under reduced pressure gave meso-2,3-dibromobutane (**148**). Compound **148** was then treated with DBU in DMSO to bring about elimination of HBr.[114] The reaction mixture was then subjected to high vacuum, from which (*E*)-2-bromo-2-butene (**48**) could be collected in a cold trap.



Reagent and conditions: a. i. CH_2Cl_2, -78 ^oC to -15 ^oC; ii. Br_2 (1 eq), -15 ^oC; **b.** DBU (8 eq), DMSO, rt, 45 min.

Scheme 2.79: Synthesis of (*E*)-2-bromo-2-butene (**48**).

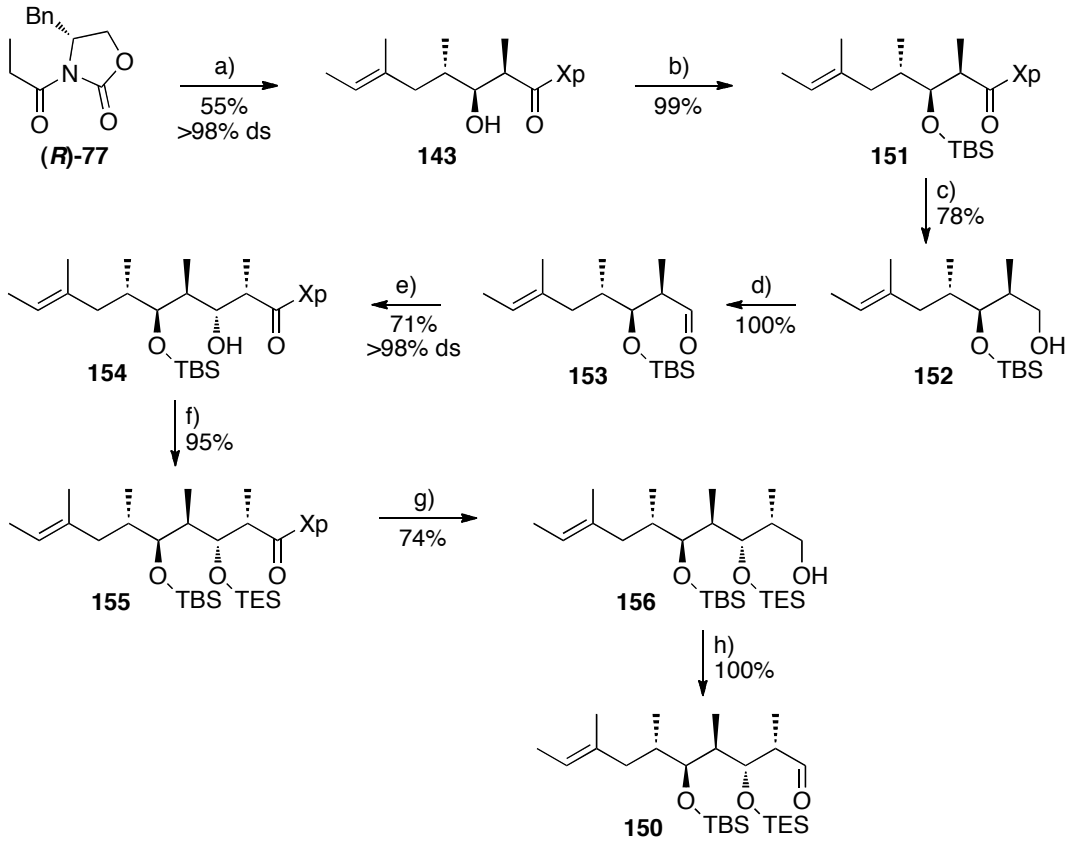
Coupling of zinc bromide **144** with (*E*)-2-bromobutene (**48**) was achieved using catalytic $Pd(Ph_3)_2Cl_2$ in THF at rt for 24 h to produce ester **145**.[115] Catalyst loadings of 10% and 5% were trialled, and no significant difference in product yield was found. A 5% loading was therefore used as it was both economically sensible and was easier to purify (on a large scale the product needed to be purified twice by column chromatography to remove all of the catalyst). Ester **145** was consistently produced in reasonable yield (68%) and could be reduced to aldehyde **138** in one step using DIBAL.[115] Very low temperature (-90 ^oC) and a short reaction time (1h, as indicated by TLC analysis) were crucial to prevent over-reduction to the alcohol. This process resulted in production of aldehyde **138** in 100% ee in 2 steps, as opposed to 6 steps and 86% ee (though isolable as a single isomer) from the kinetic resolution pathway.



Reagent and conditions: a. i. (*R*)-3-methoxy-2-methyl-3-oxopropylzinc bromide (**144**) (1.2 eq), THF, 0 ^oC, 1 min; ii. $Pd(PPh_3)_2Cl_2$ (0.05 eq), 0 ^oC, 5 min to rt, 24 h; **b.** DIBAL (1.05 eq), CH_2Cl_2, -78 ^oC, 1 h.

Scheme 2.80: Synthesis of aldehyde **148** from zinc homoenolate **144**.

Aldehyde **138** could then be used, as shown in scheme 2.81, to readily produce aldehyde fragment **150** in good yield (21% over 8 steps) and purity (> 98% ds), as per the conditions used to make model aldehyde **107**. Aldehyde **138** was first reacted with oxazolidinone **(*R*)-77** in a doublestereodifferentiating Evans aldol to give aldol aduct **143**, which was readily protected as the TBS ether **151**. Reductive cleavage of the auxiliary gave alcohol **152**, followed by Swern[62] oxidation to afford aldehyde **153**, ready for a second Evans aldol with oxazolidinone **(*S*)-77**. The new hydroxyl in aldol adduct **154** was then protected as the TES ether **155**, followed by a second reduction-oxidation sequence to furnish aldehyde **150** *via* alcohol precursor **156.** The structure of aldehyde **150** was confirmed on the basis of 1D and 2D NMR and IR. The ^{1}H and ^{13}C NMR spectra of aldehyde **150** are shown in appendix A (figures A23 and A24. Aldehyde **150** was too unstable for mass spectral analysis, however HRESIMS of precursor alcohol **156** confirmed a molecular formula of $C_{26}H_{56}O_3Si_2$ (calc. for $C_{26}H_{56}O_3Si_2Na^+$: 495.3660; found: 495.3661).



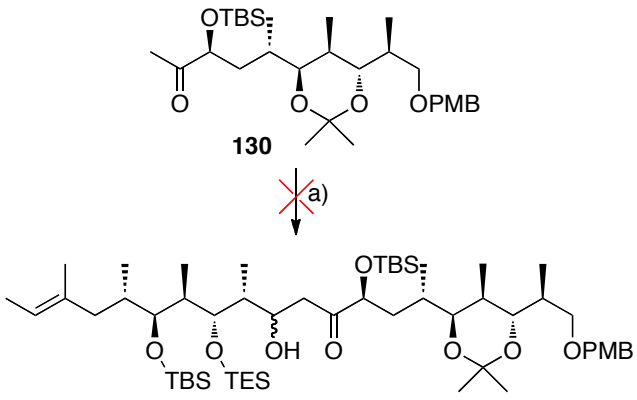
Reagent and conditions: a. i. Bu_2BOTf (1.2 eq), 0 ^oC, 30 min; ii. Et_3N (1.3 eq), 0 ^oC, 30 min; iii. aldehyde **138** (1 eq), -78 ^oC, 30 min to 0 ^oC, 4 h; **b.** 2,6-lutidine (2 eq), TBSOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 7 h; **c.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^oC, 4 h; **d.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **152**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78^oC, 30 min to 0 ^oC, 30 min; **e.** i. oxazolidinone **(*S*)-77**, 0 ^oC, ii. Bu_2BOTf (1.2 eq), 0 ^oC, 30 min; iii. Et_3N (1.3 eq), 0 ^oC, 30 min; iv. aldehyde **153** (1 eq), -78 ^oC, 30 min to 0 ^oC, 4 h; **f.** 2,6-lutidine (2 eq), TESOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 7 h, **g.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^oC, 4 h; **h.** i. DMSO (3 eq), CH_2Cl_2, -78 ^oC; ii. $(COCl)_2$ (1.5 eq), -78 ^oC, 30 min; iii. alcohol **156**, -78 ^oC, 45 min; iv. Et_3N (6 eq), -78 ^oC, 30 min to 0 ^oC, 30 min.

Scheme 2.81: Synthesis of aldehyde **150** from aldehyde **138**.

2.5.3 Aldol Coupling and Spirocyclisation

The results of the model aldol system (section 2.4.3) did not conclusively identify optimal conditions for the synthesis of the desired aldol adduct [C23-(*R*)], but highlighted the many factors that influence the selectivity of the reaction and the consequent difficulty in achieving high diastereoselectivity in either direction. It was however apparent from the model system that the protecting group strategy for the ketone fragment would require further investigation.

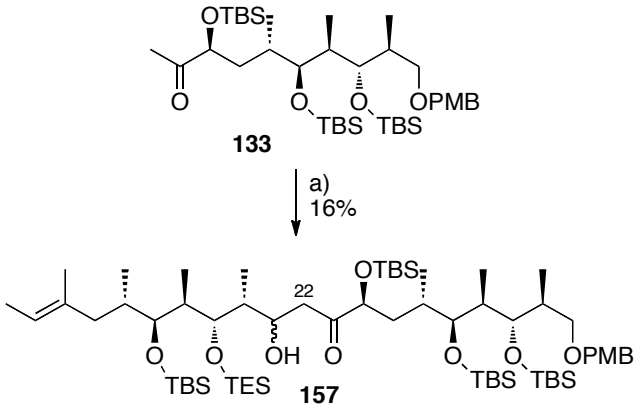
The results of the Paterson group[10,12] showed that the use of the chiral enolising reagents (-)-Ipc_2BCl/Et_3N overcame the inherent facial selectivity of the reaction between acetonide protected aldehyde **7** and ketone **8**, giving the desired diastereoselectivity of the aldol adduct (section 2.2.1). These conditions were trialled for the coupling of ketone **130** and aldehyde **133** (scheme 2.82), however, as with the model system, this reaction was unsuccessful and returned only the starting materials. The Cossy group was also unable to effect a similar reaction under the same conditions.[21]



Reagent and conditions: a. i. (-)-Ipc_2BCl (1 eq), Et_3N (1.1 eq), Et_2O, 1 h, 0 ^oC; ii. aldehyde **150** (0.9 eq), -78 ^oC, 3 h to -20 ^oC, 12 h.

Scheme 2.82: Attempted aldol coupling of methyl ketone **130** with aldehyde **150** using (-)-Ipc_2BCl/Et_3N.

The reaction of silyl protected ketone **133** with aldehyde **150** was then attempted, as per scheme 2.83. Due to the limited amount of ketone **133**, only the Li aldol was trialled, in the hope that it would provide results comparable to those of Kalesse[17] and Cossy.[21] Ketone **133** was treated with LiHMDS (2 eq) in THF at -78 ^{o}C for 30 min before aldehyde **150** was added. After stirring at -78 ^{o}C for 3 h the limiting reagent, ketone **133**, had apparently been consumed, according to TLC analysis. Purfication by column chromatography gave two fractions, the first of which was a mixture of decomposition products and an apparent aldol adduct. The second fraction appeared to be a mixture of products that could not be separated or conclusively identified. The first fraction was separated into its individual components by further chromatographic separation, affording predominantly decomposition products and some pure aldol adduct **157** (2.0 mg; 16% yield) as a single isomer.



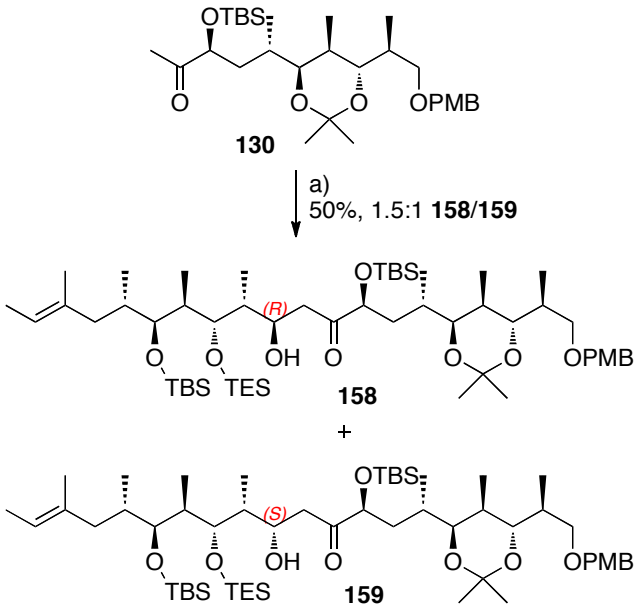
Reagent and conditions: a. i. LiHMDS (2 eq), THF, -78 ^{o}C, 30 min; ii. aldehyde **150** (1.7 eq), -78 ^{o}C, 3 h to rt 1 h.

Scheme 2.83: Attempted aldol coupling of methyl ketone **133** with aldehyde **150** using LiHMDS.

Although only one isomer of aldol adduct **157** could be identified by NMR, the diastereoselectivity of the reaction could not be determined with certainty as a large amount of decomposition had occurred during the reaction. These decomposition products could be masking the presence of another aldol isomer, or

one isomer of aldol adduct may have been more susceptible to decomposition than the other (for example, by elimination of H_2O across C22-23, PMB or silyl ether deprotection). The ^{1}H NMR chemical shifts observed for H22a and H22b were δ 2.74 and δ 2.65. These two protons are diastereotopic due to their close proximity to the C23 stereocentre. Cossy reported shifts of δ 3.01 and 2.35 for an analogous aldol adduct **38** (section 2.2.3),[21] which was shown to bear the correct configuration at C23 for the natural product. The ^{1}H NMR shifts for H22a and H22b are markedly different for aldol adduct **157** from those observed by Cossy, which implies that it has the opposite stereochemistry at C23, however further analysis would be required to confirm this. The large difference in chemical shift observed for H22a and H22b is a phenomenon that is also observed later and examined in more detail.

Finally, the Li aldol between acetonide protected ketone **130** and aldehyde **150** was investigated (scheme 2.84). Ketone **130** was treated with LiHMDS (2 eq) in THF at -78 ^{o}C for 30 min before aldehyde **150** was added. The reaction mixture was stirred at -78 ^{o}C for 3 h before placing in the freezer (-20 ^{o}C) overnight. This resulted in a 2.5:1 mixture of aldol adducts **158** and **159**, which were separable by column chromatography. The reaction was repeated on a larger scale and after 4 hours at -78 ^{o}C the reaction had apparently ceased (observed by TLC analysis) and the ratio of products observed for this reaction was 1.5:1. This apparent difference in selectivity was attributed to the sensitivity of the reaction to temperature variations. Considering temperature control is more difficult on a larger scale, these variations could result in reversibility and lithium aldolate equilibration. Importantly, the major product was the same in both cases.



Reagent and conditions: a. i. LiHMDS (2 eq), THF, -78 ^{o}C, 30 min; ii. aldehyde **150** (1 eq), -78 ^{o}C, 3 h to -20 ^{o}C, 12 h.

Scheme 2.84: Aldol coupling of methyl ketone **130** with aldehyde **150** using LiHMDS.

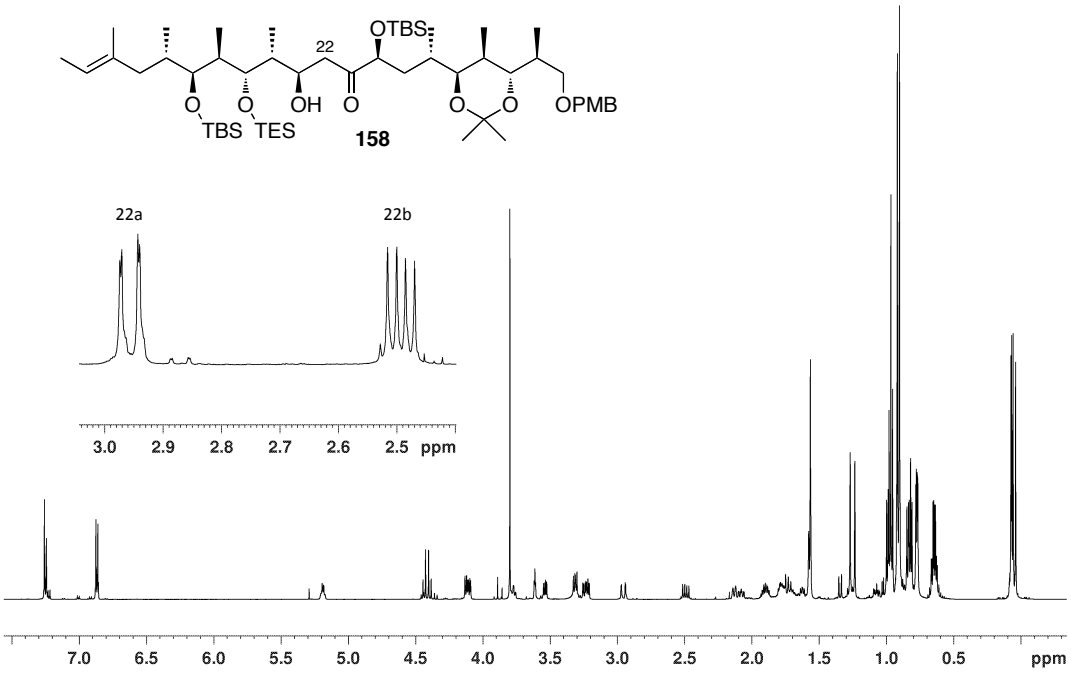


Figure 2.19: 600 MHz ^{1}H NMR spectrum of major aldol adduct **158**.

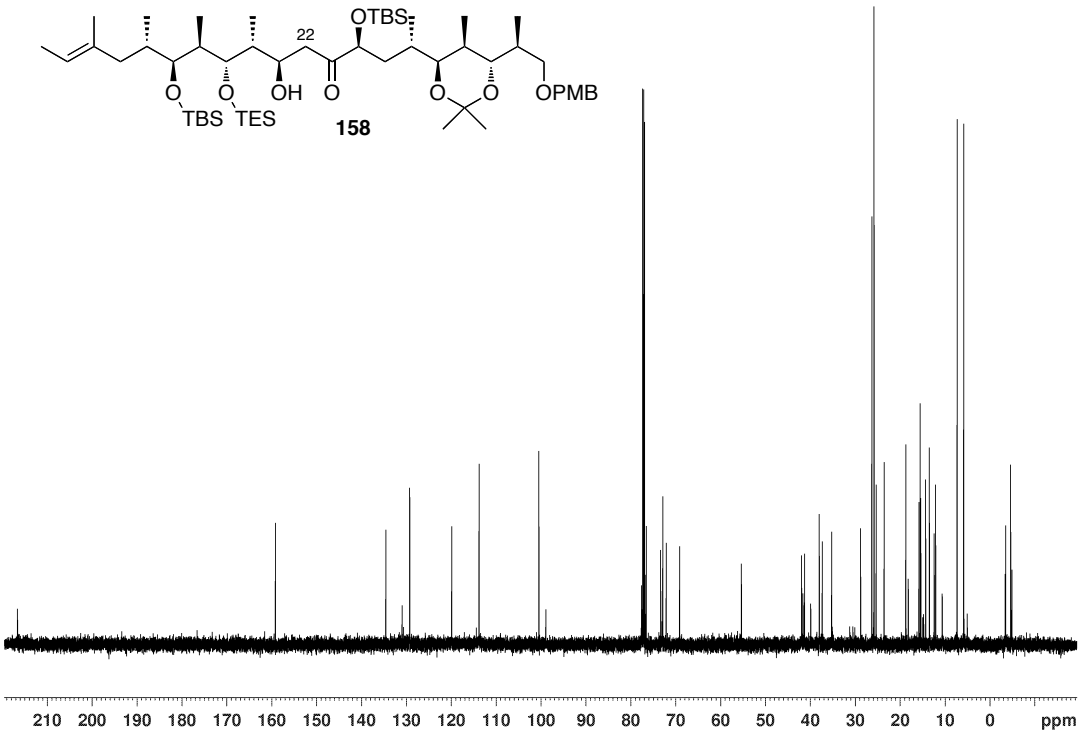


Figure 2.20: 151 MHz ^{13}C NMR spectrum of major aldol adduct **158**.

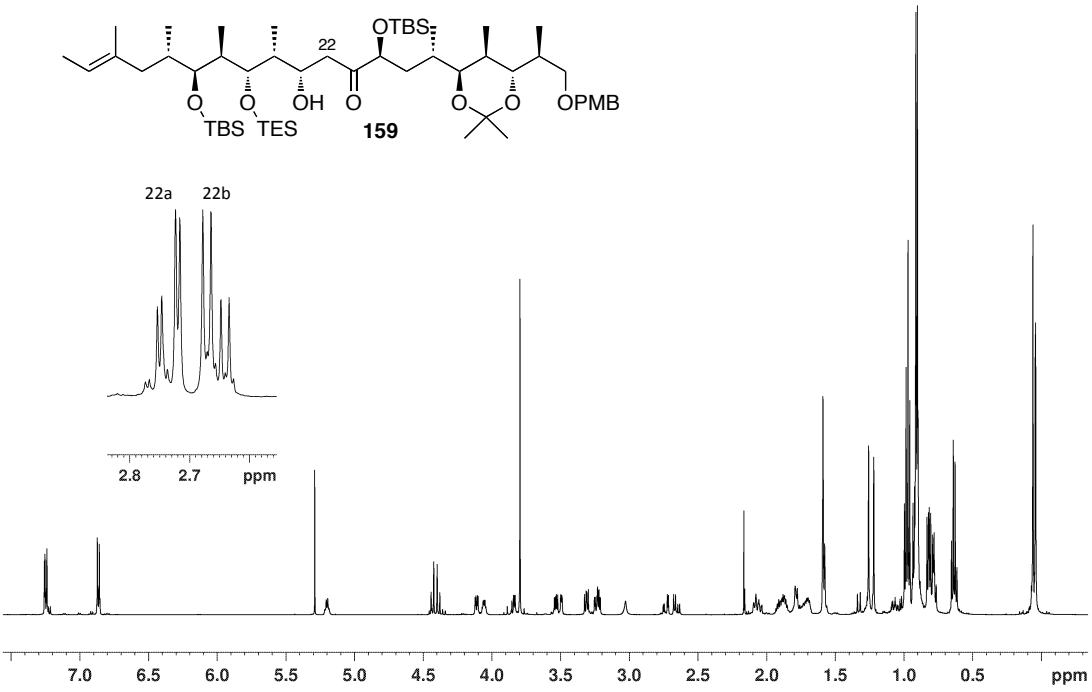


Figure 2.21: 600 MHz ^{1}H NMR spectrum of major aldol adduct **159**.

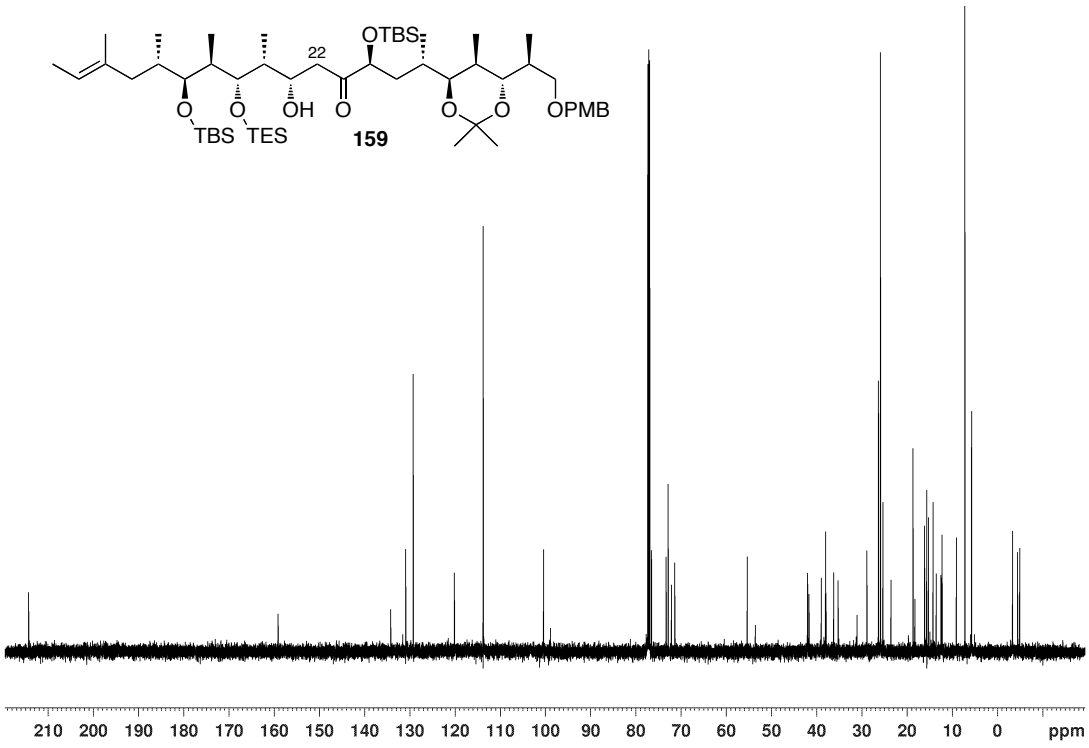


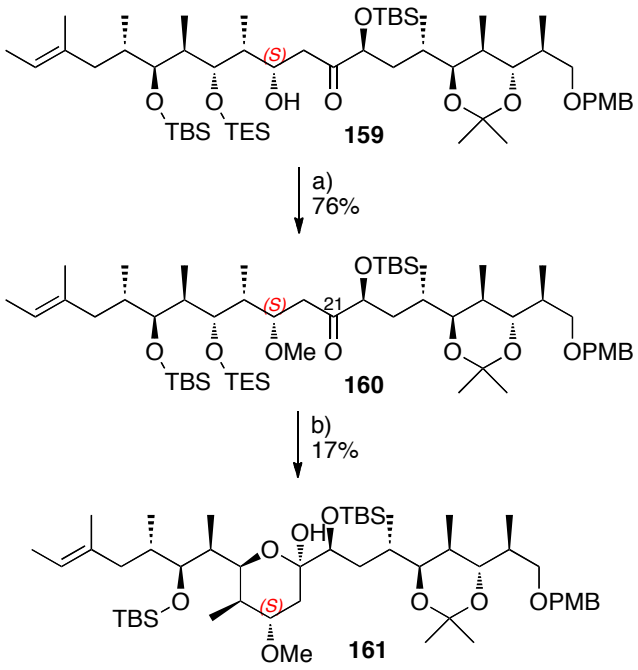
Figure 2.22: 151 MHz ^{13}C NMR spectrum of major aldol adduct **159**.

Comparison of the ^{1}H NMR chemical shifts around the reaction site with the analogous proton shifts in the model system indicated that the stereochemistry of the major isomer **158** matched the minor isomer **113** of the model system. Specifically, the C22 and 23 proton shifts are compared, as summarised in table 2.4. It is apparent from the model system that when the C23 is in the (*R*)-configuration (natural product), the chemical shifts of H22a and 22b are far apart ($\Delta\delta$ 0.46), while the (*S*)-configuration sees these two protons close together ($\Delta\delta$ 0.08) in a more apparent AB fashion. This phenomenon is also observed by Cossy[21] (Kalesse does not report his spectra for the aldol adduct) and is due to the different chemical environments created for H22a and H22b due to H-bonding between the H23 hydroxyl and C21 carbonyl. It can be seen from table 2.4 that the chemical shift of H23 is significantly different depending on the configuration of C23, and is almost identical for the natural product major isomer **158** and model system minor isomer **113**, and vice versa. This strongly implies that the selectivity of the aldol reaction has been reversed, apparently due to the change in C17 functionality.

Compound	**H23** (δ ppm)	**H22a, H22b** (δ ppm)
Major isomer **158**	3.77	2.95, 2.49
Minor isomer **159**	4.06	2.73, 2.65
Model major isomer **112**	4.05	2.65
Model minor isomer **113**	3.77	2.75, 2.59
Cossy major isomer **38**	not assigned	3.01, 2.35

Table 2.4: Comparison of ^{1}H chemical shifts (δ) for H22 and H23 in LiHMDS mediated aldols.

To confirm the assumed sterochemistry, the C23 hydroxyl in minor isomer **159** was methylated, as per the natural product, using the commercially available (Sigma Aldrich Chemical Co.) Meerwein's salt[116] $Me_3O.BF_4$ as the alkylating agent.[117] Methyl ether **160** was then subjected to HF/pyr/pyr with catalytic H_2O,[71-73] with monitoring by TLC to ensure removal of only the TES protecting group. This resulted in cyclisation onto C21 to afford hemiacetal **161** in poor yield (17%) (scheme 2.85). This poor yield was evidently a result of the limited solubility of hemiacetal **161** in the extraction solvent, which was unfortunately discovered after the aqueous phase was discarded.



Reagent and conditions: a. 4 Å sieves, proton sponge (6 eq), $Me_3O.BF_4$ (6 eq), 0 ^{o}C to rt, 1 h; **b.** HF/pyr/pyr, THF, H_2O (cat.), rt, 6 h.

Scheme 2.85: Synthesis of hemiacetal **161** from minor aldol adduct **159**.

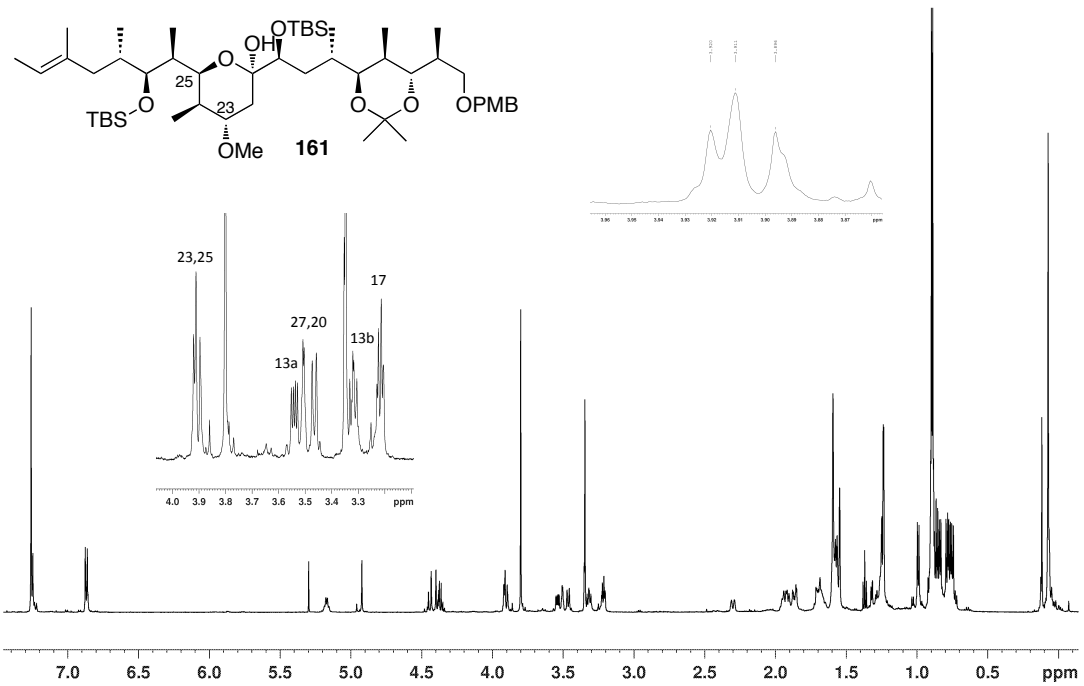


Figure 2.23: 600 MHz ^{1}H NMR spectrum of minor hemiacetal **161** in $CDCl_3$.

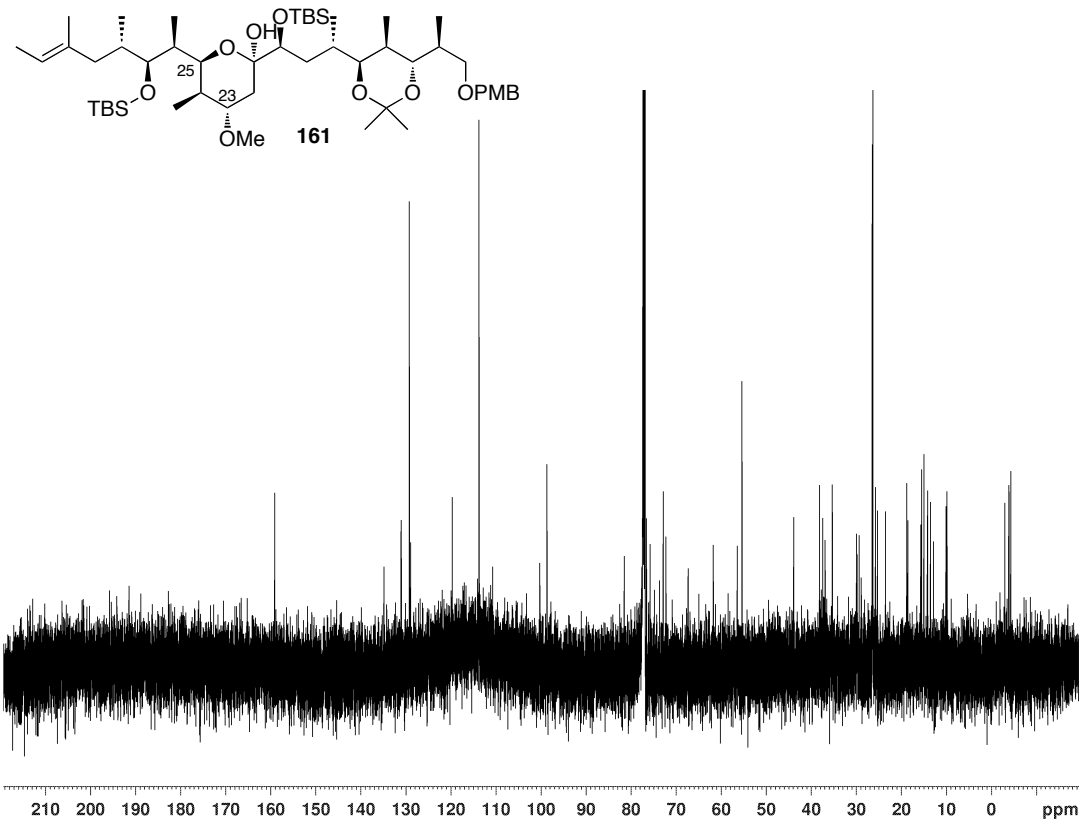


Figure 2.24: 151 MHz ^{13}C NMR spectrum of minor hemiacetal **161** in $CDCl_3$.

Analysis of the nOe interactions in hemiacetal **161** was indicative of an (*S*)-configuration at C23, as per the unwanted isomer, **159** (figure 2.25). NOESY correlations were observed between H23 and the C24 methyl group. It was not clear (due to overlapping peaks) whether there was a real nOe correlation between the methoxy protons and H25, but the absence of an nOe correlation between H23 and H25 was also a strong indication of the assigned configuration.

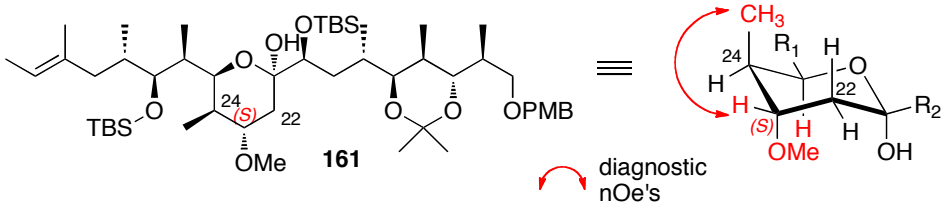
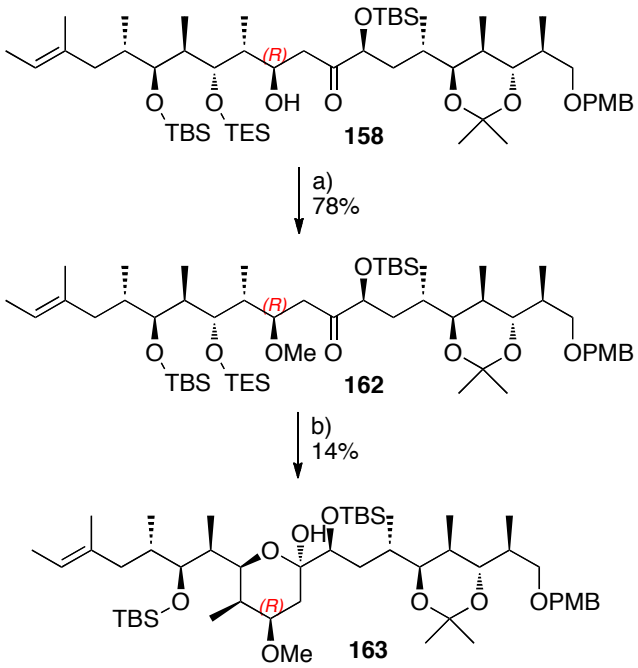


Figure 2.25: Diagnostic nOe interactions in hemiacetal **161**.

The same sequence of reactions was followed for major aldol diastereomer **158** to produce methyl ether **162**, followed by hemiacetal **163** (11%, 2 steps) (scheme 2.86). The poor yield of hemiacetal **163** was once again attributable to solubility, as the reaction was carried out at the same time and under the same conditions as hemiacetal **161**.

Notably, in the *O*-methylated intermediates **160** and **162**, the ability for H-bonding between the C23 hydroxyl and C21 carbonyl is lost and the ^{1}H NMR shifts of H22a and H22b are identical, δ 2.80 and 2.55, for both isomers **160** and **162** (see appendix A for ^{1}H and ^{13}C NMR spectra).



Reagent and conditions: a. 4 Å sieves, proton sponge (6 eq), $Me_3O.BF_4$ (6 eq), 0 ^{o}C to rt, 1 h; **b.** HF/pyr/pyr, THF, H_2O (cat.), rt, 6 h.

Scheme 2.86: Synthesis of hemiacetal **163** from major aldol adduct **158**.

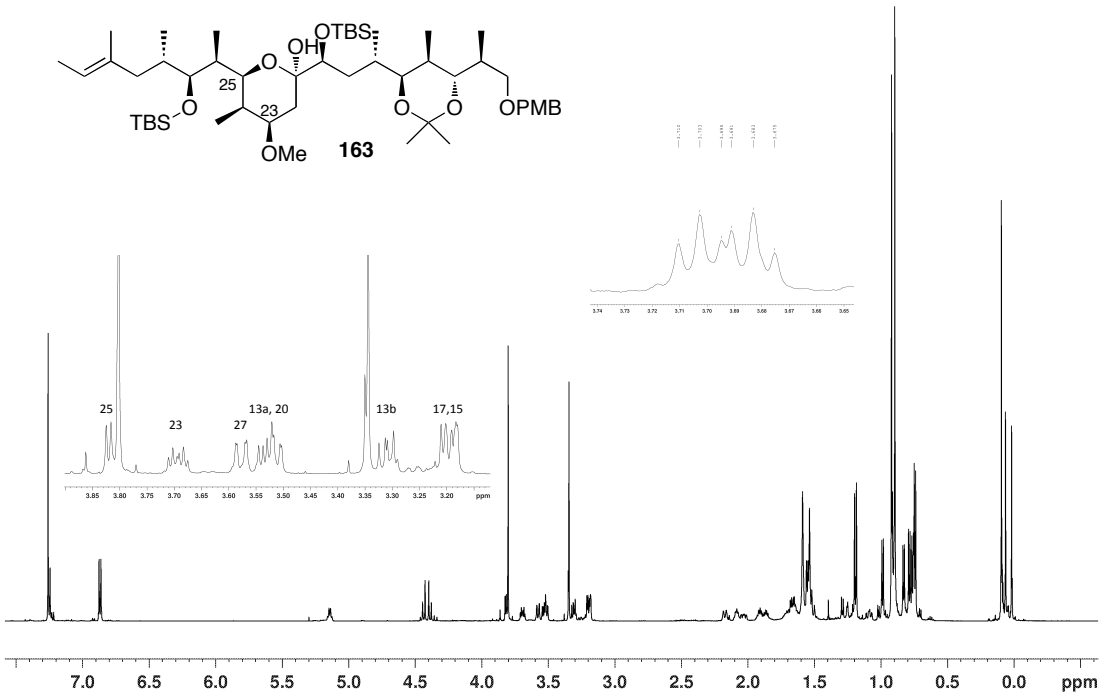


Figure 2.26: 600 MHz ^{1}H NMR spectrum of major hemiacetal **163** in $CDCl_3$.

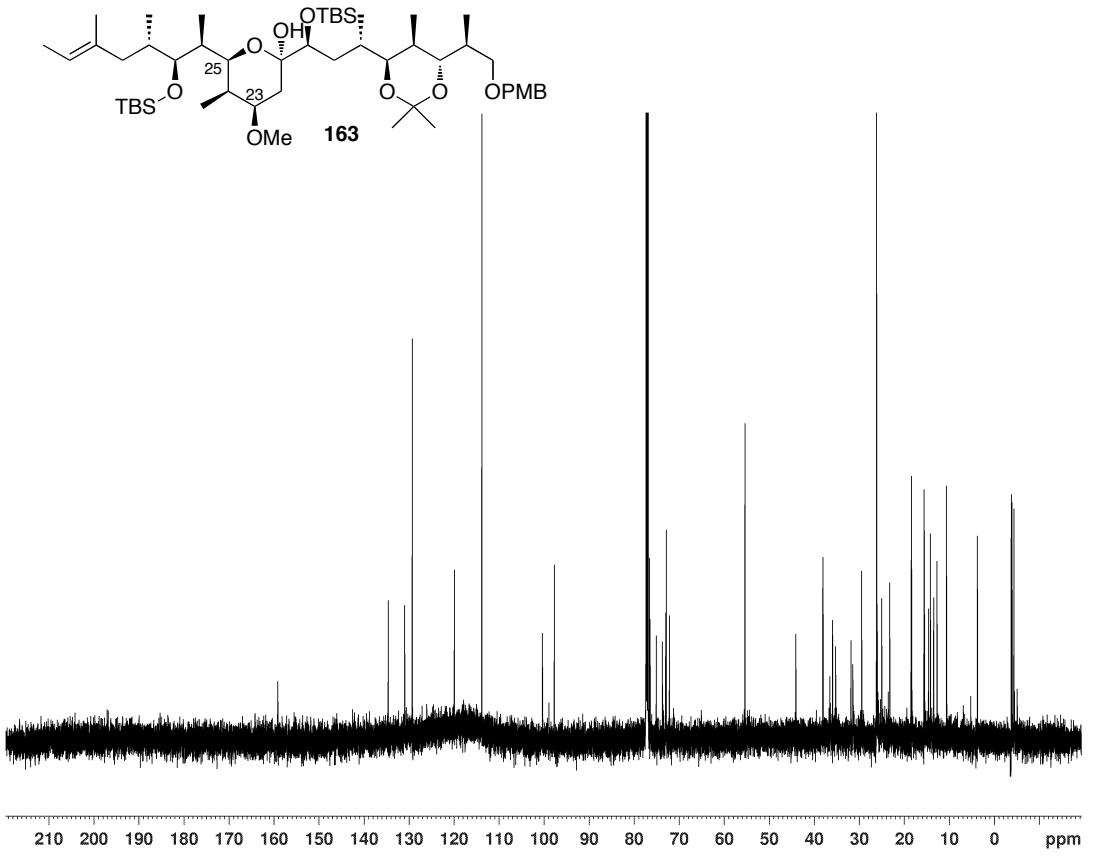


Figure 2.27: 151 MHz ^{13}C NMR spectrum of major hemiacetal **163** in $CDCl_3$.

Analysis of the diagnostic nOe correlations in hemiacetal **163** were difficult due to interfering NOESY signals for H23 and H25. However, there was a clear nOe interaction between the methoxy protons and the C24 methyl protons (as shown in figure 2.28), which would only occur if C23 was (*R*). Notably, there was also an absence of NOESY correlations between the C24 methyl and H23. This was further evidence that the major aldol isomer was the desired C23-(*R*) isomer.

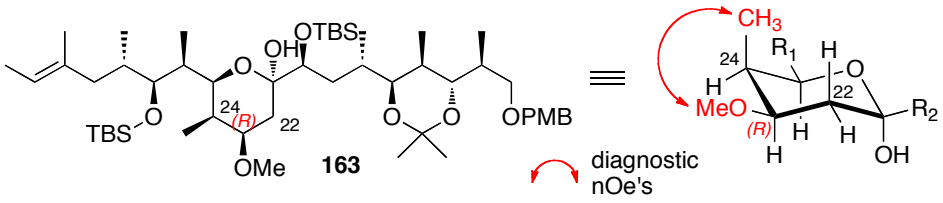


Figure 2.28: Diagnostic nOe interactions in hemiacetal **163**.

The coupling patterns of protons in cyclohexanes was determined by Garbisch and Griffith[118] by analysis of the coupling patterns in 1,1,2,2,3,3,4,4-octadeuteriocyclohexane, and analogous patterns can be observed in 6-membered cyclic hemiacetals and 6,6-spiroacetals. They showed that the axial-axial coupling constants for vicinal protons are comparable in size to geminal coupling (ie. ~11-14 Hz), but that axial-equatorial and equatorial-equatorial coupling is very small (~ 3 Hz). On this basis the coupling pattern of H23 in the major hemiacetal **163** (figure 2.29) strongly supports the stereochemical assignment. H23 has a large coupling constant (J = 11.4 Hz) which is indicative of an axial-axial interaction (ie. H23 to H22a) and two small coupling constants (J = 4.8 and 4.2 Hz), evidence of the axial-equatorial interactions with H22b and H24 (figure 2.29). In the minor hemiacetal **161**, H23 is a doublet (J = 5.4 Hz), presumably due to coupling with the axial proton H22a, as the equatorial-equatorial couplings are apparently too small to be observed (figure 2.29). Indeed, a COSY correlation is only detected between H23 and one other proton (at C22). Furthermore, the chemical shift of axial protons is typically upfield of its equatorial equivalent in cyclohexanes.[119] For major isomer

163, δ_{H23} = 3.69 and for minor isomer **161**, δ_{H23} = 3.90, further evidence that in major isomer **163** H23 is axial and thus the correct isomer for the natural product.

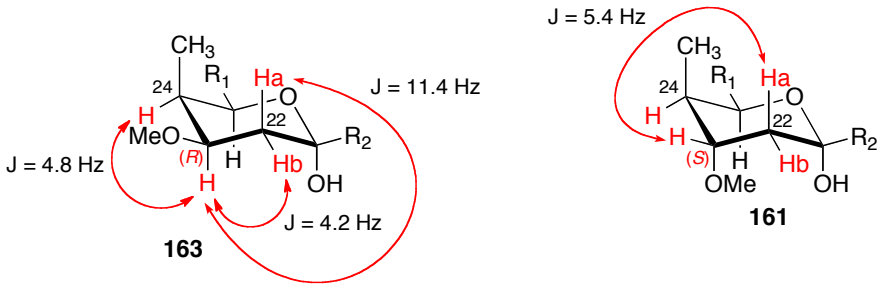
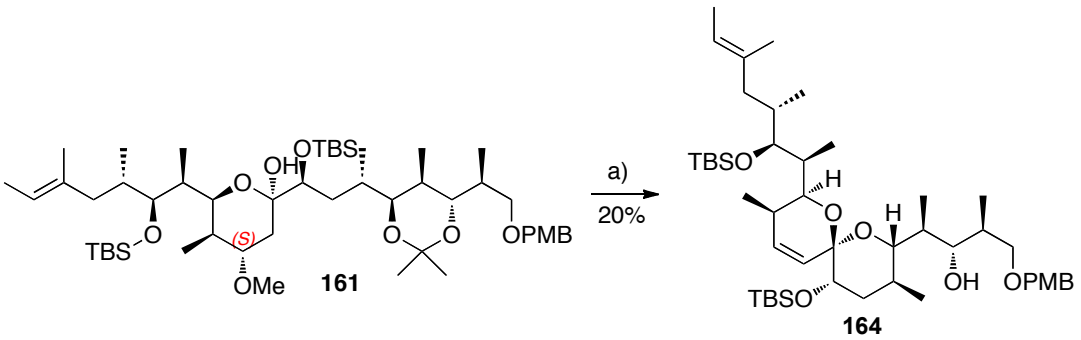


Figure 2.29: Observed coupling constants (J) for H23 axial as per hemiacetal **163** and equatorial as per hemiacetal **161**.

With a small amount of hemiacetals **161** and **163** in hand, it was anticipated that they could be converted to the corresponding spiroacetals to further confirm the stereochemical assignment of C23. This would require removal of the acetonide group under mild condition to invoke spirocyclisation. As such, both isomers of hemiacetal were treated separately with a catalytic amount of CSA in MeOH, according to literature precedent.[10,21]

As shown in scheme 2.87, the minor hemiacetal **161** did cyclise to give a 6,6-spiroacetal, but unfortunately elimination of MeOH occurred across C22-23, removing the stereocentre under investigation. This was evidenced in the ^{1}H NMR spectrum (figure 2.30) by the absence of the methoxy peak and C23 proton and the addition of two olefinic protons (δ 5.96 and 5.76) with coupling that matched the proposed structure.



Reagent and conditions: a. CSA (cat.), MeOH, rt, 12 h.

Scheme 2.87: Spirocyclisation of minor hemiacetal **161**.

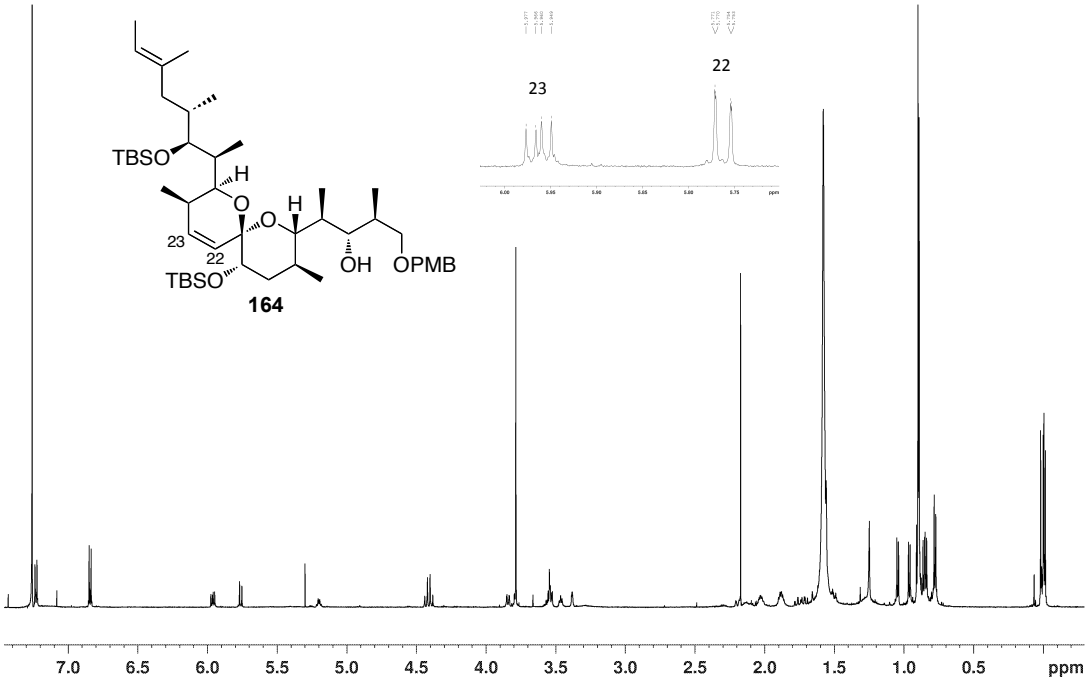
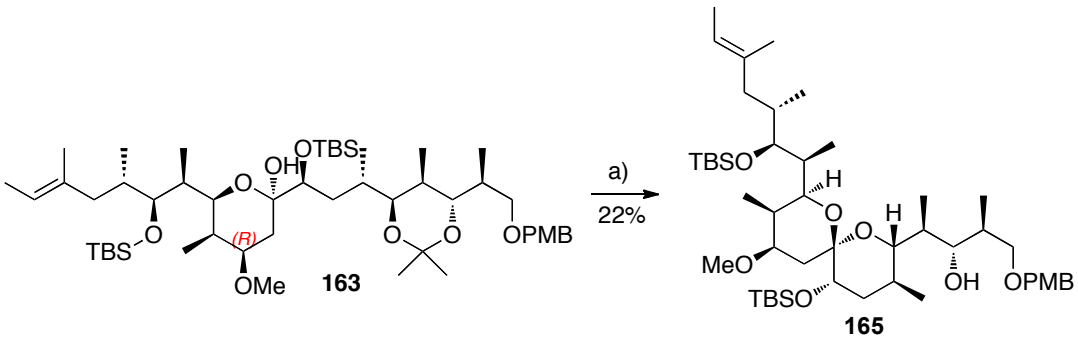


Figure 2.30: 600 MHz ^{1}H NMR spectrum of spiroacetal **164** in $CDCl_3$.

Fortunately, when major hemiacetal **163** was treated under the same conditions, there was no elimination of MeOH and spiroactal **165** was produced, albeit in poor yield (22%) (scheme 2.88). This was perhaps attributable to the scale of reaction, or CSA may have been too acidic for the sensitive substrate and PPTS may have been a better choice to catalyse spirocyclisation, as per the model system.



Reagent and conditions: a. CSA (cat.), MeOH, rt, 12 h.

Scheme 2.88: Spirocyclisation of major hemiacetal **163**.

^{1}H NMR, COSY and NOESY spectra of spiroacetal **165** were initially obtained in $CDCl_3$, however there was significant overlapping of peaks that prevented accurate assignment (see appendix A, figures A31-35). The spectra were also acquired in C_6D_6 and this allowed for identification of individual protons and coupling constants. Figure 2.31 shows the ^{1}H NMR spectrum of spiroacetal **165**, while the nOe and COSY spectra can be seen in appendix A (figures A36 and A37).

The ^{1}H NMR spectrum of spiracetal **165** in C_6D_6 shows two distinct spin systems, separated by the C21 acetal. The diastereotopic oxymethylene protons at C17 appear as AB coupled doublets of doublets at δ 3.62 (J = 9.0, 3.6 Hz) and 3.27 (J = 9.0, 3.0 Hz). These protons both couple to the methine proton at C16, which in turn couples to the oxymethine at C15 (δ 3.77). H15 shows coupling (J = 9.0, 9.0, 3.6 Hz) to H16, H17 and the C15 hydroxyl, which resonates at δ 4.26. The axial H17 resonates as a doublet of doublets at δ 4.17 (J = 10.8, 1.8 Hz) due to coupling with both H16 and H18. The diastereotopic C19 methylene protons resonate downfield at δ 2.08 and 1.66, and couple to the oxymethine proton at δ 3.66 (H20). The other axial proton adjacent an acetal oxygen, H25, is represented by the doublet at δ 4.24 (J = 5.4 Hz). H25 exhibits COSY correlations to H26, which in turn couples to the oxymethine doublet of doublets at δ 3.97 (J = 10.2, 1.8 Hz), attributed to H27. H27 couples with methylmethine H28, which in turn couples to the diastereotopic methylene protons at C29. The remaining oxymethine proton H23 (δ 3.86) couples

to H22a, H22b and H24 with a distinctive coupling pattern that is discussed further below. The associated methoxy methyl resonates as a singlet at δ 3.12. Vinyl proton H31 resonates, as expected, as a quartet at δ 5.44 (J = 6.6 Hz) and the adjacent methyl is a doublet at δ 1.57 (J = 6.6 Hz), while the C30 methyl is a singlet at δ 1.70. The remaining methyl doublets were assigned on the basis of their COSY correlations with the corresponding methylmethine protons and the PMB and TBS protons resonated at the usual frequencies.

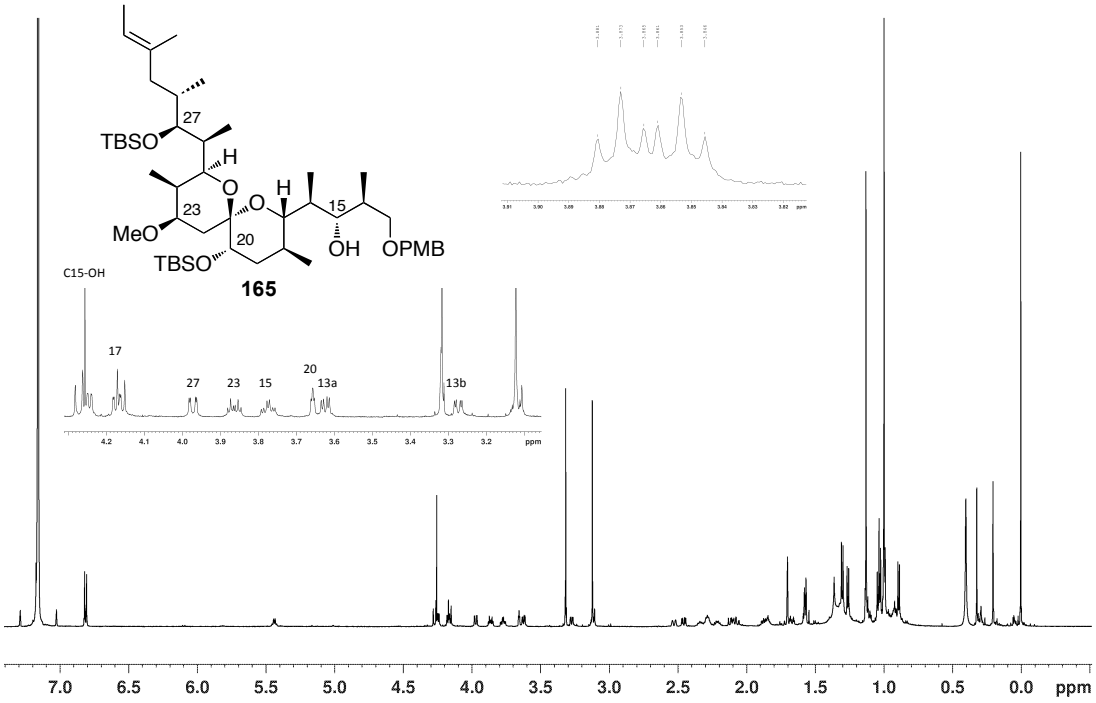


Figure 2.31: 600 MHz ^{1}H NMR spectrum of spiroacetal **165** in C_6D_6.

Figure 2.32 shows the diagnostic nOe correlations observed in C_6D_6 (also seen in $CDCl_3$) for spiroacetal **165**. These nOe interactions irrefutably confirm the (*R*)-stereochemistry at C23, as evident from correlation between C23-OMe and C24-Me, as well as correlations with both H22a and H22b. An nOe interaction between H23 and H25 is also observed, which is only possible in the C23-(*R*) isomer.

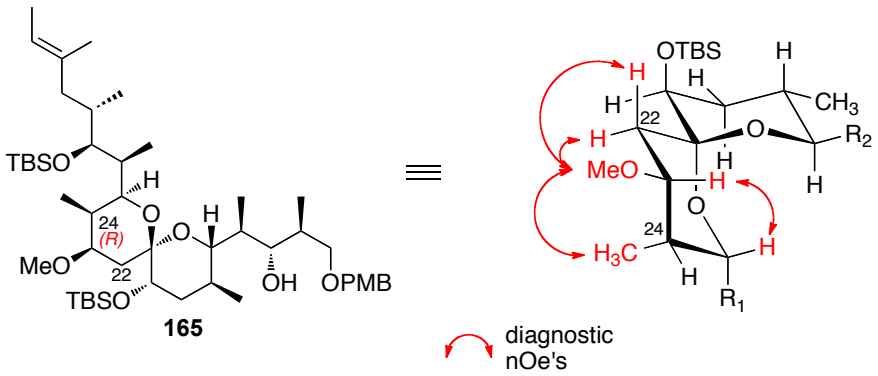


Figure 2.32: Diagnostic nOe correlations in spiroacetal **165**.

As with hemiacetal **163**, the coupling constants for H23 in spiroacetal **165** (seen in C_6D_6, figure 2.31) were indicative of an axial configuration. A large axial-axial interaction was observed between H23 and H22a (J = 11.4 Hz), and two smaller couplings (J = 4.8 and 4.2 Hz) representing the axial-equatorial interactions (to H22b and H24). As such, the major isomer from the Li aldol coupling between ketone **130** and aldehyde **150** was conclusively assigned to be the correct stereochemistry for the natural product (ie. C23-(*R*)).

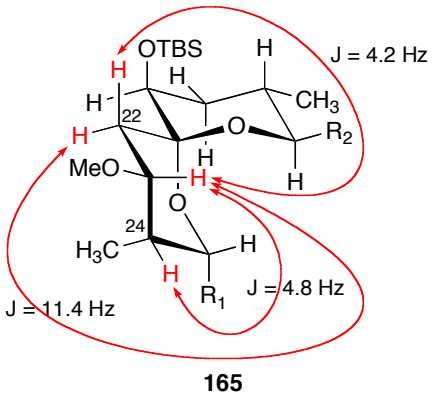
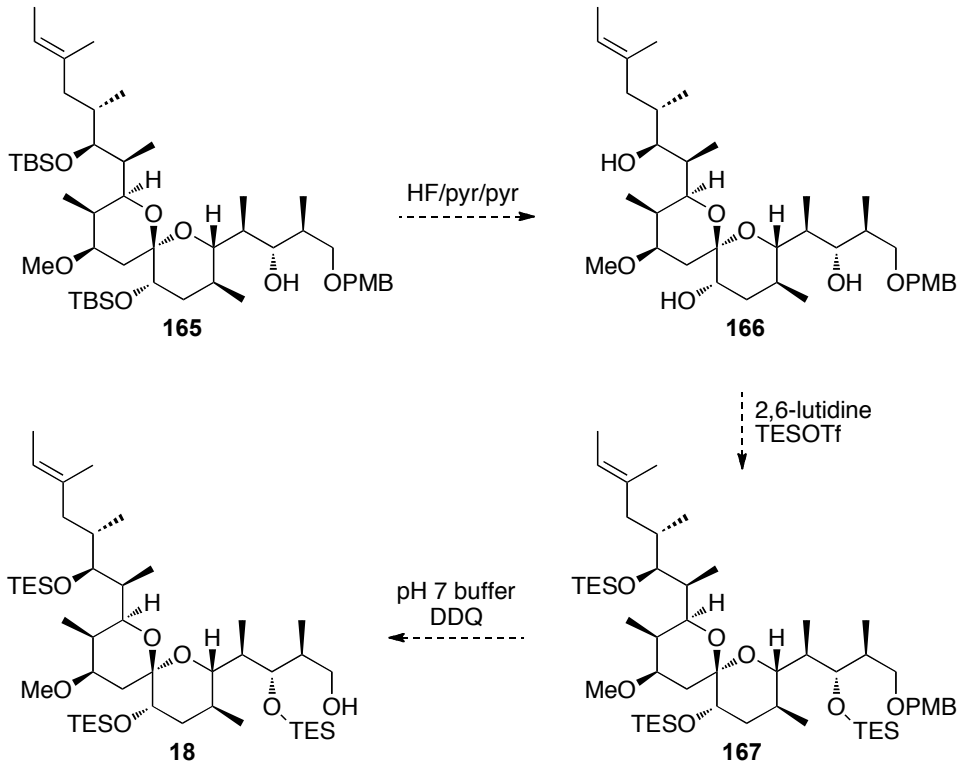


Figure 2.33: Observed coupling constants (J) for spiroacetal **165**.

2.5.4 Proposed Strategy for a Formal Synthesis

Having synthesised spiroacetal core **165**, bearing the correct stereochemistry for spirangien A, it was anticipated that a formal synthesis would be achieved. However, due to the solubility issues associated with hemiacetals **161** and **163**, as well as time constraints, there was not enough of spiroacetal **165** produced to proceed to a formal synthesis in the given timeframe.

The advanced intermediate that was to be intersected was alcohol **18**, a precursor to both the synthesis of spirangien diene (**3**) and spirangien A (**1**) by Paterson.[12,11] The proposed pathway to **18** from siproacetal **165** is represented in scheme 2.89, below. This would involve a 3 step process, whereby the silyl protecting groups would be removed under mild conditions (HF/pyr/pyr)[73,71,72] from spiroacetal **165** to give the free hydroxyls at C27, 20 and 17, compound **166**. Triol **166** would then need to be re-protected using TES groups to give compound **167**, according to Paterson's protecting group strategy. Finally, the PMB protecting group would be removed using aqueous DDQ to liberate the terminal hydroxyl, giving compound **18**, thus completing a formal synthesis of spirangien A (**1**).



Scheme 2.89: Proposed pathway to a formal synthesis of spirangien A (**1**) from spiroacetal **165**.

2.6 Conclusion

The work presented above describes studies towards the synthesis of spirangien A, a highly cytotoxic and antifungal polyketide, isolated from the myxobacterium *Sorangium cellulosum*. The synthetic approach to spirangien A exploited the obvious C22-C23 acetate aldol disconnection in linear precursor, **158**. Model studies were conducted which showed, in conjuction with previous work by other groups, that the diastereoselectivity of this aldol reaction is highly substrate controlled and depends heavily on the hydroxyl protecting group strategy. Coupling was achieved between model ketone **53** and model aldehydes **85** and **107** using LiHMDS, giving 3:1 and 2.5:1 ds respectively, both in favour of the unwanted C23-(*S*) isomer. This model system lacked the C17 stereocentre of the natural product, which apparently exhibited strong 1,7-stereoinduction, therefore the model was concluded to be an inadequate representation of the natural product system.

The aldehyde coupling partner **150** was synthesised in 10 steps (10% yield) using Evans *syn* aldol chemistry, utilising a highly efficient cross-coupling of zinc homoenolate **144** with (*E*)-2-bromo-2-butene (**48**) to install the C28 stereocentre. Ketone coupling partner **130** was synthesised from (*R*)-Roche ester **(*R*)-32** in 16 steps (22 % yield), using a *syn,syn* selective aldol reaction with dipropionate equivalent **(*S*)-10**. Coupling of these two compounds was achieved using a LiHMDS aldol to give 1.2-2.5:1 ds in favour of the desired product **158** (figure 2.90). This is consistent with the related results of Kalesse[17] and Cossy,[21] as discussed in sections 2.3 and 2.4.3. The stereochemistry of the aldol adducts was assigned by conversion to the corresponding hemiacetals and subsequent nOe analysis. Spirocyclisation of the major product hemiacetal gave **165**, from which stereochemical assignment was confirmed. Further manipulation of **165** in 3 steps would result in a formal synthesis of spirangien A (**1**) *via* advanced intermediate **18**, however low cyclisation yields prevented a formal synthesis in the given timeframe.

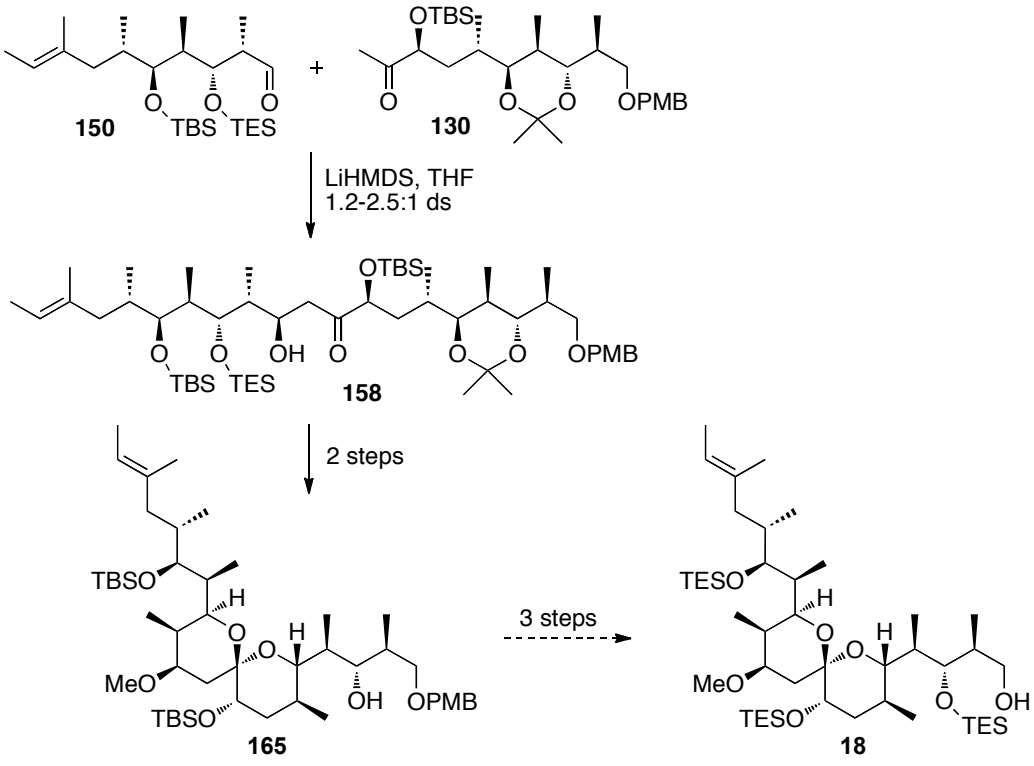


Figure 2.90: Synthesis of spiracetal **165** and proposed synthesis of formal synthesis intermediate **18**.

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Chapter Three:

Total Synthesis of (+)-Ascosalipyrone and *ent*-Micropyrone

3.1 Introduction

3.1.1 Isolation and Biological Evaluation of Ascosalipyrone

Over the last 20 years, compounds with novel chemical structures have been isolated from algicolous fungi with biological activities that include antimicroalgal properties and cytoxicity towards lymphocytic leukemia cells and human colon carcinoma cells.[1] In 2000, Osterhage and co-workers[1] isolated the obligate marine fungus *Aschochyta salicorniae* from the inner tissue of the green alga *Ulva* sp., collected from the North Sea, Tönning, Germany. An EtOAc extract of *A. salicorniae* was found to have antimicrobial and antiplasmodial properties so further investigations were pursued in order to identify the biologically active natural products.

A. salicorniae was cultivated on a solid biomalt medium with added artificial sea salt. Successive fractionation of the EtOAc extract by VLC (vacuum liquid chromatography) and normal and reversed phase HPLC resulted in the isolation of a number of known and unprecedented secondary metabolites. These novel compounds included ascosalipyrrolidinone A (**168**), which exhibited antiplasmodial, antimicrobial and tyrosine kinase inhibiting activity, as well as the new polyketide natural product ascosalipyrone (**4**) (figure 3.1).[1]

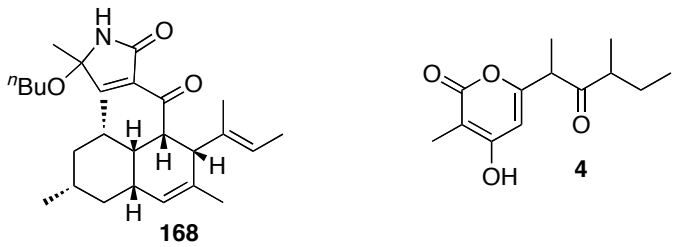


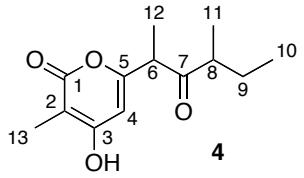
Figure 3.1: Ascosalipyrrolidinone A (**168**) and ascosalipyrone (**4**).

Ascosalipyrone (**4**) was tested for antimicrobial, antialgal, nematicidal, antiplasmodial, antitrypanosomal and cytotoxic properties, but failed to show any

activity in all of the applied tests.[1] In a later study by Seibert *et al*.[2] in which secondary metabolites from *A. salicorniae* were identified as potential protein phosphatase inhibitors, ascosalipyrone was further tested against seven different phosphatases but was found to be inactive.

3.1.2 Structure Elucidation of Ascosalipyrone

The molecular formula of ascosalipyrone was determined by high-resolution mass spectrometry (HRMS) and NMR analysis was used to elucidate the skeletal structure (figure 2.2). This structure contains the 4-hydroxy-α-pyrone moiety, with a β-carbonyl in the C5-side chain and two stereocentres, one at C8 and the other at C6, between the pyrone and carbonyl functionalities.



4

Figure 3.2: Skeletal structure of ascosalipyrone (**4**).

Double resonances for C5-9 and C11-12 in the ^{13}C NMR spectrum indicated that ascosalipyrone (**4**) was isolated as an unequal mixture of diastereomers which were unable to be separated by GCMS.[1] The absolute configuration of the two stereocentres at C6 and C8 were unable to be determined and no optical activity of the diastereomeric mixture was reported. The inseparable mixture of diastereomers is presumably due to epimerisation of the C6 centre as it carries a potentially acidic proton, and the mixture must therefore comprise compounds (**(6*R*,8*R*)-4** and/or **(6*S*,8*S*)-4**) and (**(6*R*,8*S*)-4** and/or **(6*S*,8*R*)-4**) (figure 3.3).

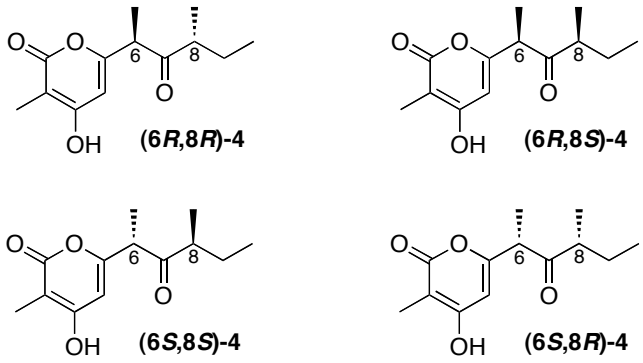


Figure 3.3: The four possible stereoisomers of ascosalipyrone (**4**).

The biosynthetic process that leads to the formation of polyketides usually gives rise to stereoisomerically pure natural products.[2] However, in the case of ascosalipyrone and a select number of other compounds diastereomeric products are observed. Seibert and coworkers[2] identified ascosalipyrone (**4**) and a number of other compounds isolated from the same source as potential protein phosphatase inhibitors. While ascosalipyrone (**4**) was found to be inactive in this respect, it was shown through biological feeding experiments with ^{13}C labeled methionine units (^{13}C abundance ~80%) that ascosalipyrone was derived from a polyacetate pentaketide chain precursor **169**, which is not unusual for fungal metabolites. Siebert *et al.*[2] deduced that all methyl groups, except for CH_3-10, were derived from *S*-adenosyl-methionine in nature. Interestingly, C4 is the only methylene unit that is not methylated. It was also postulated that epimerisation of C6 occurs in the linear precursor (ie. before cyclisation) to ascosalipyrone by keto-enol tautomerisation (figure 3.4).

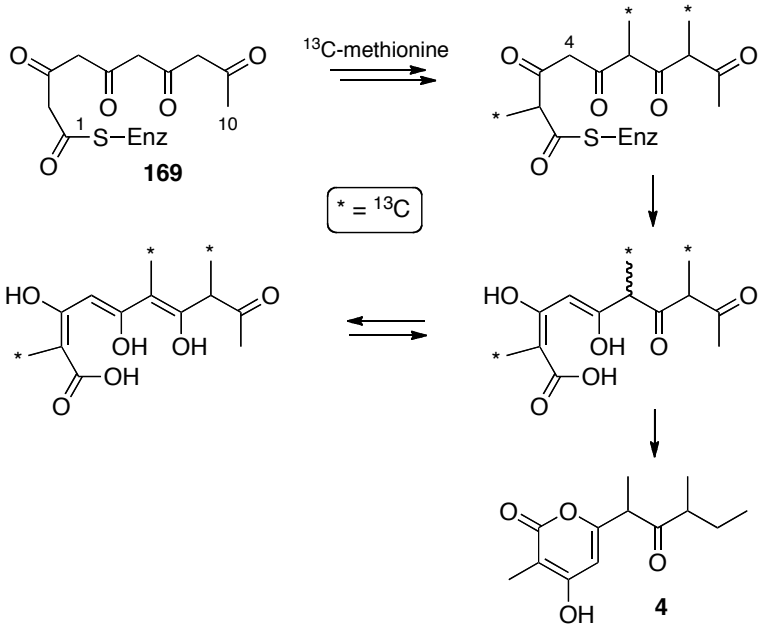


Figure 3.4: Proposed biosynthetic pathway for ascosalipyrone (**4**).[2]

3.1.3 Isolation and Biological Evaluation of Micropyrone

Plants from the genus *Helichrysum*, one of the most well known medicinal plants from the Mediterranean, have been recognised for centuries for their anti-inflammatory and anti-infective properties. *Helichrysum italicum* in particular is a stalwart of folk medicine dating back to the ancient Greek and Roman civilisations for these very properties.[3] In the 1940s systematic clinical studies were carried out on *H. italicum*, revealing that it is a fruitful source of bioactive secondary metabolites, but these results were largely ignored at this time.[3] Not until a revival of interest in new anti-inflammatory agents occurred in recent years was *H. italicum* thoroughly investigated for its potential as a source of medicinal compounds.

In 2007, Appendino and coworkers[3] published a study in which they sought to identify some of the unidentified anti-inflammatory compounds present in *H. italicum*. They began by investigating the subspecies *microphyllum*, from which acetone extracts exhibited potent inhibition of the transcription nuclear factor κB (NF-κB) ($IC_{50} \approx 25\ \mu gmL^{-1}$), a target for inflammation and whose malfunctioning can also be involved in cancer and AIDS.[3-5] The acetone extract was separated into three

components by solid-phase extraction. The active EtOAc component was dissolved in 1:1 EtOAc/petroleum ether, causing a yellow precipitate to form. This precipitate, arzanol (**170**) (figure 3.5), showed powerful NF-kB-inhibiting activity (IC_{50} ≈ 5 μgmL^{-1}). Several other compounds were isolated from the mother liquor, the major component of which was micropyrone (**5**) (figure 3.5).

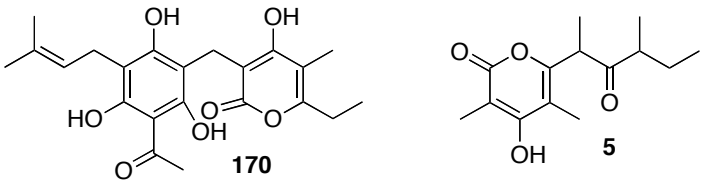


Figure 3.5: Arzanol (**170**) and micropyrone (**5**).

Micropyrone (**5**), which was obtained as a colourless powder, showed no NF-κB-inhibition.[3] The compounds islated from *H. italicum ssp. microphyllum* were also evaluated for antioxidant and cytoxic activity, and while arzanol displayed useful antioxidant activity, micropyrone was found to be relatively inactive.[6]

3.1.4 Structure Elucidation of Micropyrone

The molecular formula of micropyrone was determined by HRMS and the gross structure was deduced by NMR analysis (figure 3.6). ^{1}H NMR studies identified two separate spin systems, which were connected (confirmed by HMBC correlations) by a ketone carbonyl and 3,4-dimethyl-4-hydroxy-α-pyrone moiety.[3]

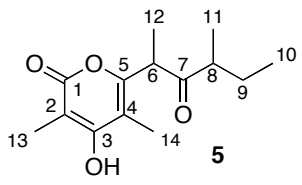
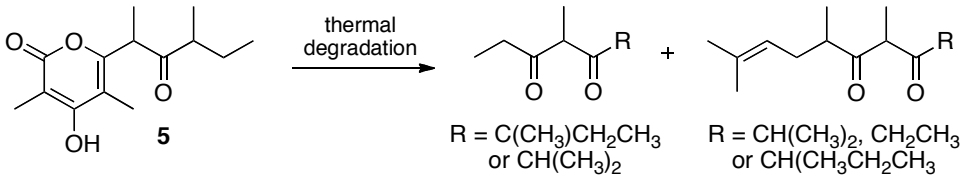


Figure 3.6: Skeletal structure of micropyrone (**5**).

Prior to the isolation of micropyrone (**5**) by Appendino and co-workers[3] in 2007, the steam distillation of *H. italicum* was carried out to isolate the essential oil.[7,8] A series of β-diketones related in structure to microyrone were isolated from the essential oil of *H. italicum*, but not micropyrone (**5**) itself (scheme 3.1).[3] It was postulated that these compounds could arise from the hydrolytic thermal degradation of micropyrone (**5**) during steam distillation of the plant material,[3,7,8] presumably resulting from decarboxylation and other functional group transformations.



Scheme 3.1: Micropyrone (**5**) and related compounds isolated from the essential oil of *H. italicum*.

Micropyrone (**5**) is also very closely related in structure to ascosalipyrone (**4**), the only apparent difference being that micropyrone has a dimethyl substituted 4-hydroxy-α-pyrone ring, while ascosalipyrone is mono-substituted. Unlike ascosalipyrone (**4**) however, micropyrone is reported as a single isomer and an optical rotation is also reported.[3] It is not clear whether micropyrone arises from a polypropionate or polyacetate biosynthetic pathway in nature, however the lack of epimerisation at C6 in the linear precursor implies that the extra methyl group on C4 imparts some steric hindrance to epimerisation. As neither the relative nor absolute configuration of micropyrone has been assigned, its structure consists of one of the four possible stereoisomers shown in figure 3.7.

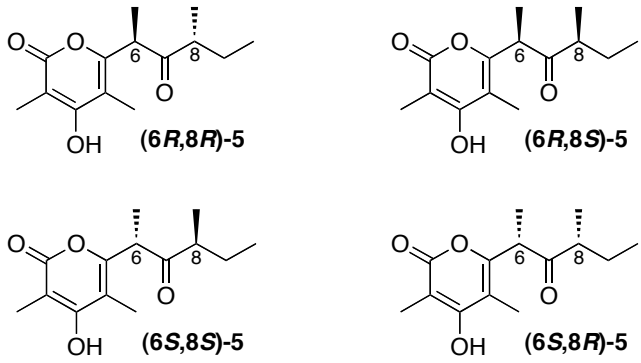


Figure 3.7: The four possible stereoisomers of micropyrone (**5**).

3.2 The Synthetic Approach to Ascosalipyrone and Micropyrone

As ascosalipyrone (**4**) and micropyrone (**5**) are so closely related in structure, the use of analogous reaction pathways and common intermediates was preferred to simplify the overall construction of the two compounds. A synthetic pathway that could potentially prevent the epimerisation of the C6 centre in ascosalipyrone was also sought, so that each stereoisomer could be targeted selectively.

The challenge of retaining the stereochemical integrity at C6 in ascosalipyrone (**4**) arises due to the acidity of the C6 proton during biosynthesis, as it is situated between two carbonyl groups in the linear precursor.[9] Protecting the C7 carbonyl as a silyl ether until after cyclisation was proposed to prevent epimerisation before cyclisation, however it was unclear whether cyclisation or later oxidation would inevitably cause C6 epimerisation.

There have been no previous reports of stereocontrolled syntheses containing the same structural motif to ascosalipyrone (**4**) and micropyrone (**5**) (that is, a 4-hydroxy-α-pyrone with a C5 side chain carrying a β-ketone functionality and a stereocentre at the α- position), nor have there been any synthetic reports towards the natural products themselves.

3.2.1 Retrosynthetic Analysis

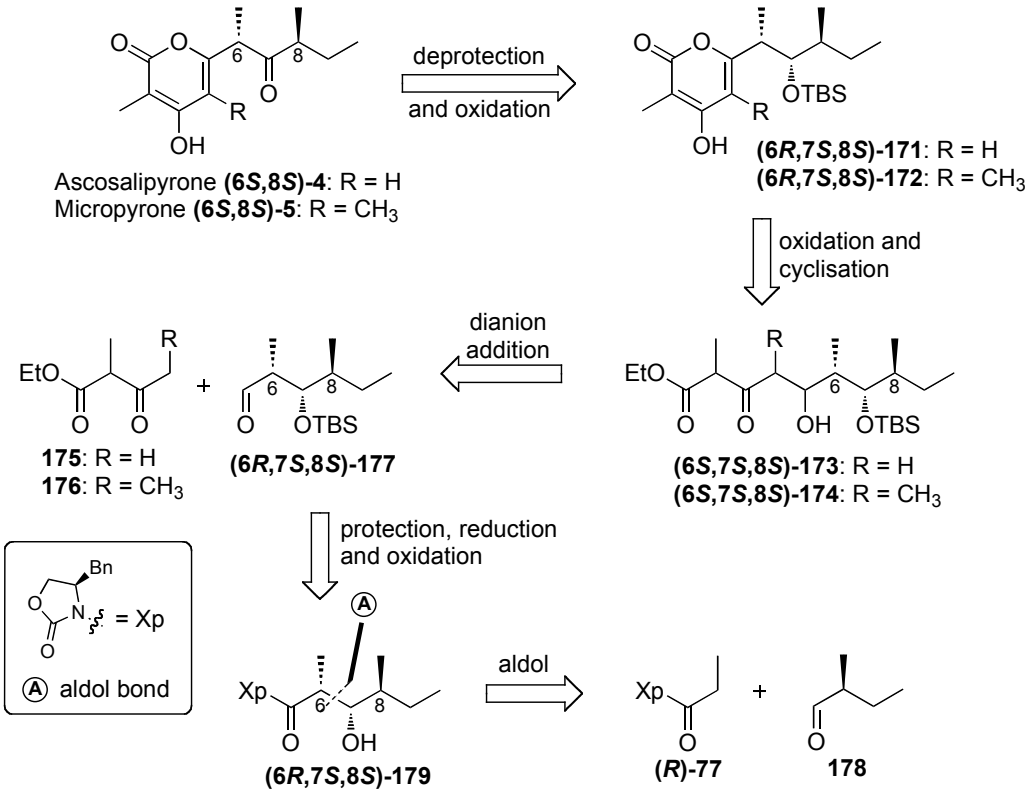
As synthesis of cyclic polyketides in nature typically involves cyclisation of a linear precursor, retrosynthetic efforts towards these products will usually involve unraveling of the ring system to a synthetically attainable linear polyketide precursor with the required functionality already present. However, in an attempt to avoid epimerisation at C6, installation of the C7 carbonyl was planned as the final step in the synthesis. Therefore, it was anticipated that the two natural products, ascosalipyrone **(6*S*,8*S*)-4** and micropyrone **(6*S*,8*S*)-5**, would arise from the deprotection and oxidation of silyl ethers **(6*R*,7*S*,8*S*)-171** and **(6*R*,7*S*,8*S*)-172** respectively (scheme 3.2).

Unraveling of the 4-hydroxy-α-pyrone ring in both **(6*R*,7*S*,8*S*)-171** and **(6*R*,7*S*,8*S*)-172** reveals linear pentaketide precursors **(6*S*,7*S*,8*S*)-173** and **(6*S*,7*S*,8*S*)-174** respectively, which in turn are anticipated to arise from an aldol-type dianion addition of a β-ketoester (**175** or **176** respectively) to aldehyde **(6*R*,7*S*,8*S*)-177**. The structure of the β-ketoester (**175**: R = H or **176**: CH_3) determines which natural product will result, while aldehyde **(6*R*,7*S*,8*S*)-177** serves as a common intermediate to each ascosalipyrone **(6*S*,8*S*)-4** and micropyrone **(6*S*,8*S*)-5**. It is also the stereochemistry of this aldehyde that determines the overall stereochemistry of the natural product and therefore it is necessary to be able to synthesise a number of different stereoisomers of this compound.

Aldehyde **(6*R*,7*S*,8*S*)-177** was envisaged to arise from the aldol coupling of a suitable chiral enolate with a single enantiomer of 2-methylbutanal. Due to the commercial availability of chiral alcohol (*S*)-2-methylbutan-1-ol (Sigma-Aldrich Chemical Co.) and its simple conversion to the corresponding aldehyde by Swern[10] oxidation, the (8*S*)- isomers of both natural products were targeted (though only the (6*S,*8*S*) isomer in each case is shown in scheme 3.2 for simplicity). Aldehyde intermediate **(6*R*,7*S*,8*S*)-177** (as well as **(6*S*,7*R*,8*S*)-177**) could be targeted using Evans' aldol chemistry as this procedure gives high diastereoselectivity in the *syn*-aldol products. It was not essential that the *syn* aldol product be produced, as the stereochemistry at C7 is of little consequence in the final products. However,

defined stereochemistry at C7 was desired for ease of identification and characterisation.

The coupling of Evans' oxazolidinone **(*R*)-77** with (*S*)-2-methylbutanal (**178**) would give rise to *syn*-aldol adduct **(6*R*,7*S*,8*S*)-179**, while the other enantiomer of Evans' oxazolidinone **(*S*)-77** would give rise to the diastereomeric *syn*-aldol adduct **(6*S*,7*R*,8*S*)-179** and therefore the other targeted isomer of the natural products. Standard functional group manipulations would be used to convert aldol adduct **(6*R*,7*S*,8*S*)-179** to the corresponding aldehyde **(6*R*,7*S*,8*S*)-177**.



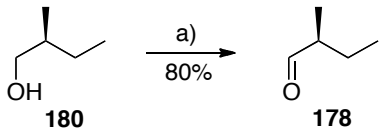
Scheme 3.2: Retrosynthetic analysis of ascosalipyrone (**4**) and micropyrone (**5**).

3.3 Synthesis of Ascsalipyrone and Micropyrone

3.3.1 Synthesis of Diastereomeric Aldehydes (6*R*,7*S*,8*S*)-177 and (6*S*,7*R*,8*S*)-177 *via* a *syn*-Aldol Coupling

The first step in the synthesis of both ascosalipyrone (**4**) and micropyrone (**5**) was to install the required stereochemistry for the targeted isomers of the natural products. To achieve this, a double stereodifferentiating aldol reaction was proposed. As the C7 stereochemistry is absent in the final product, a *syn* or *anti* aldol reaction could be used, as long as it gave high diastereoselectivity in the product. The Evans auxiliary was chosen as it typically gives >98% ds in the *syn*-aldol adducts, according to the transition state model presented in section 1.3.1.3.[11,12]

Aldehyde **178** was readily synthesised *via* a Swern[10] oxidation of (*S*)-2-methylbutan-1-ol (**180**) (scheme 3.3). This method reportedly yields approx. 80% of aldehyde **178**.[13,14] Due to the volatility of aldehyde **178**, solvent was not completely removed after workup and purification (column chromatography, 100% CH_2Cl_2) to avoid loss of material. Therefore, an 80% yield was assumed for the following step.



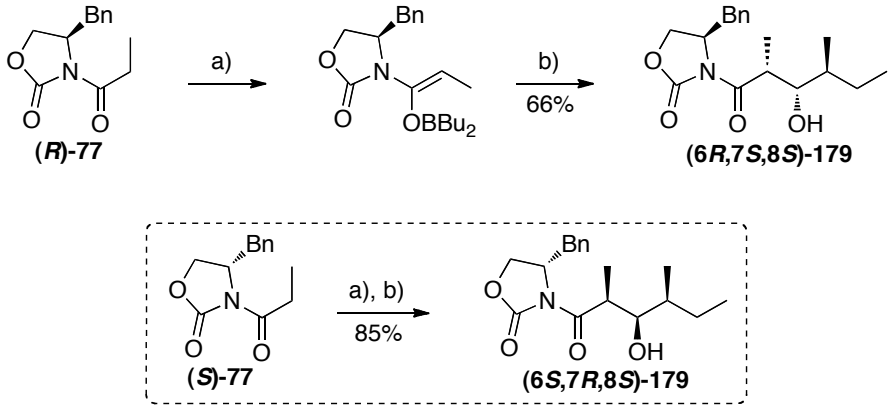
180 **178**

Reagents and conditions: a. i. DMSO (3 eq), CH_2Cl_2, -78 ^{o}C; ii. $(COCl)_2$ (1.5 eq), -78 ^{o}C, 30 min; iii. alcohol **180**, -78 ^{o}C, 45 min; iv. Et_3N (6 eq), -78 ^{o}C, 30 min to 0 ^{o}C, 30 min.

Scheme 3.3: Swern oxidation of (*S*)-2-methylbutan-1-ol (**180**).

Both enantiomers of Evans auxiliary **(*R*)-77** and **(*S*)-77** were synthesised from (*R*)- and (*S*)-phenylalanine respectively, according to the standard procedure as described in section 2.4.2.[11] The dibutylboron enolate of these two compounds was prepared at 0 ^{o}C using Bu_2BOTf/Et_3N,[11] followed by addition of excess aldehyde **178**

(2 eq) at -78 °C and warming to 0 °C after 30 min to complete the reaction (scheme 3.4). The reaction of **(*R*)-77** with aldehyde **178** gave *syn*-aldol adduct **(6*R*,7*S*,8*S*)-179** in 66% yield and with no detectable (by ^{1}H NMR) minor isomer (>98% ds). Similarly, the reaction of **(*S*)-77** with aldehyde **178** gave a single observable diastereomer of *syn* aldol adduct **(6*S*,7*R*,8*S*)-179** (85%, >98% ds). The ^{1}H and ^{13}C NMR spectra of both aldol adducts can be viewed in appendix B (figures B1-4).

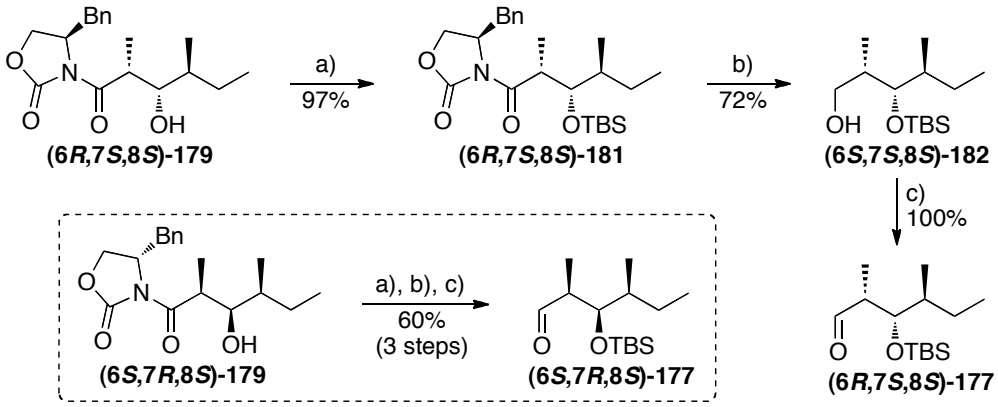


Reagents and conditions: a. i. Bu_2BOTf (1.2 eq), 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; **b. 178** (2 eq), -78 °C, 30 min to 0 °C, 4 h.

Scheme 3.4: *Syn*-aldol reaction between Evans auxiliaries (*R*)- and (*S*)- **77** and aldehyde **178**.

The resultant hydroxyl group from the Evans aldol coupling in compounds **(6*R*,7*S*,8*S*)-179** and **(6*S*,7*R*,8*S*)-179** was protected as the corresponding TBS ether (2,6-lutidine,TBSOTf)[15] to give **(6*R*,7*S*,8*S*)-181** and **(6*S*,7*R*,8*S*)-181** as white solids in high yields (97% and 91% respectively) after purification by column chromatography. The auxiliary was then reductively cleaved using $LiBH_4$/ EtOH[16] to afford alcohols **(6*S*,7*S*,8*S*)-182** (72%) and **(6*R*,7*R*,8*S*)-182** (66%) as colourless oils, with recovery of the chiral auxiliary by chromatographic separation. Subsequent Swern[10] oxidation produced the two desired diastereomeric aldehyde intermediates **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177** (scheme 3.5). The ^{1}H and ^{13}C NMR spectra of aldehyde **(6*R*,7*S*,8*S*)-177** are shown in figures 3.8 and 3.9 respectively.

The characteristic aldehyde peaks are clearly visible, at δ 9.72 in the ^{1}H spectrum for the aldehyde proton and δ 205.5 in the ^{13}C spectrum for the carbonyl carbon. The same spectral features were observed for aldehyde **(6*S*,7*R*,8*S*)-177** (see appendix B for spectra).



Reagents and conditions: a. 2,6-lutidine (2 eq), TBSOTf (1.5 eq), CH_2Cl_2, -78 ^{o}C, 6 h; **b.** EtOH (2.4 eq), $LiBH_4$ (2.4 eq), Et_2O, -10 ^{o}C, 4 h; **c.** i. DMSO (3 eq), CH_2Cl_2, -78 ^{o}C; ii. $(COCl)_2$ (1.5 eq), -78 ^{o}C, 30 min; iii. alcohol **182**, -78 ^{o}C, 45 min; iv. Et_3N (6 eq), -78^{o}C, 30 min to 0 ^{o}C, 30 min.

Scheme 3.5: Synthesis of key aldehyde intermediates **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177**.

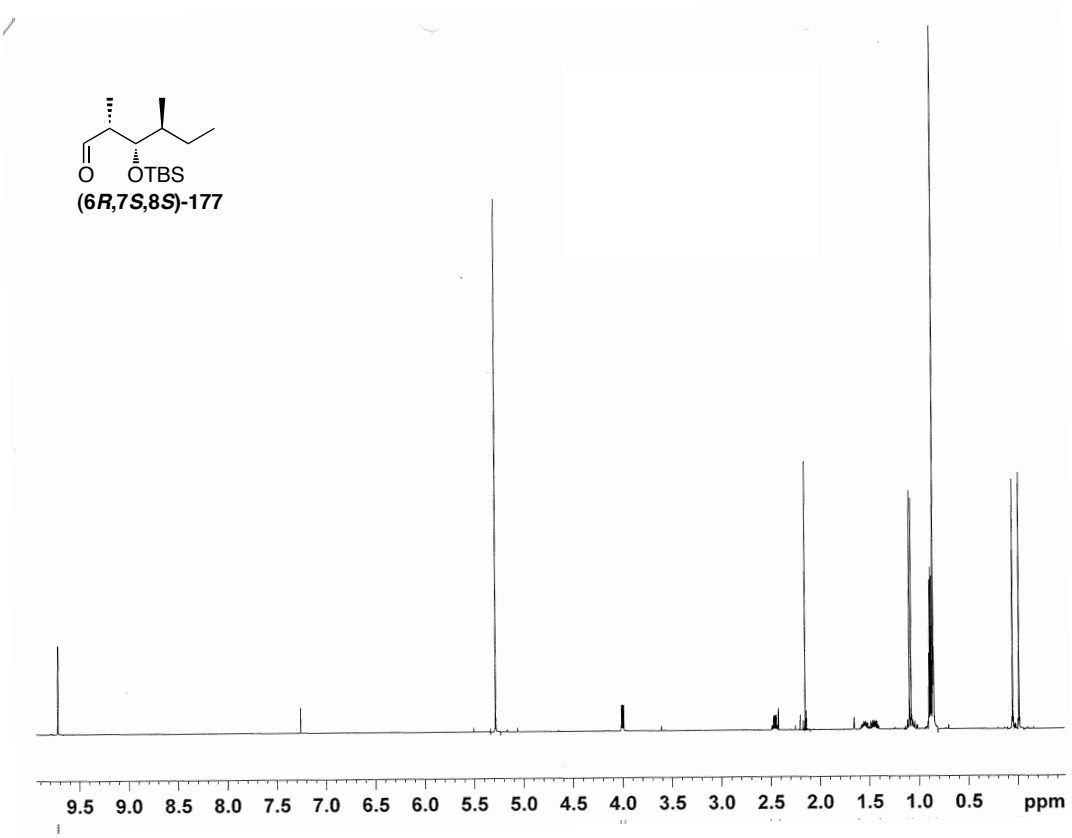


Figure 3.8: 600 MHz ^{1}H NMR spectrum of aldehyde **(6*R*,7*S*,8*S*)-177** in $CDCl_3$.

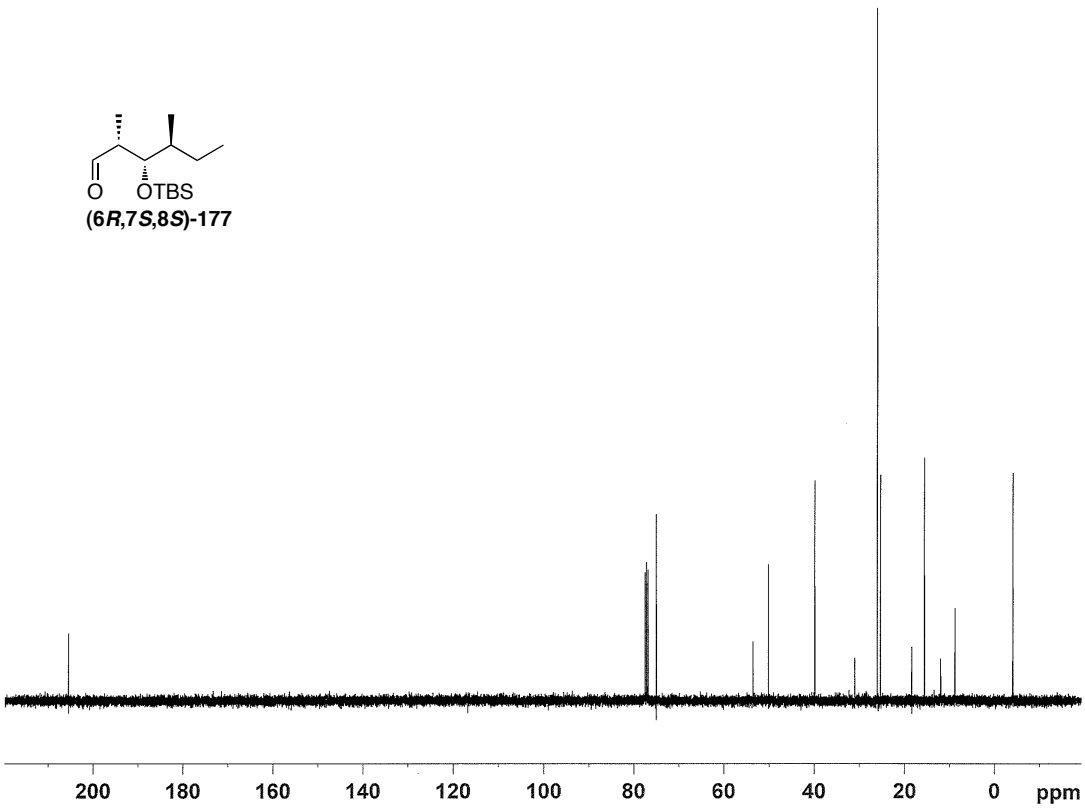
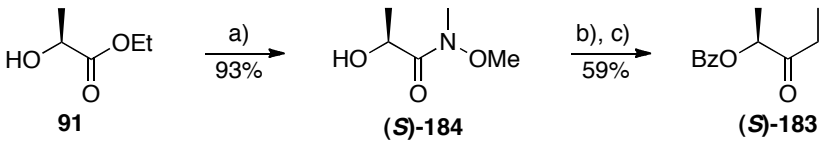


Figure 3.9: 151 MHz ^{13}C NMR spectrum of aldehyde **(6*R*,7*S*,8*S*)-177** in $CDCl_3$.

3.3.2 Studies Towards the Synthesis of an Alternative Aldehyde Intermediate *via* an *anti*-Aldol Coupling

Due to the successful application of the *anti*-aldol coupling between (*S*)-2-methylbutanal (**178**) and Paterson's lactate-derived chiral ketone[17] **(*S*)-183** by Crossman and Perkins,[13] this approach to the synthesis of a common aldehyde intermediate to both ascosalipyrone (**4**) and micropyrone (**5**) was also investigated.

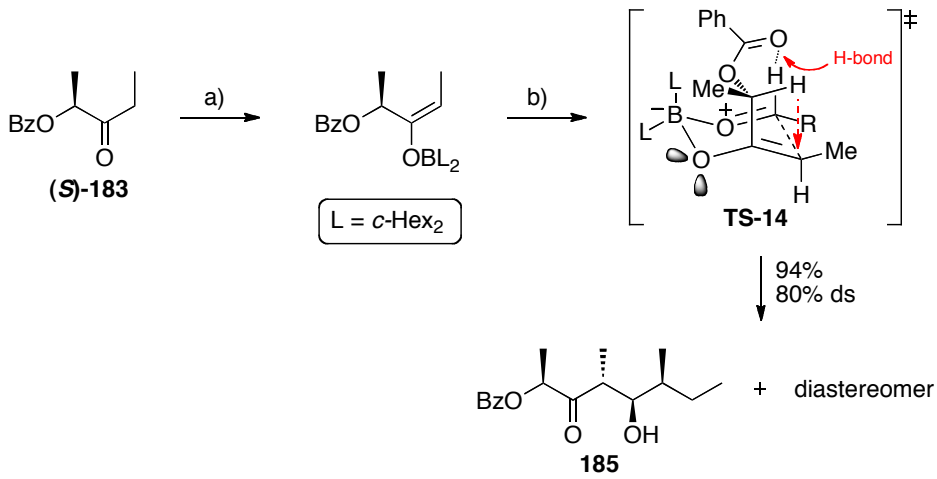
Both the (*R*)- and (*S*)- enantiomers of ketone **183** are readily synthesised from commercially available isobutyl (*R*)-lactate and ethyl (*S*)-lactate respectively in a 3 step process *via* their respective Weinreb amide[18] intermediates, according to literature procedures[19] (scheme 3.6). Weinreb amides react cleanly with Grignard or organolithium reagents to produce exclusively ketone products, with no over-addition due to formation of a metal chelated tetrahedral intermediate.[20] Ethyl-(*S*)-lacate (**91**) was cleanly converted to the corresponding Weinreb amide **(*S*)-184** by addition of MeN(OMe)H.HCl/*i*-PrMgCl,[19,21] with purifaction by Kügelrohr distillation. EtMgBr was then added to **(*S*)-184** to afford the ethyl ketone.[19,21] Extraction of the product (without purification) was followed immediately by protection of the volatile hydroxyl intermediate as the benzoate ester using Bz_2O, DMAP and *i*-Pr_2NEt (scheme 3.6).[19,21] Purification by column chromatography gave enantiomerically pure **(*S*)-183** in 55% yield (2 steps).



Reagents and conditions: a. MeN(OMe)H.HCl (2.5 eq), *i*-PrMgCl (5eq), 1:1 THF/Et_2O, −20 °C, 1 h to 0 °C, 30 min; **b.** EtMgBr (3.2 eq), THF, 0°C to rt, 1 h; **c.** Bz_2O (1.5 eq), DMAP (0.11 eq), *i*-Pr_2NEt (1.9 eq), THF, rt, 14 h.

Scheme 3.6: Preparation of Paterson's lactate derived chiral ketone **(*S*)-183**.

The Paterson aldol requires generation of the the *E*-enolborinate, using *c*-Hex_2BCl/Me_2NEt at 0 °C for 2 h.[22] Freshly prepared aldehyde (in this case (*S*)-2-methylbutanal **178**) is then added dropwise at -78 °C, with stirring at -78 °C for a minimum of 2 h before placing in the freezer (-20 °C) overnight to complete the reaction (scheme 3.7). The reaction proceeds *via* **TS-14**, as rationalised in section 1.3.1.3, in which steric and electronic factors direct the diastereofacial preference of the enolate.[22,21,19] In fact, the π-face selectivity of the enolate overrides the inherent Felkin-Anh preference of aldehyde **178** to give the *anti*-Felkin (or *anti,anti*) product.[23-25] The dicyclohexylboron chloride (*c*-Hex_2BCl) is prepared *via* hydroboration of cyclohexene using $BH_2Cl.Me_2S$, as per the procedure of Brown *et al*.[26]

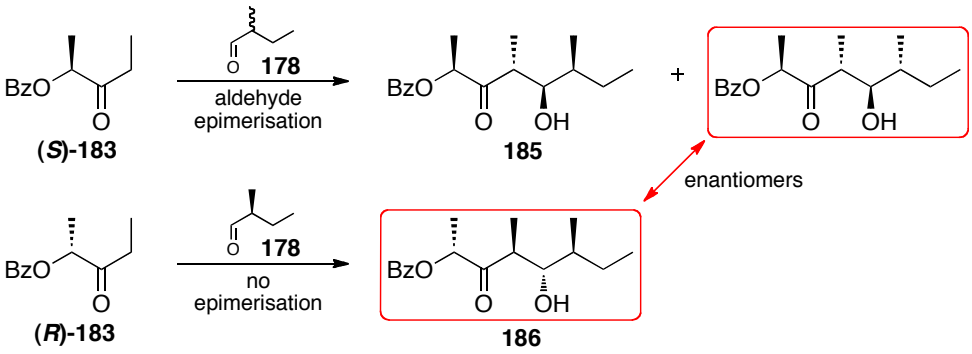


Reagents and conditions: a. (*c*-Hex)$_2$BCl (1.5 eq), Me_2NEt (1.8 eq), Et_2O, 0 °C, 2 h; **b.** aldehyde **178** (2 eq), Et_2O, −78 °C, 2 h to −23 °C, o/n.

Scheme 3.7: Double stereodifferentiating *anti*-aldol coupling between **(*S*)-183** and aldehyde **178**.

According to literature precedent, diastereoselectivities of >90% should be achieved for the mismatched aldol reaction (ie. **(*R*)-183** with **178**) and >95% for the matched aldol (ie. **(*S*)-183** with **178**).[13] However, when the reaction was carried out between

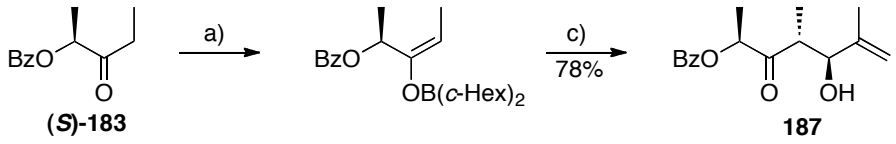
(*S*)-183 and (*S*)-2-methylbutanal (**178**), the ^{1}H and ^{13}C NMR spectra showed a ~5:1 mixture of diastereomeric products (ie. ~80% ds) (see appendix B for spectra, figures B7 and B8). Comparison of spectral data (NMR and optical rotation) with known[13] aldol adduct **185** confirmed that it was the major product. The spectral data for the minor product was identical to the known compound **186** - a diastereomer of compound **185** - derived from the reaction of **(*R*)-183** with enantiomerically pure aldehyde **178**.[13] A mixture of diastereomeric products can result if alcohol **180** (precursor to aldehyde **178**) is not enantiomerically pure or the α-centre epimerises in a subsequent step, causing the minor product to be the enantiomer of known compound **186** and thus identical by NMR (scheme 3.8).



Scheme 3.8: Comparison of the products of the *anti*-aldol reaction between **(*S*)-183** and partially epimerised aldehyde **178** with known compound **186**.

It seemed unlikely that the reduced diastereoselectivity was a result of the aldol reaction itself, since the rationale for the *anti* outcome of the reaction (section 1.3.1.3) and the results previously obtained by Crossman and Perkins[13] for a near identical reaction strongly support almost exclusive formation of the *E*-enolate (giving the *anti* product). *Si* face attack of the aldehyde is also unlikely due to the high energy associated with the corresponding transition state. To conclusively exclude the aldol reaction as the source of epimerisation, a model reaction was carried out between **(*S*)-183** and methacrolein (**46**) (an inexpensive, achiral α-methyl aldehyde substitute for aldehyde **178**), under identical conditions to those

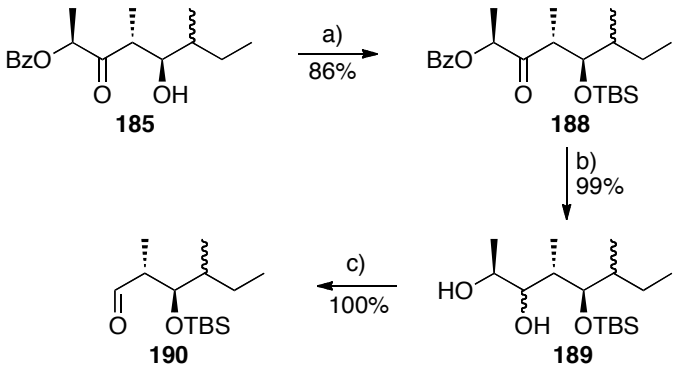
employed in scheme 3.7. This reaction produced a single observable diastereomer of aldol product **187** (scheme 3.9), confirming that the aldehyde stereocentre was the source of low product diastereomeric purity. It remains unclear whether this was a result of epimerisation during the Swern[10] oxidation or poor enantiopurity of the purchased starting material (*S*)-2-methylbutan-1-ol (**180**).



Reagents and conditions: a. (*c*-Hex)$_2$BCl (1.5 eq), Me$_2$NEt (1.8 eq), Et$_2$O, 0 ^{o}C, 2 h; **b.** methacrolein (**46**) (2 eq), Et$_2$O, −78 ^{o}C, 2 h to −23 ^{o}C, o/n.

Scheme 3.9: Paterson *anti*-aldol coupling between **(*S*)-183** and methacrolein **46**.

The mixture of aldol adducts **185** was readily protected as TBS ethers under standard conditions (2,6-lutidine/TBSOTf)[15] to give compound **188** in high yield (99%). This was followed by reduction of the benzoate using LiBH$_4$ to yield 1,2-diol **189**, then oxidative cleavage of acetaldehyde with sodium periodate (6 eq) in MeOH/H$_2$O to furnish aldehyde **190** (scheme 3.10) in near quantitative yields.[22,21] The ^{1}H and ^{13}C spectra of aldehyde **190** can be seen in figures 3.10 and 3.11 respectively. They clearly show the characteristic aldehyde peaks at δ 9.76 (^{1}H) and δ 205.5 (^{13}C), with double resonances to mark the presence of the minor epimer.



Reagents and conditions: a. 2,6-lutidine (2 eq), TBSOTf (1.5 eq), CH_2Cl_2, -78 ^oC, 5 h; **b.** $LiBH_4$ (20 eq), THF, -78 ^oC to 0 ^oC, 10 min to rt o/n; **c.** $NaIO_4$ (6 eq), 2:1 MeOH/H_2O, rt, 15 min.

Scheme 3.10: Synthesis of epimeric aldehyde **190** from epimeric aldol adduct **185**.

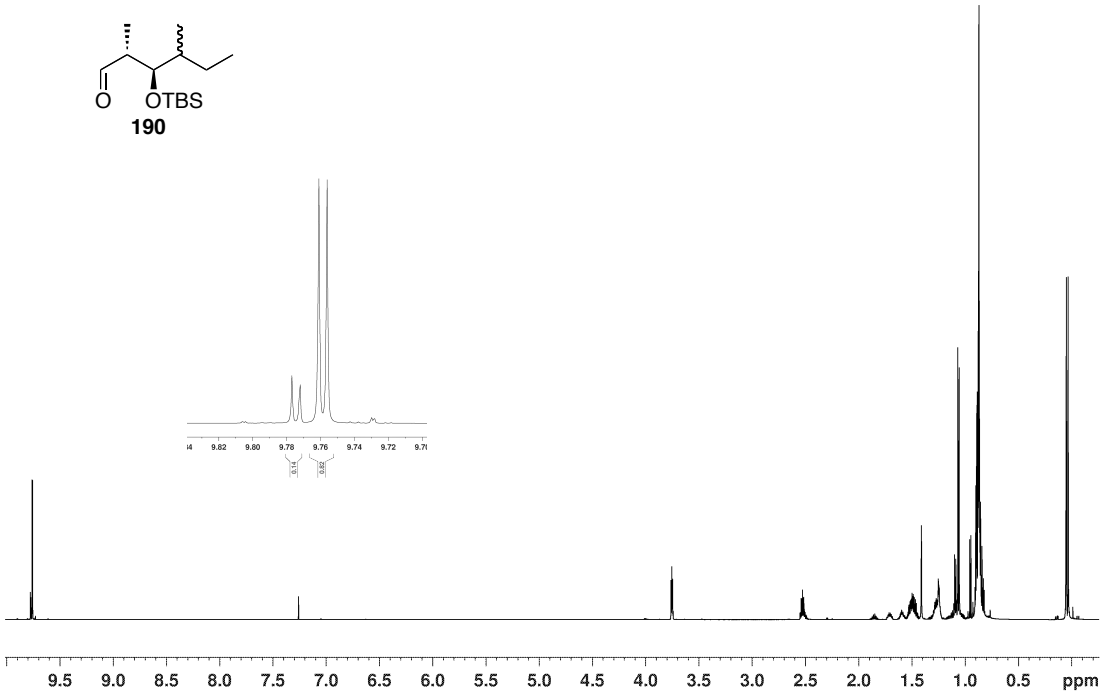


Figure 3.10: 600 MHz ^1H NMR spectrum of aldehyde **190** in $CDCl_3$.

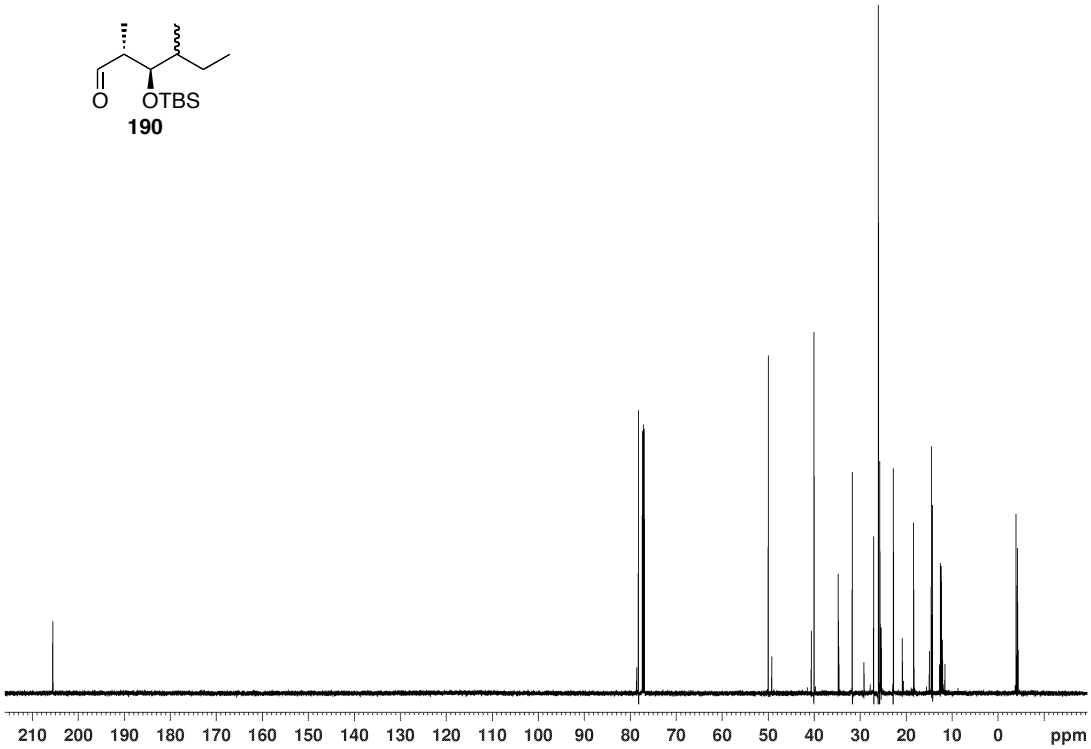


Figure 3.11: 151 MHz ^{13}C NMR spectrum of aldehyde **190** in $CDCl_3$.

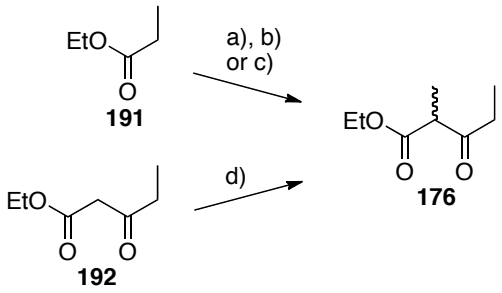
If this pathway were to be pursued selectively it would give rise to aldehydes that are diastereomeric with aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177** but would give rise to the same two targeted diastereomers of the natural products as the C7 hydroxyl is oxidised to the carbonyl in the final step. Due to the success of the *syn* aldol pathway (>98% ds for both aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177**), the *anti* aldol pathway was not pursued selectively and synthesis of ascosalipyrone (**4**) and micropyrone (**5**) was continued with aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177** only.

3.3.3 Extension of the Linear Chain

In order to produce the linear precursor to the natural products, addition of the appropriate dianion equivalent to aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177** for the synthesis of ascosalipyrone (**4**) and micropyrone (**5**) was required: ethyl-2-

methylacetoacetate (**175**) and ethyl 2-methyl-3-oxopentanoate (**176**) respectively. β-Ketoester **175** was commercially available (Sigma-Aldrich Chemical Co.), while β-ketoester **176** was to be obtained synthetically.

Synthesis of β-ketoester **176** was attempted *via* a solvent-free Claisen condensation of ethyl propionate (**191**) in the presence of *t*-BuOK,[27] however this reaction only gave 3% yield of β-ketoester **176** (scheme 3.11). Condensation of ethyl propionate (**191**) was also tried in solvent (THF) using NaH, but this did not give any of the desired product.[28] Methylation of ethyl 3-oxopentanoate (**192**) was then tried using MeI and K_2CO_3 in dry acetone, but this resulted in a mixture of starting material and product that could not be separated.[29] Eventually, the dimerisation of ethyl propionate was achieved by treatment of neat ethyl propionate (**191**) with NaH at 70 °C for 18 h to give β-ketoester **176** (30% yield).[30]



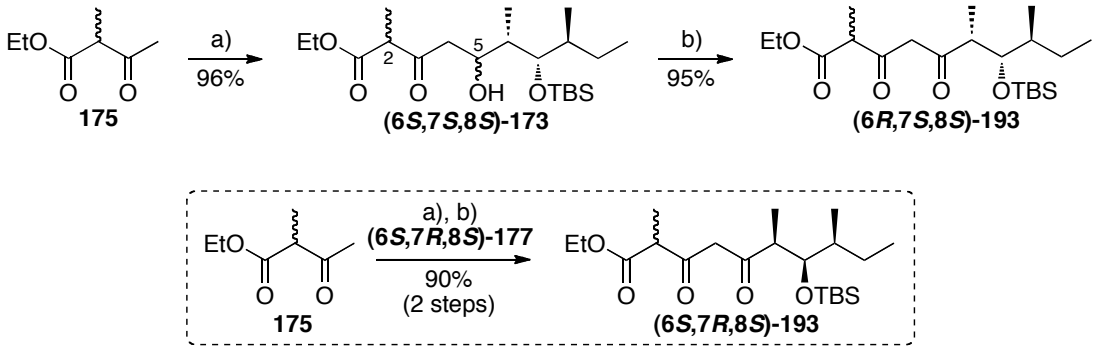
Reagents and conditions: a. *t*-BuOK (0.7 eq), 80 °C, 2 h; **b.** NaH (1.1 eq), THF, rt, 1 h; **c.** NaH (0.37 eq), 70 °C, 18 h; **d.** K_2CO_3 (0.93 eq), MeI (1.23 eq), acetone, reflux, 6 h.

Scheme 3.11: Synthetic pathways to β-ketoester **176**.

The dienolates of β-ketoesters **175** and **176** were prepared according to a procedure modified from Huckin and Weiler.[31,32] β-Ketoester **175** was first deprotonated using NaH (1 eq) in THF at 0 °C for 10 min, followed by deprotonation of the less acidic proton using *n*-BuLi (1 eq) at -10 °C for 10 min. The solution was then cooled to -78 °C and aldehyde **(6*R*,7*S*,8*S*)-177** was added (scheme 3.12). The reaction was allowed to stir at -78 °C for 1 h to allow completion, though the

addition typically occurred instantaneously. The reaction gave **(6*S*,7*S*,8*S*)-173** in a yield of 96% after purification by filtering through a buffered silica gel plug (100% CH_2Cl_2) and removal of any excess β-ketoester under high vacuum. NMR analysis indicated that the product **(6*S*,7*S*,8*S*)-173** was a mixture of at least 4 isomers resulting from the β-ketoester epimeric centre (C2) and the newly generated epimeric hydroxyl stereocentre (C5), making characterisation difficult (see appendix B for spectra). The same procedure was followed with aldehyde **(6*R*,7*S*,8*S*)-177**, resulting again in a mixture of diastereomeric products of **(6*R*,7*R*,8*S*)-173** (99%).

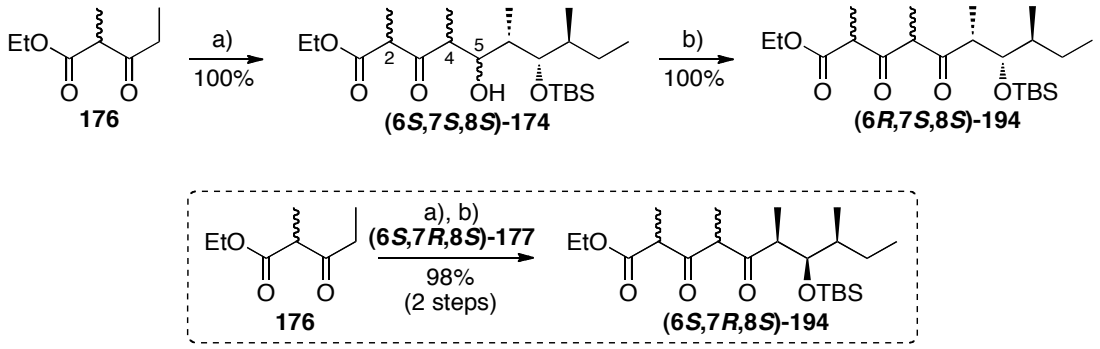
Both mixtures were subjected to oxidation using Dess-Martin periodinane[33-35] (DMP) with a one equivalent of H_2O to accelerate the reaction.[36,37] The 3,5-diketoester products **(6*R*,7*S*,8*S*)-193** and **(6*S*,7*R*,8*S*)-193** were once again filtered through a buffered silica gel plug (CH_2Cl_2) to give complex mixtures of two diastereomeric products. From the ^1H NMR spectrum it was apparent that these diastereomers were present exclusively in their enol forms (95 and 91% yields respectively) (scheme 3.12).



Reagents and conditions: a. i. NaH (1 eq), THF, 0 °C, 10 min; ii. *n*-BuLi (1 eq), -10 °C, 10 min; iii. aldehyde **(6*R*,7*S*,8*S*)-177** (0.5 eq), -78 °C, 1 h; **b.** DMP (1.5 eq), H_2O (1 eq), CH_2Cl_2, rt, o/n.

Scheme 3.12: Synthesis of the linear carbon chains required for the synthesis of ascsalipyrone (**4**).

To synthesise the linear precursor to micropyrone (**5**), β-ketoester **176** was treated under the same conditions as described above to generate the dianion, and aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177** were added to produce adducts **(6*S*,7*S*,8*S*)-174** (100%) and **(6*R*,7*R*,8*S*)-174** (98%) respectively. Again, these products were purified by filtration through buffered silica, resulting in a mixture of diasteromeric products, due to the presence of 3 new epimeric centres (C2, 4 and 5). (scheme 3.13). Oxidation was achieved using DMP[33] with a catalytic amount of H_2O[34,35] (as above) to give the linear pentaketide precursors to micropyrone, **(6*R*,7*S*,8*S*)-194** and **(6*S*,7*R*,8*S*)-194** in quantitative yields. This resulted in mixtures of 4 different diastereomers of each product, with no apparent enol tautomers.



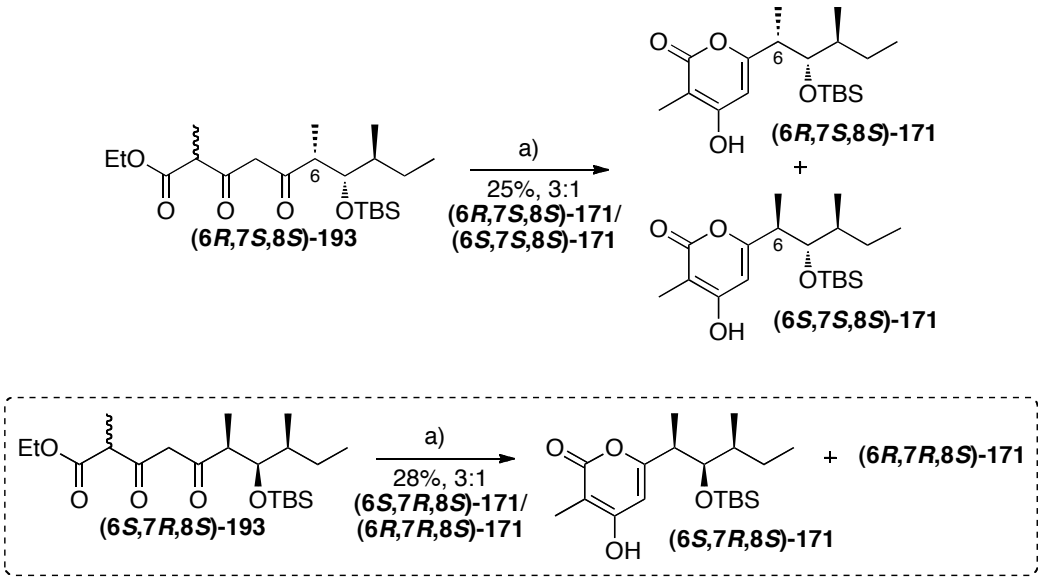
Reagents and conditions: a. i. NaH (1 eq), THF, 0 °C, 10 min; ii. *n*-BuLi (1 eq), -10 °C, 10 min; iii. **(6*R*,7*S*,8*S*)-177** (0.5 eq), -78 °C, 1 h; **b.** DMP (1.5 eq), H_2O (1 eq), CH_2Cl_2, rt, o/n.

Scheme 3.13: Synthesis of the linear carbon chains required for the synthesis of micropyrone (**5**).

3.3.4 Cyclisation, Deprotection and Oxidation

Cyclisation of linear δ,β-diketoesters to 4-hydroxy-α-pyrones is commonly achieved using a strong, non-nuclephilic base such as DBU.[37,38] Accordingly, cyclisation of δ,β-diketoester **(6*R*,7*S*,8*S*)-193** was achieved by treating with 2 equivalents of DBU in benzene, with warming to 60 °C for 3 h. The DBU was basic enough to remove the

C4 proton, causing tautomerisation and ensuing cyclisation onto the ester with elimination of the ethoxide ion. 4-Hydroxy-α-pyrone **(6*R*,7*S*,8*S*)-171** was thus produced in 25% yield as an amorphous solid (scheme 3.14). While it was hoped that protecting the C7 hydroxyl as a silyl ether until the final step would prevent epimerisation of the C6 stereocentre, it was apparent from double resonances in both the ^{1}H and ^{13}C NMR spectra (figures 3.12 and 3.13 respectively) of the cyclisation product (a precursor to ascosalipyrone) that partial epimerisation had occurred upon cyclisation, giving a 3:1 mixture of diastereomers **(6*R*,7*S*,8*S*)-171** and **(6*S*,7*S*,8*S*)-171**. This is testament to the acidity of the C6 proton, even in the absence of an adjacent carbonyl. These two isomers were unable to be separated. Synthesis of diastereomeric 4-hydroxy-α-pyrone **(6*S*,7*R*,8*S*)-171** was achieved under identical conditions, also giving a 3:1 ratio of isomers **(6*S*,7*R*,8*S*)-171** and **(6*R*,7*R*,8*S*)-171** (28% yield). The limited solubility of these compounds made purification by column chromatography difficult and trituration with hexanes was a more effective method for purification.



Reagents and conditions: a. DBU (2 eq), benzene, 60 ^{o}C, 3 h.

Scheme 3.14: Formation of the 4-hydroxyl-α-pyrone precursors **(6*R*,7*S*,8*S*)-171** and **(6*S*,7*R*,8*S*)-171** to ascosalipyrone (**4**).

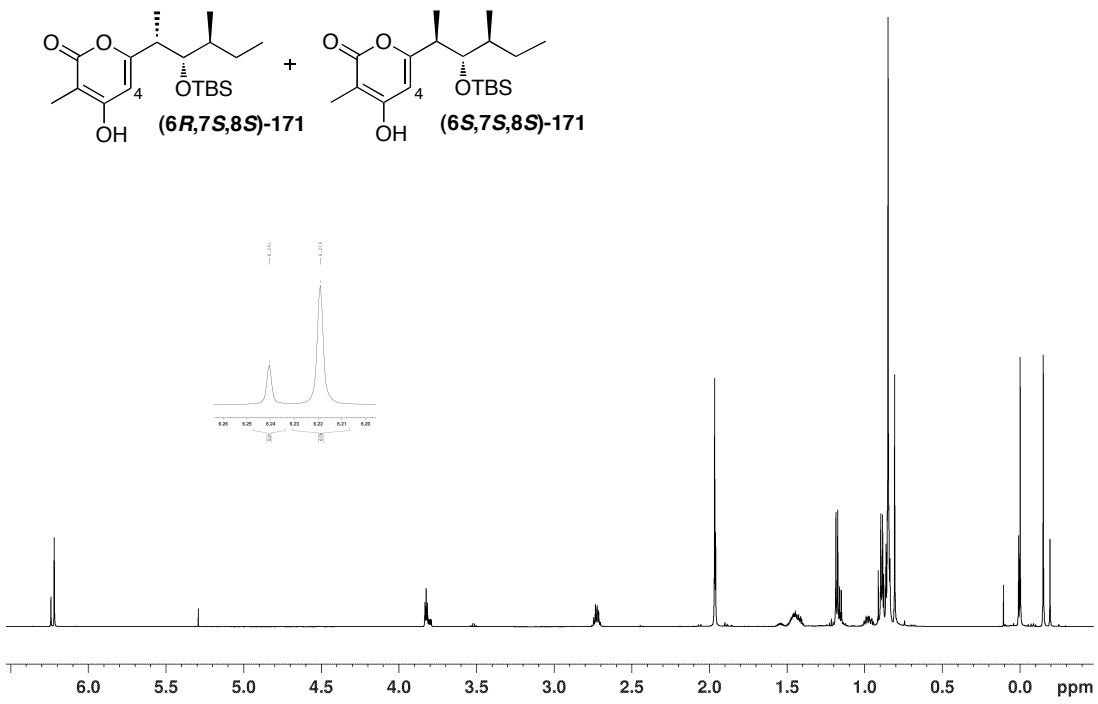


Figure 3.12: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-171**/**(6*S*,7*S*,8*S*)-171** in $CDCl_3$**.**

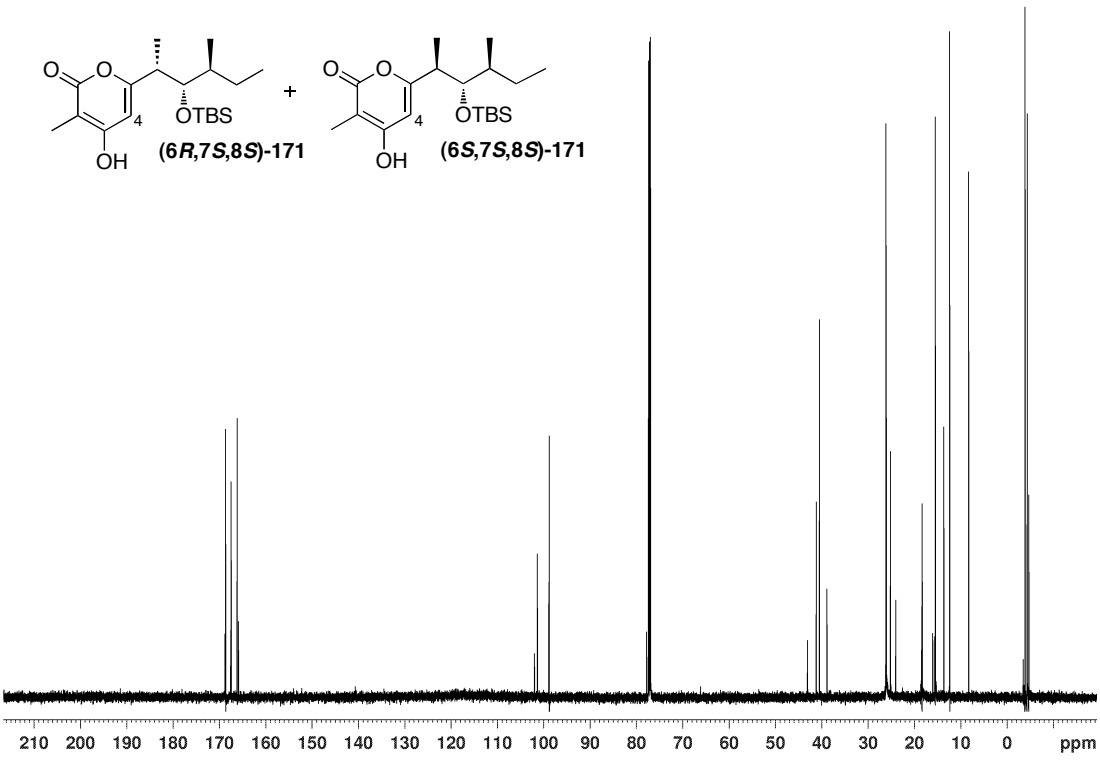
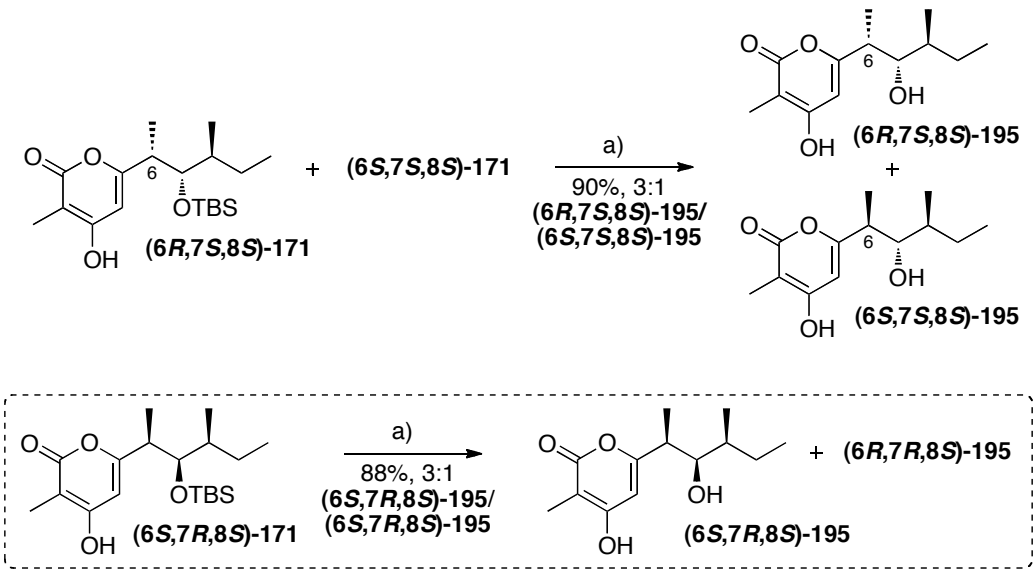


Figure 3.13: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-171**/**(6*S*,7*S*,8*S*)-171** in $CDCl_3$.

The TBS protecting group in **(6*R*,7*S*,8*S*)-171/(6*S*,7*S*,8*S*)-171** mixture was removed using 40% aqueous HF in 1:1 CH_3CN/CH_2Cl_2 at rt for 3.5 h to give mixture of alcohols **(6*R*,7*S*,8*S*)-194/(6*S*,7*S*,8*S*)-195** with no further epimerisation (scheme 3.15).[39] Alcohols **(6*R*,7*S*,8*S*)-194/(6*S*,7*S*,8*S*)-195** proved to be insoluble in most organic solvents, but could be purified by trituration with acetone to afford pure alcohols **(6*R*,7*S*,8*S*)-194/(6*S*,7*S*,8*S*)-195** in 90% yield. The molecular formula, $C_{13}H_{20}O_4$, was confirmed by HRESIMS analysis of **(6*R*,7*S*,8*S*)-194/(6*S*,7*S*,8*S*)-195** (calc. for $C_{13}H_{20}O_4Na^+$: 263.1259; found: 263.1263). Mixture of alcohols **(6*S*,7*R*,8*S*)-194/(6*R*,7*R*,8*S*)-195** was produced *via* the same method from TBS ethers **(6*S*,7*R*,8*S*)-171/(6*R*,7*R*,8*S*)-171** (88% yield) (scheme 3.15). HF/pyr/pyr[40-42] and TBAF[40] were also tried, but no deprotection occurred, probably due to the insolubility of the starting materials in the reaction solvent (THF in both cases).



Reagents and conditions: a. 40% aq. HF, 1:1 CH_3CN/CH_2Cl_2, rt, 3.5 h.

Scheme 3.15: Cleavage of silyl ethers **(6*R*,7*S*,8*S*)-171/(6*S*,7*R*,8*S*)-171** and **(6*S*,7*R*,8*S*)-171/(6*R*,7*R*,8*S*)-171**.

Oxidation of the C7 hydroxyl was initially anticipated to be achieved under mild conditions such as a Swern[10] or Dess-Martin[34,33] oxidation. However, alcohols

(6*R*,7*S*,8*S*)-194/**(6*S*,7*R*,8*S*)-195** and **(6*S*,7*R*,8*S*)-194**/**(6*R*,7*R*,8*S*)-195** were completely insoluble in CH_2Cl_2 (the solvent for both of these reactions), making oxidation *via* these methods virtually impossible. Fortunately, in the non-stereoselective synthesis of the related 4-hydroxy-α-pyrone compound elasnin (**196**),[28] a Jones oxidation[43] was successfully applied to achieve oxidation of the C7 hydroxyl in the immediate precursor **197** (scheme 3.16). The same conditions (Jones reagent – CrO_3 in dilute H_2SO_4)[43] were employed to oxidise alcohols **(6*R*,7*S*,8*S*)-194**/**(6*S*,7*R*,8*S*)-195**, and indeed oxidation was achieved to give **(6*S*,8*S*)-4**/**(6*R*,8*S*)-4**, again without further epimerisation (scheme 3.17). The oxidation products were purified by trituration with hexanes, giving rise to ascosalipyrone isomers **(6*S*,8*S*)-4**/**(6*R*,8*S*)-4** (to be referred to hence forth as **(6*S*,8*S*)-4** to avoid confusion) as a yellow, amorphous solid (56%). The same condition were applied to alcohols **(6*S*,7*R*,8*S*)-194**/**(6*R*,7*R*,8*S*)-195**, giving ascosalipyrone isomers **(6*R*,8*S*)-4**/**(6*S*,8*S*)-4** (to be referred to hence forth as **(6*R*,8*S*)-4** to avoid confusion), also as a yellow amorphous solid (51%) (scheme 3.17). HRESIMS of **(6*S*,8*S*)-4** confirmed the molecular formula of ascosalipyrone, $C_{18}H_{18}O_4$ (calc. for $C_{13}H_{18}O_4Na^+$: 261.1103; found: 261.1109). As expected, the NMR spectra of major isomer of one product matched the minor isomer of the other and vice versa as these isomers are identical.

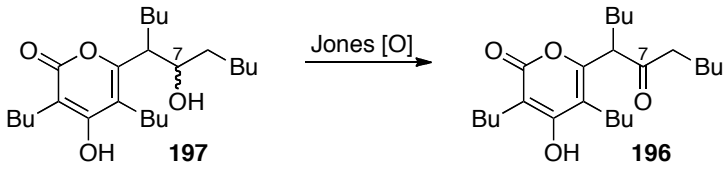
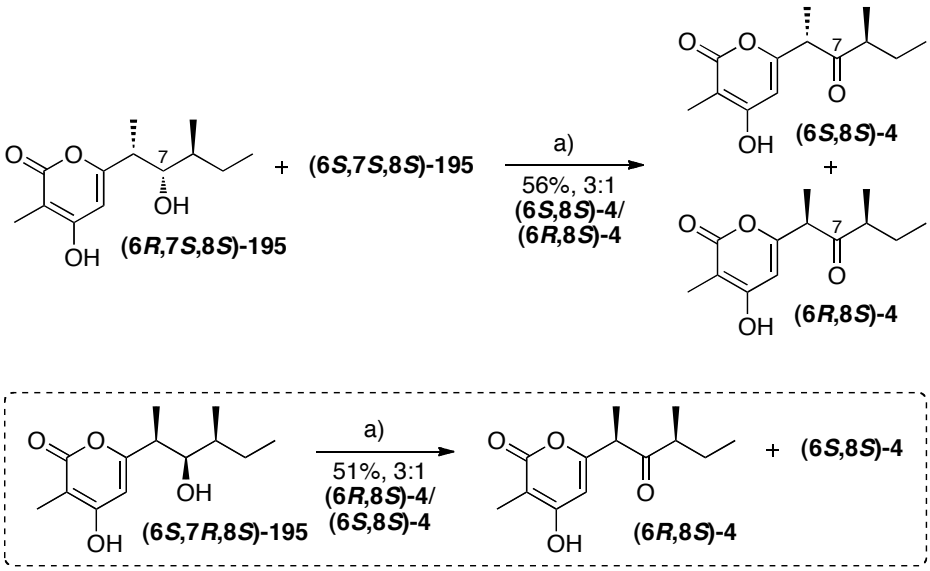


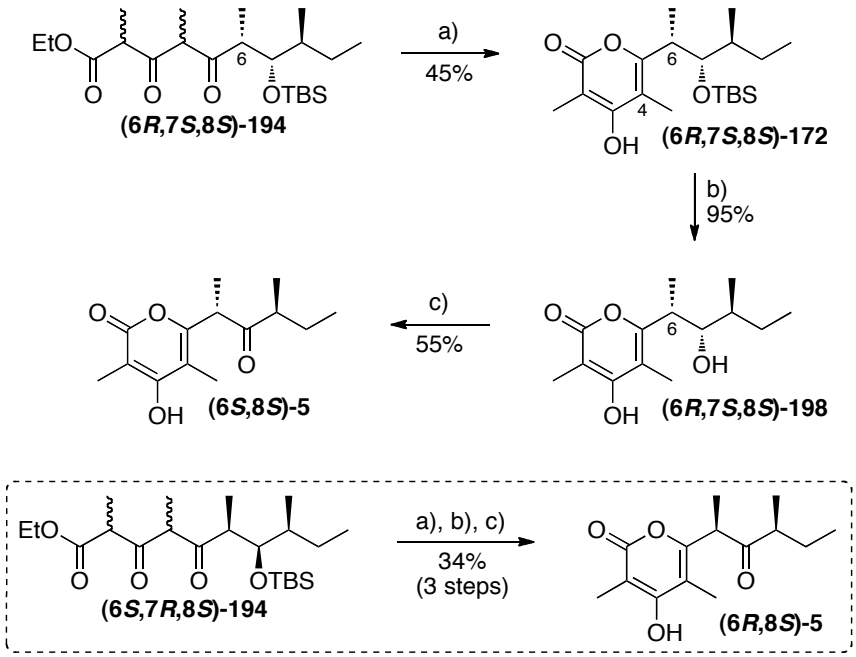
Figure 3.16: Jones oxidation of alcohol **197** to elasnin (**196**).[28]



Reagents and conditions: a. Jones reagent, acetone, 0 ^{o}C to rt, 10 min.

Scheme 3.17: Completion of the synthesis of two diastereomers of ascosalipyrone (**4**).

Preparation of the two targeted isomers of micropyrone (**4**) was achieved *via* the same 3 step sequence as ascosalipyrone, as indicated in scheme 3.18, from δ,β-diketoesters **(6*R*,7*S*,8*S*)-194** and **(6*S*,7*R*,8*S*)-194**. Upon cyclisation of these two compounds, no epimerisation was observed by NMR, lending strong support to the theory that the presence of the extra methyl group at C4 hinders epimerisation. Epimerisation did not occur after deprotection and cyclisation either, giving rise to **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5** as single isomers. HRESIMS of **(6*S*,8*S*)-5** confirmed the molecular formula of micropyrone, $C_{14}H_{20}O_4$ (calc. for $C_{14}H_{20}O_4Na^+$: 275.1259; found: 274.1265).



Reagents and conditions: a. DBU (2 eq), benzene, 60 ^{o}C, 3 h; **b.** 40% aq. HF, 1:1 CH_3CN/CH_2Cl_2, rt, 3.5 h; **c**. Jones reagent, acetone, 0 ^{o}C to rt, 10 min.

Scheme 3.18: Completion of the synthesis of two diastereomers of micropyrone (**5**).

Both diastereomers **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5** were isolated as white crystalline solids and recrystallised from CH_2Cl_2 to produce samples suitable for X-ray analysis. Single crystal structure analysis confirmed the assigned structures of the two isomers, including the configuration at C6 (figure 3.14). Notably in both cases, the conformation around the C5-C6 bond, places the small C6-H eclipsing the C4-Me, thus minimising the A-1,3 strain with the C6-Me. This low energy conformation also suggests the configurational stability of the C6 stereocentre (between the pyrone ring and the carbonyl) may be explained by the unfavorable A1,3 strain that would be present in the planar enol tautomer. This concept is demonstrated more clearly in figure 3.15 using diastereomer **(6*S*,8*S*)-5**.

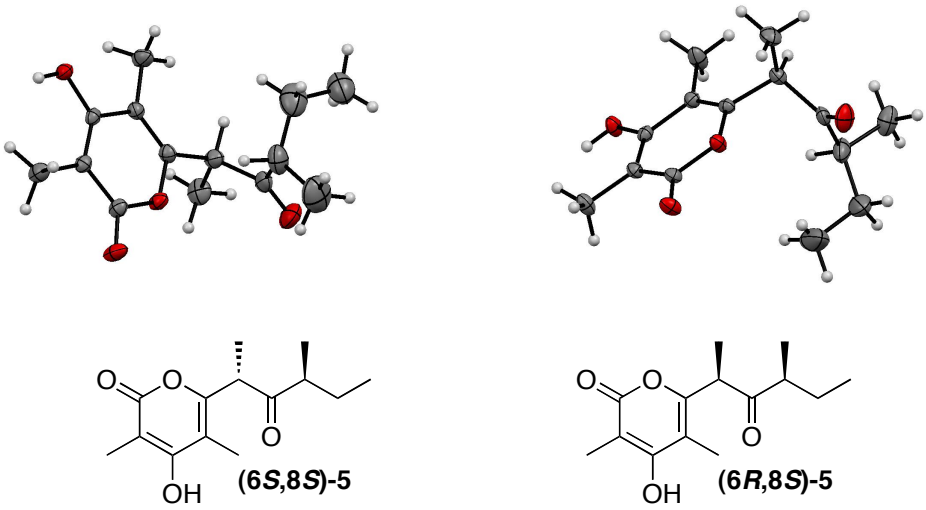


Figure 3.14: Crystal structures of **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5**.

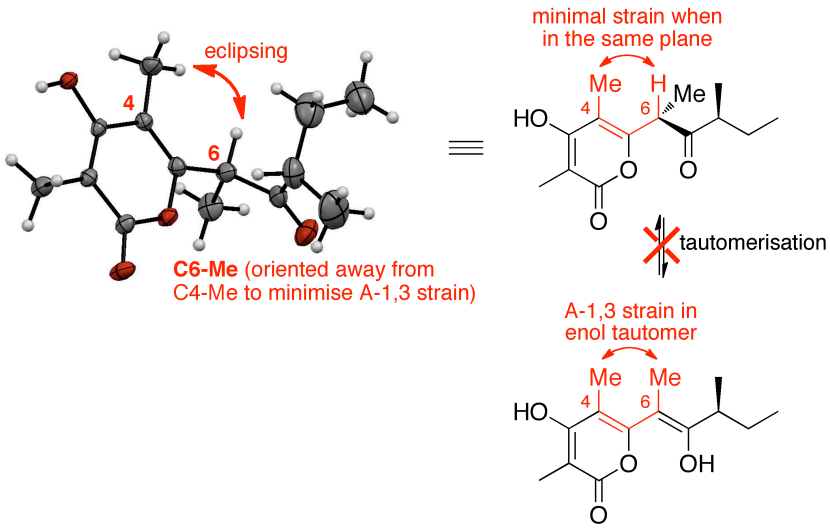


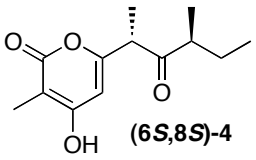
Figure 3.15: Crystal structure of **(6*S*,8*S*)-5** showing the favoured configuration to minimise A-1,3 strain.

3.4 Structural assignment

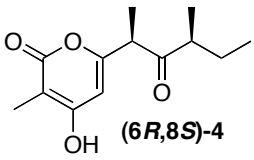
With the two targeted diastereomers of each of the natural products ascosalipyrone (**4**) and micropyrone (**5**) in hand, ^{1}H and ^{13}C NMR spectral comparison was then used to assign the relative and absolute configuration of the natural products.

Table 3.1 shows a comparison of the ^{1}H and ^{13}C NMR data for authentic ascosalipyrone (**4**)[1] (major isomer only) and synthetic isomers **(6*S*,8*S*)-4** and **(6*R*,8*S*)-4**. There are no significant differences in the ^{1}H NMR chemical shifts for either isomer that could be used to identify the natural product. However, all the ^{13}C chemical shifts of isomer **(6*S*,8*S*)-4** are ≤0.1 ppm different from those reported for the natural product, while variation of >0.1 ppm is seen in carbons 5-9 and 11 of the ^{13}C chemical shifts of isomer **(6*R*,8*S*)-4**. These differences can be seen in figure 3.17, which charts the difference in ^{13}C chemical shift ($\Delta\delta$) for **(6*S*,8*S*)-4** and **(6*R*,8*S*)-4** compared to the natural product **4**.

On this basis, the relative configuration of ascosalipyrone (**4**) is assigned as *anti* (as per **(6*S*,8*S*)-4**). The observed optical rotation for diastereomer **(6*S*,8*S*)-4** (as a 3:1 mixture with its C6 epimer **(6*R*,8*S*)-4**) was $[\alpha]^{20}_{D}$ = +60.7 (c 1.57, MeOH), however since no optical rotation was reported for the natural product, it is only possible to assign the relative configuration of the natural product as *anti* and report the synthesis of (+)-ascosalipyrone [**(6*S*,8*S*)-4**]. In other words, the absolute configuration of ascosalipyrone (**4**) is either **(6*S*,8*S*)-4** or **(6*R*,8*R*)-4** (figure 3.16). The ^{1}H and ^{13}C NMR spectra of synthetic (+)-ascosalipyrone [**(6*S*,8*S*)-4**] and the natural product[1] are shown in figures 3.18-3.21 for comparison.



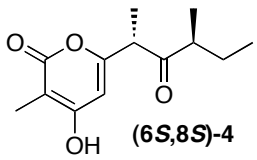
(6*S*,8*S*)-4



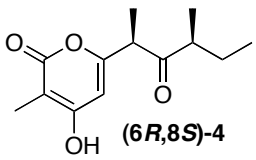
(6*R*,8*S*)-4

C no.	**Ascosalipyrone (4)**		**(6*S*,8*S*)-4**			**(6*R*,8*S*)-4**		
	δH (m, J[Hz])	δC	δH (m, J[Hz])	δC	Δδ	δH (m, J[Hz])	δ	Δδ
1		167.6		167.6	0.0		167.6	0.0
2		99.8		99.7	0.1		99.7	0.1
3		166.2		166.3	-0.1		166.3	-0.1
4	6.21 (s)	101.6	6.25 (s)	101.6	0.0	6.22 (s)	101.7	-0.1
5		160.7		160.7	0.0		160.5	0.2
6	3.77 (q, 7.0)	49.3	3.80 (q, 7.2)	49.2	0.1	3.82 (q, 7.2)	49.0	0.3
7		211.5		211.5	0.0		211.4	0.2
8	2.68 (m)	47.1	2.70 (ddq, 7.5, 7.2, 6.6)	47.0	0.1	2.69 (ddq, 7.2, 7.2, 6.6)	46.9	0.2
9a	1.69 (m)	26.1	1.67 (ddq, 13.8, 7.5, 6.6)	26.0	0.1	1.68 (ddq, 13.8, 7.5, 7.2)	25.6	0.5
9b	1.38 (m)		1.38 (m)			1.35 (dqd, 13.8, 7.5, 6.6)		
10	0.82 (t, 7.3)	11.6	0.85 (t, 7.5)	11.6	0.0	0.81 (t, 7.5)	11.5	0.1
11	1.38 (d, 7.2)	15.9	1.36 (d, 7.2)	15.9	0.1	1.37 (d, 7.2)	16.3	-0.4
12	1.05 (d, 7.0)	14.4	1.05 (d, 6.6)	14.3	0.1	1.07 (d, 6.6)	14.4	0.0
13	1.94 (s)	8.2	1.94 (s)	8.2	0.0	1.94 (s)	8.2	0.0
OH	9.7 (br s)		9.91 (br s)			9.69 (br s)		

Table 3.1: Comparison of the ^{1}H and ^{13}C NMR data for ascosalipyrone (**4**) and synthetic isomers **(6*S*,8*S*)-4** and **(6*R*,8*S*)-4**.



(6*S*,8*S*)-4



(6*R*,8*S*)-4

Figure 3.16: The two possible isomers of ascosailpyrone (**4**).

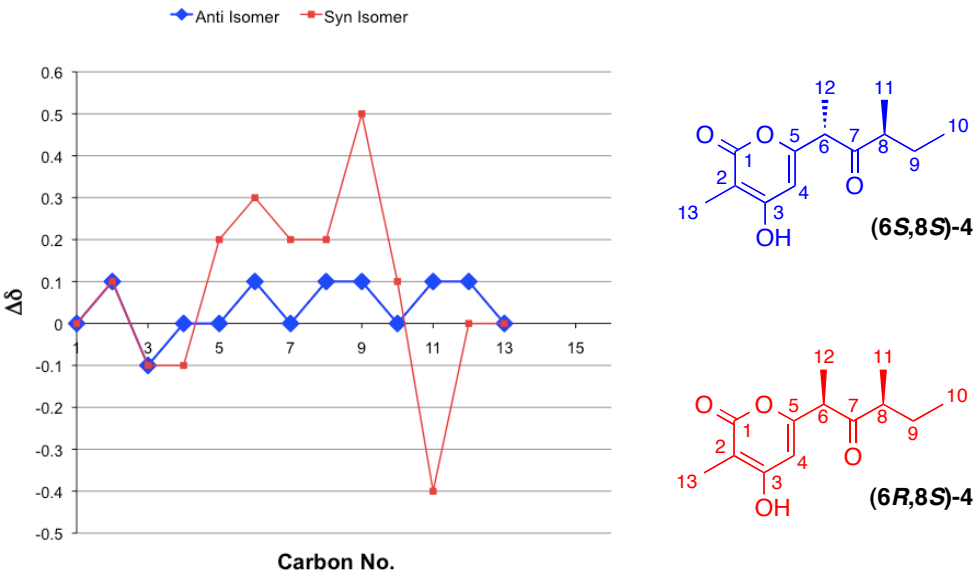


Figure 3.17: Plot of difference in ^{13}C chemical shift for diastereomers **(6*S*,8*S*)-4** and **(6*R*,8*S*)-4** compared to the natural product, ascosalipyrone **4**.

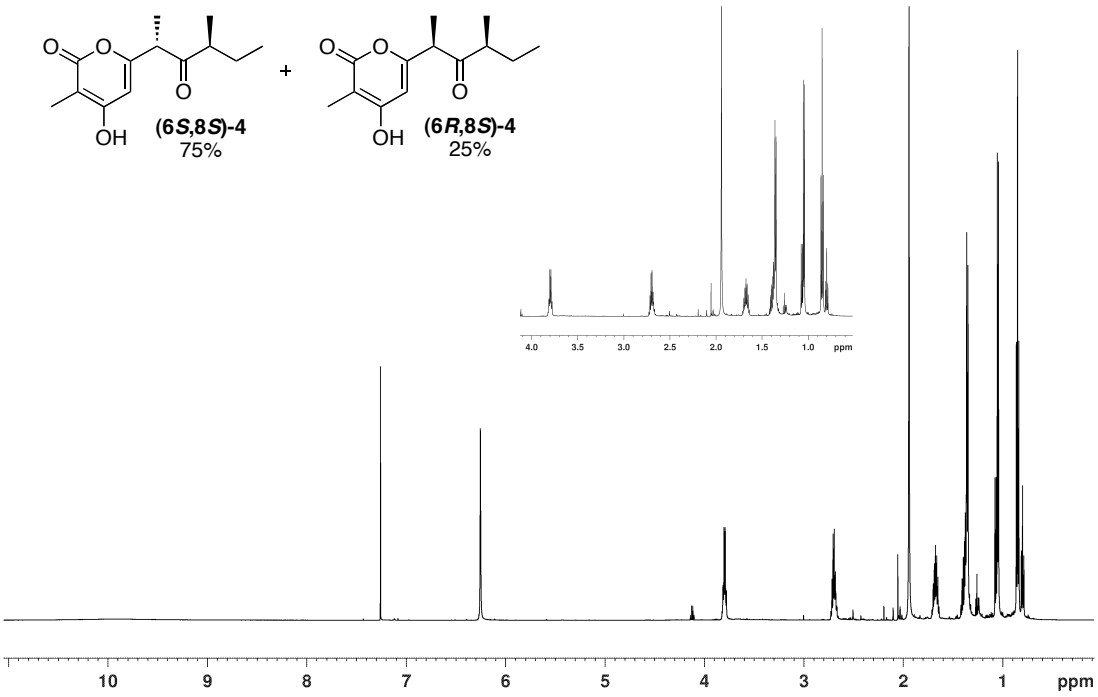


Figure 3.18: 600 MHz ^{1}H NMR spectrum of 3:1 **(6*S*,8*S*)-4** in $CDCl_3$.

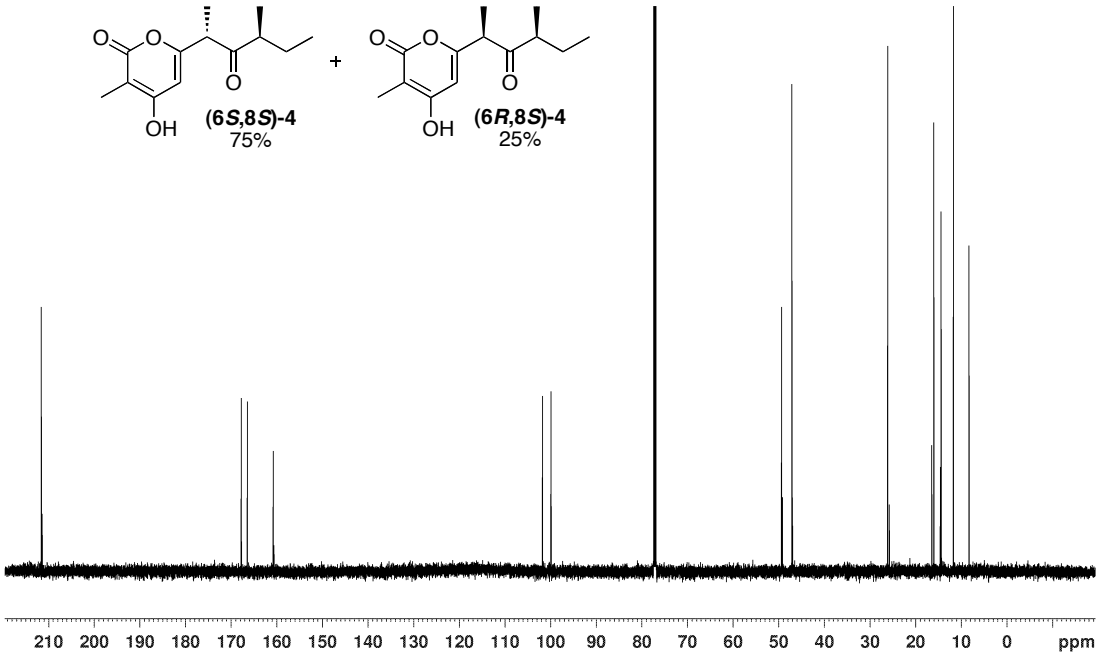


Figure 3.19: 151 MHz ^{13}C NMR spectrum of synthetic **(6*S*,8*S*)-4** in $CDCl_3$.

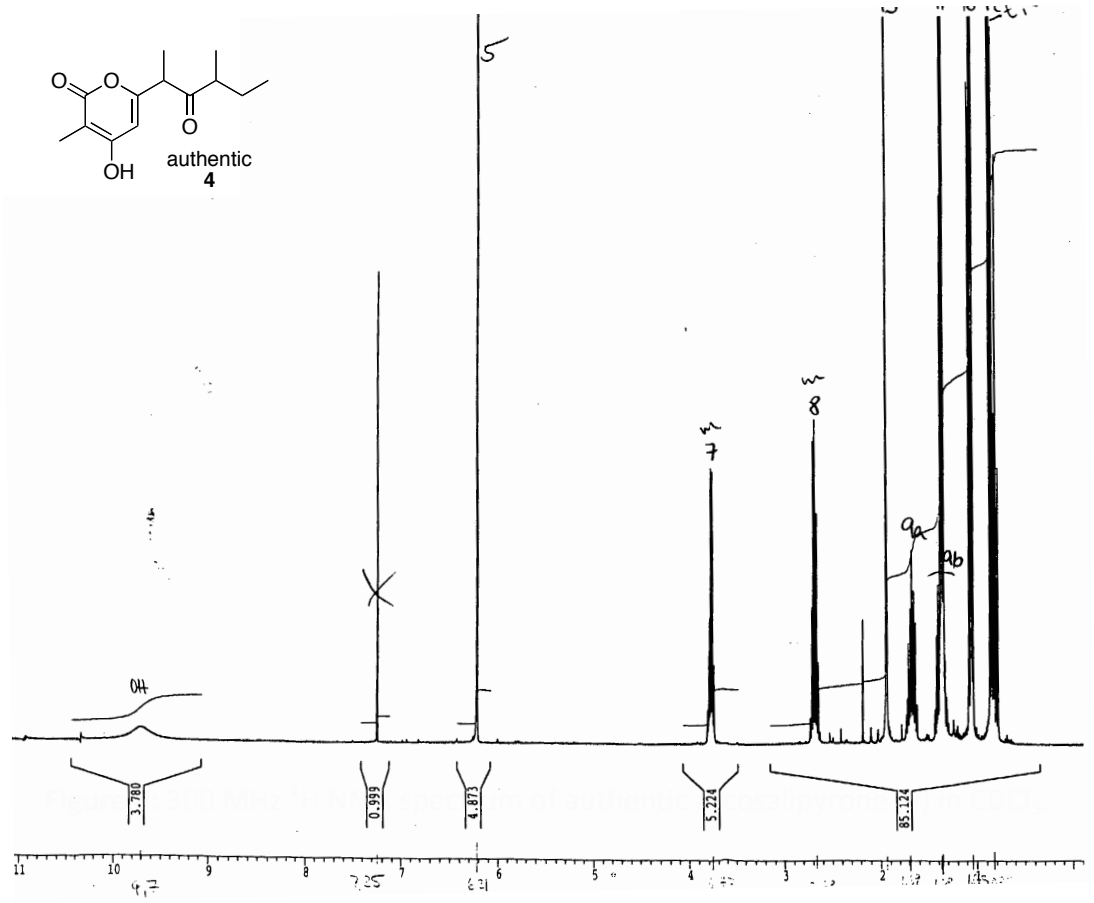


Figure 3.20: 300 MHz ^{1}H NMR spectrum of authentic ascosalipyrone **4** in $CDCl_3$.

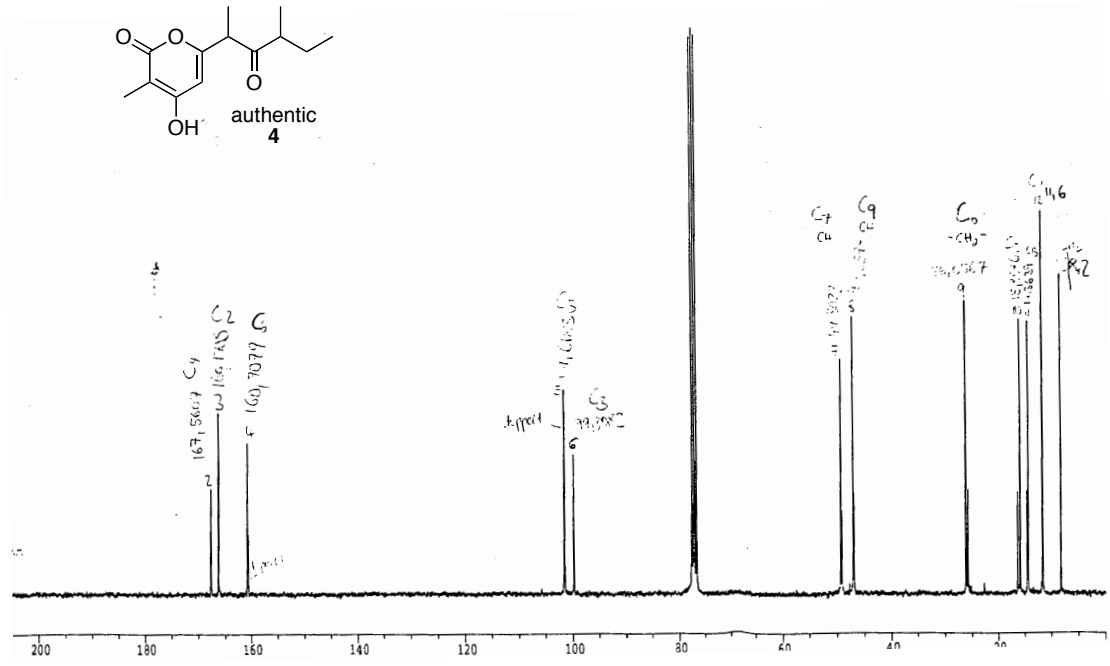
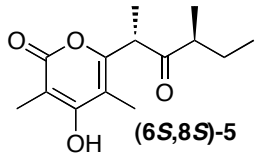


Figure 3.21: 75.5 MHz ^{13}C NMR spectrum of authentic ascosalipyrone **4** in $CDCl_3$.

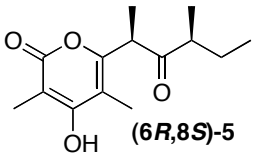
Table 3.2 shows a comparison of the ^{1}H and ^{13}C NMR data reported for micropyrone[3] (**5**) and synthetic isomers **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5**. The chemical shifts observed for carbons 6, 9 and 11 of diastereomer **(6*S*,8*S*)-5** are significantly different (≥1 ppm) from those reported for micropyrone (**5**) while all the ^{13}C chemical shifts of diastereomer **(6*S*,8*S*)-5** are ≤0.2 ppm different from those reported for the natural product. These differences are apparent in figure 3.23, which charts the difference in ^{13}C chemical shifts for **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5** compared to the natural product.

Also notable is the near perfect match between the ^{1}H NMR of diastereomer **(6*S*,8*S*)-5** and the natural product **5** whereas significant differences are seen for diastereomer **(6*R*,8*S*)-5**. On this basis the relative configuration of micropyrone (**5**) is assigned as **(6*S*,8*S*)-5** (ie. the *anti* isomer). The observed rotation for isomer **(6*S*,8*S*)-5** was $[\alpha]^{20}_{D}$ = +28.8 (c 1.36, MeOH) which is of the opposite sign to that reported ($[\alpha]^{20}_{D}$ = –21 (c 1.0, MeOH)) for the natural product. This shows that compound **(6*S*,8*S*)-5** is the *enantiomer* of the natural product micropyrone (**5**), ie. the absolute configuration of micropyrone (**5**) is **(6*R*,8*R*)-5** (figure 3.22). The ^{1}H and ^{13}C NMR spectra of synthetic isomer **(6*S*,8*S*)-5** are shown in figures 3.24 and 2.25

respectively, however the original spectrum of authentic micropyrone was not available for visual comparison.



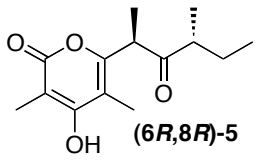
(6*S*,8*S*)-5



(6*R*,8*S*)-5

C no.	**Micropyrone (5)**		**(6*S*,8*S*)-5**			**(6*R*,8*S*)-5**		
	δH (m, J[Hz])	δC	δH (m, J[Hz])	δC	Δδ	δH (m, J[Hz])	δ	Δδ
1		166.2		166.3	-0.1		166.2	0
2		99.5		99.4	0.1		99.3	0.2
3		155.7		155.7	0		155.5	0.2
4		109.5		109.5	0		109.5	0
5		165.6		165.6	0		165.5	0.1
6	3.84 (q, 6.9)	48.2	3.83 (q, 7.2)	48.2	0	3.9 (q, 7.2)	47.2	1
7		210.5		210.7	-0.2		210.5	0
8	2.58 (m)	45.3	2.58 (ddq, 7.2, 6.6, 6.6)	45.3	0	2.54 (ddq, 7.2, 7.2, 6.6)	45.5	-0.2
9a	1.60 (m)	26.9	1.59 (ddq, 13.8, 7.2, 6.6)	26.9	0	1.65 (ddq, 13.8, 7.2, 7.2)	25.7	1.2
9b	1.34 (m)		1.34 (m)			1.28 (ddq, 13.8, 7.2, 6.6)		
10	0.81 (t, 6.7)	11.5	0.81 (t, 7.2)	11.6	-0.1	0.75 (t, 7.2)	11.7	-0.2
11	1.36 (d, 6.7)	16.1	1.36 (d, 7.2)	16.1	0	1.39 (d, 7.2)	17.4	-1.3
12	0.99 (d, 6.7)	13.3	0.98 (d, 7.2)	13.4	-0.1	1.02 (d, 7.2)	13.4	-0.1
13	2.02 (s)	8.7	2.02 (s)	8.7	0	2.02 (s)	8.7	0
14	2.00 (s)	9.9	1.99 (s)	9.9	0	1.99 (s)	10	-0.1
OH	-		8.84 (br s)			8.74 (br s)		

Table 3.2: Comparison of the ^{1}H and ^{13}C NMR data for micropyrone (**5**) and synthetic isomers **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5**.



(6*R*,8*R*)-5

Figure 3.22: The absolute configuration of authentic micropyrone (**4**), **(6*R*,8*R*)-4**.

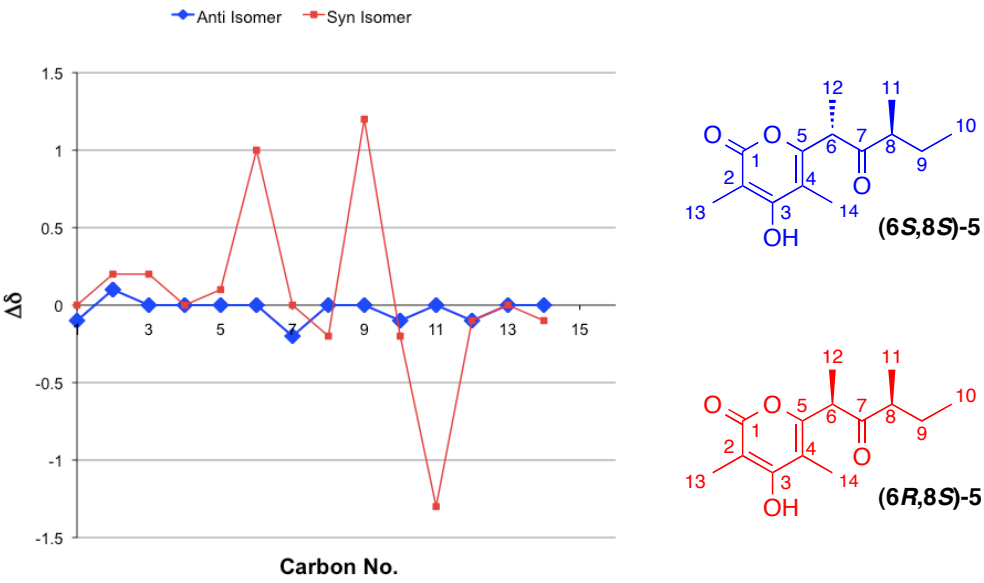


Figure 3.23: Plot of difference in ^{13}C chemical shift for diastereomers **(6*S*,8*S*)-5** and **(6*R*,8*S*)-5** compared to the natural product, micropyrone **5**.

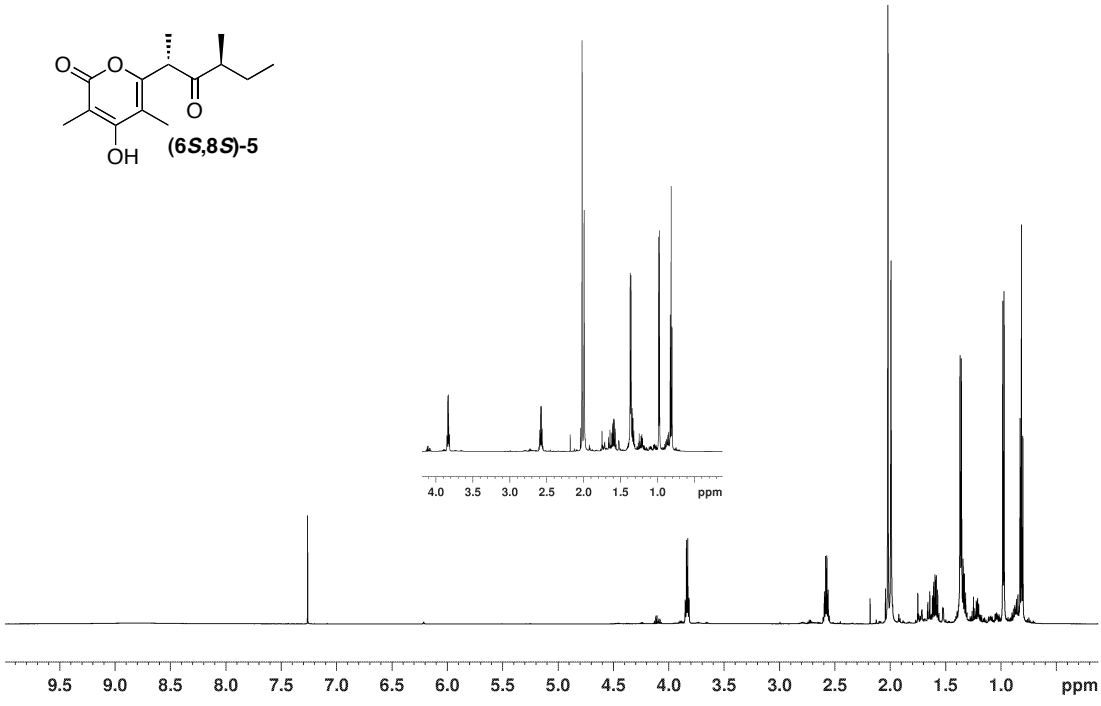


Figure 3.24: 600 MHz ^{1}H NMR spectra of synthetic isomer **(6*S*,8*S*)-5** in $CDCl_3$.

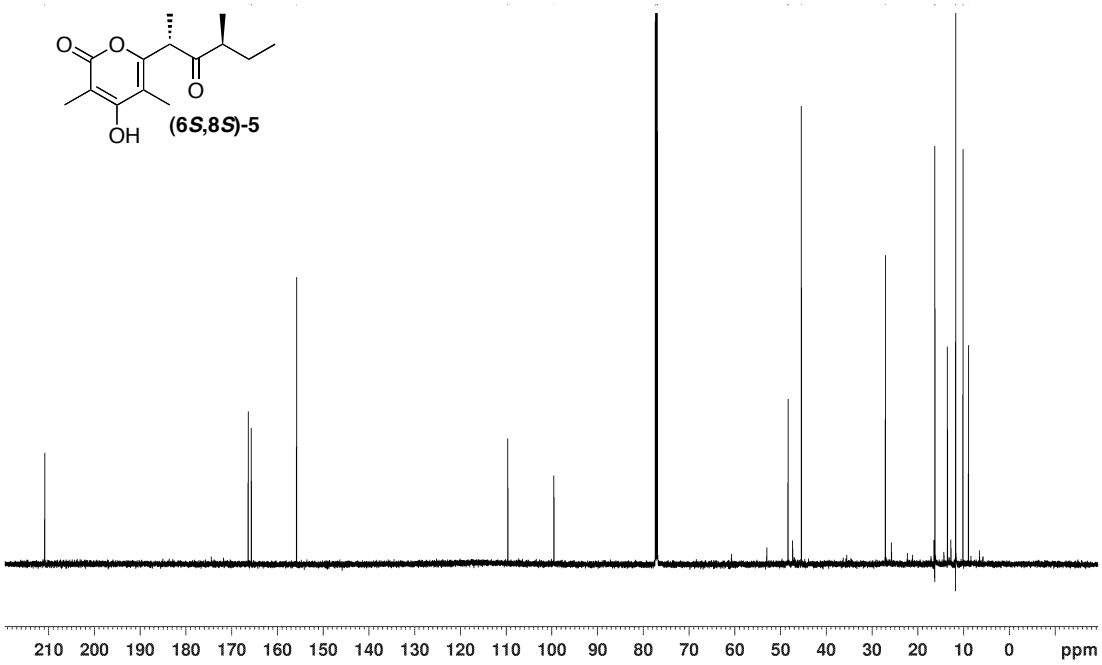


Figure 3.25: 151 MHz ^{13}C NMR spectra of synthetic isomer **(6*S*,8*S*)-5** in $CDCl_3$.

3.5 Conclusion

The total synthesis of two diastereomers each of ascosalipyrone (**4**) and micropyrone (**5**) was achieved in 9 linear steps from Evans auxiliaries **(*R*)-77** and **(*S*)-77**, *via* the common aldehyde intermediates **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177**. Ascosalipyrone was isolated as a mixture of diastereomers due to epimerisation at C6 and it was hoped that by delaying oxidation at C7 until the last step in the synthesis might prevent this occurrence. However, epimerisation was observed immediately upon cyclisation, highlighting the acidity of the C6 proton, even in the absence of the C7 carbonyl. The two targeted diastereomers of micropyrone on the other hand did not experience epimerisation upon cyclisation or oxidation of the C7 hydroxyl due to the stabilising effect of the extra methyl group on the pyrone ring.

No optical rotation was reported for the natural product ascosalipyrone, therefore only the relative stereochemistry was able to be assigned from analysis of the NMR spectra as C6-C8 *anti*, accompanied by 25% of its C6 epimer (figure 3.26). The absolute stereochemistry of micropyrone was assigned to be 6*R*,8*R* based on NMR and optical rotation comparison (figure 3.26).

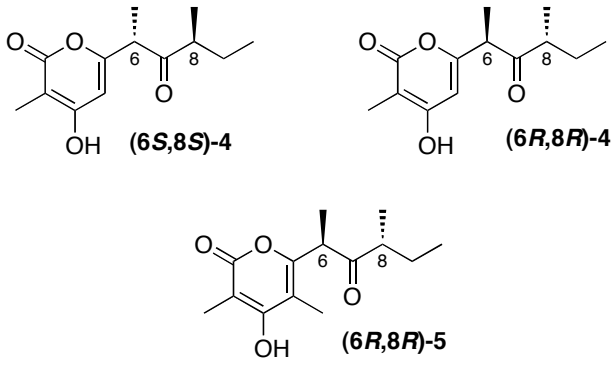


Figure 3.26: The two possible structures of ascosailpyrone (**4**): **(6*S*,8*S*)-4** or **(6*R*,8*R*)-4**; and the structure of micropyrone (**5**): **(6*R*,8*R*)-5**.

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Chapter Four:
Experimental

4.1 General Procedures

All reactions were carried out under an atmosphere of nitrogen (N_2) or argon (Ar) in oven-dried glassware, unless otherwise specified. Most starting materials and reagents were purchased from the the Sigma-Aldrich Chemical Co. and were used as supplied, or dried and distilled using standard procedures.[1] Triethylamine (Et_3N), dimethylethylamine (Me_2NEt), diisopropylamine (*i*-Pr_2NH) and pyridine were distilled from calcium hydride (CaH_2) under an atmosphere of N_2 and commercially available aldehydes, ketones and acid chlorides were distilled from calcium chloride ($CaCl_2$) under an atmosphere of N_2 prior to use. *n*-Butyllithium was freshly standardised by titration against *N*-pivaloyl-o-toluidine prior to use.[2] Inorganic materials were used as received or purified according to standard procedures.[1] Sodium hydride (NaH) (60% dispersion in mineral oil) was washed with mixed hexanes and dried under N_2 before use. Anhydrous reagents were handled under N_2 using standard techniques.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried using sodium metal and then distilled, as required, from sodium-benzophenone under N_2. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2 as required. Other solvents used for reactions, extractions and purification were distilled prior to use.

Room temperature (rt) varied between 20-25 ^oC.

For cold baths at temperatures of 0 ^oC an ice-slurry was used and for -10 ^oC an ice/NaCl mixture was used. For temperatures of -20 to -78 ^oC a dry ice/acetone bath was used and for -90 ^oC a liquid N_2/EtOH bath was used.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the plates were visualised under a 254 nm UV lamp and/or by treatment with either anisaldehyde dip (*p*-anisaldehyde, 9.2 mL; H_2SO_4, 12.5 mL; CH_3CO_2H, 3.75 mL; EtOH, 338 mL) or potassium permanganate dip ($KMnO_4$, 3 g; K_2CO_3, 20 g; 5% NaOH, 5 mL; H_2O, 300 mL), followed by heating with a heat gun. The retention factor (R*f*) quoted is rounded to the nearest 0.01. Column chromatography was conducted using silica gel 60 (mesh size 0.040-0.063

mm) as the stationary phase and the analytical reagent (AR) solvents indicated. When purifying compounds with acid sensitivity, column chromatography was performed on buffered silica as indicated. Buffered silica was prepared by spinning 100 g of silica gel 60 (mesh size 0.040-0.063 mm) with 10 mL of pH 7 phosphate buffer (prepared by dissolving one pH 7 buffer tablet in 100 mL of H_2O) on a rotary evaporator overnight at atmospheric pressure.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance II spectrometer at 400 or 600 MHz for proton and 100 or 151 MHz for carbon nuclei, respectively. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired either in deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) 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 the internal reference, for CD_3OD the peak due to residual CD_2HOD (δ 3.31) was used as the internal reference and for C_6D_6, the peak due to residual C_6D_5H (δ 7.15) was used as the internal reference. ^1H NMR spectral data are recorded as follows: chemical shift (δ), relative integral, multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, apt = apparent), coupling constant(s) *J* (Hz), assignment. For proton-decoupled ^{13}C NMR spectra recorded in $CDCl_3$, the central peak (δ 77.16) of the $CDCl_3$ triplet was used as the internal reference, for CD_3OD the central peak (δ 49.00) of the CD_3OD septet was used as the internal reference and for C_6D_6 the central peak (δ 128.06) of the C_6D_6 triplet was used as internal reference and all data are given as chemical shift (δ). ^1H and ^{13}C assignments were confirmed by conducting homonuclear (^1H-^1H) correlation spectroscopy (COSY), nuclear Overhauser effect (nOe) spectroscopy (NOESY) and heteronuclear (^1H-^{13}C) correlation spectroscopy (HMQC) experiments.

Optical rotations were recorded on a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20 ^oC, using the spectroscopic grade solvent specified ($CHCl_3$, MeOH or CH_2Cl_2) and at the concentration (*c*, g/100 mL) indicated. Measurements were carried out in a cell with a 1 dm path length.

Infrared (IR) spectra were recorded on either a Perkin-Elmer 1600 series FTIR, BIO-

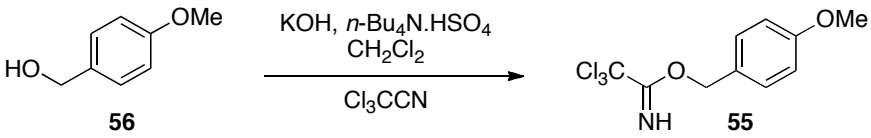
RAD FTS-40-A or Nicolet Avatar 370 DTGS Fourier Transform spectrophotometer, with the absorptions recorded in wavenumbers (n_{max}/cm^{-1}). Liquid samples were analysed as thin films on NaCl discs, with solids being dissolved in CH_2Cl_2 or $CHCl_3$ before being applied to the discs and the solvent evaporated, or alternatively were made into a KBr disc.

Melting points were carried out on a Reichert hot-stage apparatus and are uncorrected.

High resolution mass spectra were recorded on either a Bruker BioApex II 47e FTMS fitted with an Analytica ESI source or or an Agilent G1969A LC-TOF utilizing an Agilent 1100 Series LC.

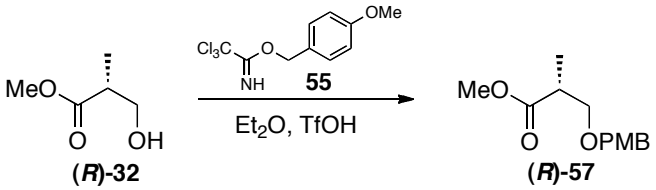
4.2 Experimental Procedures for Chapter Two

4.2.1 Model Ketone Synthesis



56 55

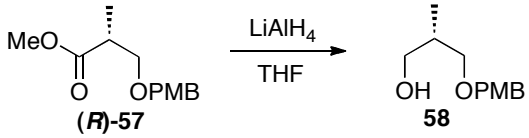
4-Methoxybenzyl-2,2,2-trichloroacetimidate (55), synthesised according to the procedure of Patil.[3] To a solution of *p*-methoxybenzyl alcohol (**56**) (10.0 mL; 80.2 mmol) in CH_2Cl_2 (110 mL) at -15 ^oC was added 50% aqueous KOH (110 mL) followed by tetrabutylammonium hydrogen sulphate (163 mg; 481 µmol) and the resulting mixture was stirred vigorously. After 5 min trichloroacetonitrile (9.65 mL; 92.2 mmol) was added dropwise and the resulting mixture was warmed to rt for 30 min, then allowed to stir at ambient temperature over an additional 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to approximately 1/3 volume, then filtered through celite (CH_2Cl_2). Concentration of the solvent *in vacuo* gave the crude PMB imidate as a yellow oil. Distillation under reduced pressure gave the pure PMB imidate (**55**) (21.4 g; 94%) as a colourless liquid. **bp.** 155-156 ^oC at 0.3 mmHg; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (1H, br s, N*H*), 7.37 (2H, d, J = 8.8 Hz, Ar*H*), 6.91 (2H, d, J = 8.8 Hz, Ar*H*), 5.28 (2H, s, OCH_2PMP), 3.82 (3H, s, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8, 159.9, 129.9, 129.6, 127.7, 114.1, 70.9, 55.4.



(*R*)-32 (*R*)-57

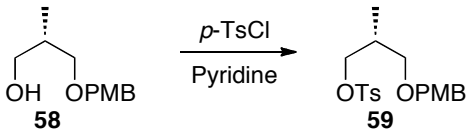
(2*R*)-Methyl-3-(4-methoxybenzyl)oxy-2-methyl-propionate [(*R*)-32], synthesised according to the procedure of Walkup *et al.*[4] To a stirred solution of (*R*)-3-hydroxy-

2-methyl-propionic acid methyl ester (0.94 mL; 8.47 mmol) and PMB imidate (**55**) (3.59 g; 12.7 mmol) in Et_2O (25 mL) was added triflic acid (6 x 5 µL aliquots over 6 h with monitoring by TLC (5% Et_2O/CH_2Cl_2)). The reaction was terminated by addition of 10 mL of Et_2O and the organic mixture was washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a white crystalline solid. The solid was triturated with X4 (3 x 15 mL), filtered, and the filtrate was concentrated *in vacuo* to give a yellow oil. Distillation under reduced pressure gave PMB ether **(*R*)-57** (2.02 g; 100%) as a colourless oil. **bp.** 170-172 ^{o}C at 0.2 mmHg; **R*f*** = 0.50 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_{D}$** = -5.1 (c 1.18, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.8 Hz, Ar*H*), 6.87 (2H, d, J = 8.8 Hz, Ar*H*), 4.45 (2H, ABq, J = 12.4 Hz, OC*H*$_2$PMP), 3.80 (3H, s, ArOC*H*$_3$), 3.68 (3H, s, C(=O)OC*H*$_3$), 3.63 (1H, dd, J = 9.2, 7.2 Hz, C*H*$_A$H$_B$OPMB), 3.45 (1H, dd, J = 9.2, 6.0 Hz, CH$_A$*H*$_B$OPMB), 2.77 (1H, ddq, J = 7.2, 6.0, 6.0 Hz, C*H*CH$_3$), 1.17 (3H, d, J = 7.2 Hz, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4, 159.3, 130.4, 129.3, 113.9, 72.9, 71.8, 55.4, 51.8, 40.3, 14.1.

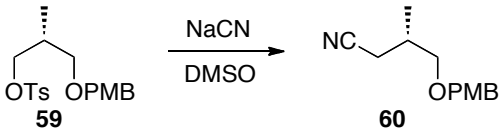


(*R*)-57 **58**

(2*S*)-3-(4-methoxybenzyl)oxy-2-methyl-propan-1-ol (58). A solution of ester **(*R*)-57** (2.04 g; 8.56 mmol) in THF (10 mL) was added *via* cannula to a stirring solution of $LiAlH_4$ (780 mg; 20.6 mmol) in THF (20 mL) at 0 ^{o}C. The resulting mixture was warmed to rt and stirred for 30 min, then recooled to 0 ^{o}C. The reaction was quenched by dropwise addition of H_2O (1.1 mL), NaOH (5 M; 1.1 mL) and H_2O (2.2 mL). The mixture was dried (Na_2SO_4), filtered (Et_2O) and concentrated *in vacuo*. Purification by column chromatography (30% Et_2O/CH_2Cl_2) gave alcohol **58** (1.76 g; 98%) as a colourless oil. **R*f*** = 0.37 (30% Et_2O/CH_2Cl_2); **[α]$^{20}_{D}$** = -16.9 (c 1.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 8.8 Hz, Ar*H*), 4.43 (2H, s, OC*H*$_2$PMP), 3.79 (3H, s, OC*H*$_3$), 3.61-3.55 (2H, m, C*H*$_2$OH), 3.49 (1H, dd, J = 8.8, 4.4 Hz, C*H*$_A$H$_B$OPMB), 3.39 (1H, dd, J = 9.2, 7.6 Hz, CH$_A$*H*$_B$OPMB), 2.61 (1H, br s, O*H*), 2.09-2.01 (1H, m, C*H*CH$_3$), 0.87 (3H, d, J = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.4, 129.4, 114.0, 75.1, 73.2, 67.8, 55.4, 35.8, 13.7.

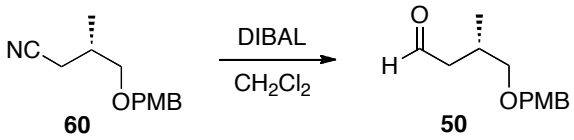


(2*R*)-3-(4-methoxyphenyl)oxy-2-methyl-1-(toluene-4-sulfonyloxy)-propane (59), synthesised according to the procedure of Organ *et al.*[5] To a mixture of alcohol **58** (1.74 g; 8.28 mmol) in dry pyridine (5.5 mL) at 0 ^{o}C was added tosyl chloride (2.21 g; 11.6 mmol) and the resulting mixture stirred at 0 ^{o}C for 9 h. Cold water (50 mL) was added to quench the reaction and after 15 min the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed successively with 1 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% CH_2Cl_2) gave tosylate **59** (2.99 g; 99%) as a colourless oil. **R*f*** = 0.47 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -3.1 (c 1.31, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.4 Hz, Ar*H*), 7.32 (2H, d, J = 8.0 Hz, Ar*H*), 7.16 (2H, d, J = 8.8Hz, Ar*H*), 6.86 (2H, d, J = 8.8 Hz, Ar*H*), 4.33 (2H, s, OCH_2PMP), 4.03 (1H, dd, J = 9.2, 5.6 Hz, CH_AH$_B$OPMB), 3.97 (1H, dd, J = 9.2, 5.6 Hz, CH$_A$$H_B$OPMB), 3.81 (3H, s, OC$H_3$), 3.32 (1H, dd, J = 9.2, 5.2 Hz, CH_AH$_B$OTs), 3.28 (1H, dd, J = 9.2, 5.2 Hz, CH$_A$$H_B$OTs), 2.43 (3H, s, ArC$H_3$), 2.09 (1H, m, C*H*CH$_3$), 0.92 (3H, d, J = 7.2 Hz, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 144.7, 133.3, 130.5, 129.9, 129.2, 128.0, 113.9, 72.9, 72.4, 71.0, 55.4, 33.8, 21.7, 13.8.



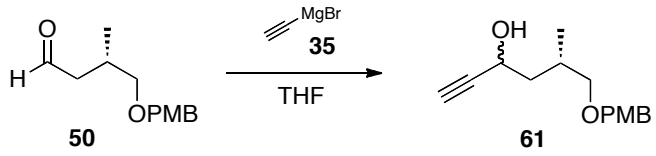
(3*S*)-4-(4-methoxyphenyl)oxy-3-methyl-butanenitrile (60), synthesised according to the procedure of Kummer *et al.*[6] To a solution of tosylate **59** (8.06 g; 22.1 mmol) in anhydrous DMSO (88 mL) was added sodium cyanide (2.28 g; 46.4 mmol). The mixture was stirred at 60 ^{o}C for 18 h and then allowed to cool to rt, whereupon it was slowly poured into brine (200 mL). The resulting mixture was extracted with Et_2O (3 x 100 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (100% CH_2Cl_2) gave nitrile **60** (4.81 g; 99%) as a colourless oil. **R*f*** = 0.40 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -15.9 (c 1.45, $CHCl_3$); **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.2 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.44 (2H, s, OC*H*$_2$PMP), 3.81 (3H, s, OC*H*$_3$), 3.43 (1H, dd, J = 9.6, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.27 (1H, dd, J = 9.2, 7.6 Hz, CH$_A$*H*$_B$OPMB), 2.49 (1H, dd, J = 16.4, 5.2 Hz, C*H*$_A$H$_B$CN), 2.37 (1H, dd, J = 16.8, 7.2 Hz, CH$_A$*H*$_B$CN), 2.15-2.09 (1H, m, C*H*CH$_3$), 1.07 (3H, d, J = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 130.2, 129.4, 118.8, 114.0, 73.1, 73.0, 55.4, 31.3, 21.6, 16.4.

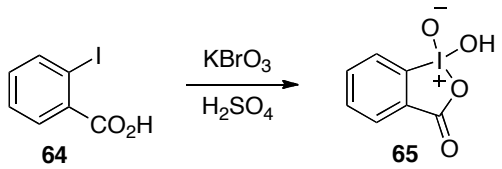


60 **50**

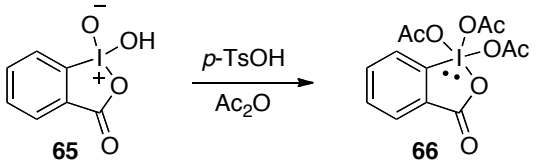
(3*R*)-4-(4-methoxybenzyl)oxy-3-methyl-propanal (50), synthesised according to the procedure of Kummer *et al.*[6] To a stirred solution of nitrile **60** (1.09 mg; 4.97 mmol) in CH_2Cl_2 (50 mL) at -78 ^oC was added diisobutylaluminium hydride (1 M in toluene; 14.9 mL; 14.9 mmol) dropwise. The reaction mixture was stirred at -78 ^oC for 2 h, whereupon 1 M HCl (15 mL) was added and the mixture allowed to warm to rt before pouring into 1 M HCl (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldehyde **50** (980 mg; 89%) as a colourless oil. **R*f*** = 0.35 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = -6.5 (c 1.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (1H, apt t, J = 2.0 Hz, C*H*O), 7.23 (2H, d, J = 8.8 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.41 (2H, s, OC*H*$_2$PMP), 3.80 (3H, s, OC*H*$_3$), 3.39 (1H, dd, J = 9.2, 5.2 Hz, C*H*$_A$H$_B$OPMB), 3.22 (1H, dd, J = 8.8, 7.6 Hz, CH$_A$*H*$_B$OPMB), 2.53 (1H, ddd, J = 16.0, 6.4, 2.4 Hz, C*H*$_A$H$_B$CHO), 2.46-2.35 (1H, m, C*H*CH$_3$), 2.26 (1H, ddd, J = 16.0, 6.8, 2.0 Hz, CH$_A$*H*$_B$CHO), 0.97 (3H, d, J = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.5, 159.3, 103.5, 129.3, 113.9, 74.8, 72.9, 55.4, 48.7, 29.3, 17.2.



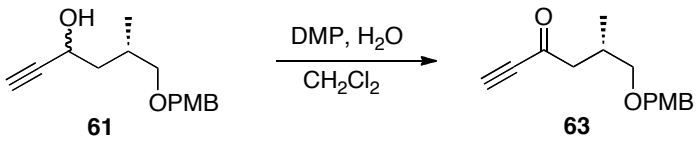
(5*R*)-3-hydroxy-6-(4-methoxybenzyl)oxy-5-methyl-hex-1-yne (61). To a stirred solution of aldehyde **50** (1.46 g; 6.57 mmol) in THF (65 mL) at rt was added ethynylmagnesium bromide (0.5 M in THF; 19.6 mL; 9.80 mmol) dropwise over 15 min. After stirring for 2 h, the reaction was quenched by slow addition of 1 M HCl (120 mL) and the mixture was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 10% Et_2O/CH_2Cl_2) gave alcohol **61** (1.07 g; 94%) as a yellow oil. **R*f*** = 0.41 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.6 Hz, Ar*H*), 6.88 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (1H, d, J = 8.4 Hz, Ar*H*), 4.51-4.47 (0.5H, m, C*H*OH), 4.47 (2H, ABq, J = 11.4 Hz, OC*H*$_2$PMP), 4.44-4.40 (0.5H, m C*H*OH), 3.79 (3H, s, OC*H*$_3$), 3.75 (1H, br s, O*H*), 3.39 (0.5H, dd, J = 9.6, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.35 (0.5H, dd, J = 9.0, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.26 (0.5H, dd, J = 7.8, 4.8 Hz, CH$_A$*H*$_B$OPMB), 3.25 (0.5H, dd, J = 9.0, 5.4 Hz, CH$_A$*H*$_B$OPMB), 2.44 (0.5H, d, J = 2.4 Hz, C*H*CCHOH), 2.43 (0.5H, d, J = 2.4Hz, C*H*CCHOH), 2.43-2.17 (0.5H, m, C*H*CH$_3$), 2.06-1.98 (0.5H, m, C*H*CH$_3$), 1.83 (0.5H, ddd, J = 16.2, 9.0, 7.2 Hz, CH(OH)C*H*$_A$H$_B$CHCH$_3$), 1.75 (1H, apt t, J = 6.0 Hz, CH(OH)C*H*$_2$CHCH$_3$), 1.68 (0.5H, ddd, J = 14.4, 6.0, 4.8 Hz, CH(OH)CH$_A$*H*$_B$CHCH$_3$), 0.95 (1.5H, d, J =6.6 Hz, CHC*H*$_3$), 0.94 (1.5H, d, J = 6.6 Hz, CHC*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 159.1, 129.7, 129.5, 129.4, 129.3, 113.8, 113.7, 85.4, 84.9, 75.4, 75.3, 72.7, 72.5, 72.0, 60.9, 60.4, 55.1, 43.6, 43.0, 31.2, 29.9, 17.8, 17.7; **IR** (film, cm^{-1}) 3394, 3289, 2956, 2932, 2859, 1612, 1586, 1513, 1463, 1421, 1362, 1302, 1247, 1174, 1081, 1034, 820, 736, 637; **HRESIMS** calculated for $C_{15}H_{20}O_3Na^+$: 271.1305; found: 271.1308.



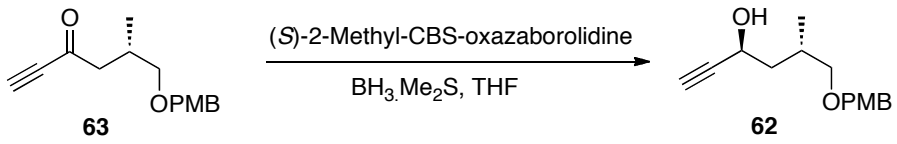
2-Iodoxybenzoic acid (65), synthesised according to the procedure of Dess and Martin.[7] To a stirred suspension of 2-iodobenzoic acid (**64**) (85.2 g; 344 mmol) in a 1 M solution of H_2SO_4 (730 mL) at 55 ^oC was added $KBrO_3$ (76.0 g; 447 mmol) in small portions over 30 minutes. The resulting mixture was stirred at 68 ^oC for 4 hours, then cooled on ice and filtered under vacuum, washing with H_2O (100 mL) and EtOH (2 x 50 mL). The product was dried under high vacuum, giving 2-iodoxybenzoic acid **64** (84.4 g; 89%) as a white solid.



1,1,1-Triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1*H*)-one (66), synthesised according to the procedure of Ireland *et al*.[8] To a stirred solution of *p*- TsOH·H_2O (286 mg; 1.51 mmol) in acetic anhydride (336 mL) at room temperature under an atmosphere of argon was added 2-iodoxybenzoic acid (**65**) (84.4 g; 301 mol). The resulting mixture was warmed to 80 ^oC and stirred for 2 hours before cooling on ice and filtering under vacuum, under a stream of argon, washing with Et_2O (5 x 40 mL). The product was dried under high vacuum to give Dess-Martin Periodinane **66** (105 g; 83%) as a white crystalline solid. The solid was transferred to an amber glass bottle under a stream of argon and stored in the freezer.

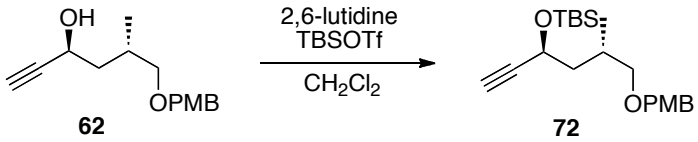


(5*R*)-6-(4-methoxybenzyl)oxy-5-methyl-3-oxo-hex-1-yne (63), synthesised according to the procedure of Meyer *et al*.[9] To a stirred solution of alcohol **61** (1.22 g; 4.91 mmol) in CH_2Cl_2 (49 mL) at rt was added DMP (3.13 g; 7.37 mmol) followed immediately by addition of a H_2O/CH_2Cl_2 mixture (8.17 mL of sat. aq. CH_2Cl_2) and addition of the moist CH_2Cl_2 continued every 5 min for 1 h (ie. 12 x 8.17 mL aliquots). The reaction mixture was stirred at rt for 4 h before diluting with Et_2O (300 mL). Sat. aq. $NaHCO_3$ (150 mL) containing $Na_2S_2O_3.5H_2O$ (20 g) was added to quench the reaction with stirring for 5 minutes. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (150 mL) and brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through buffered silica (100% CH_2Cl_2) to afford ketone **63** (1.21 g; 100%) as a yellow oil. **R*f*** = 0.38 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +2.6 (c 1.15, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.7 Hz, Ar*H*), 6.89 (2H, d, J = 8.7 Hz, Ar*H*), 4.43 (2H, d, J = 11.6 Hz, OC*H*$_2$PMP), 3.82 (3H, s, OC*H*$_3$), 3.37 (1H, dd, J = 9.2, 5.3 Hz, C*H*$_A$H$_B$OPMB), 3.24 (1H, dd, J = 9.2, 7.3 Hz, CH$_A$*H*$_B$OPMB), 3.22 (1H, s, C*H*CC=O), 2.79 (1H, dd, J = 15.8, 5.5 Hz, C(=O)C*H*$_A$H$_B$CH(CH$_3$)), 2.48 (1H, m, C*H*CH$_3$), 2.43 (1H, dd, J = 15.8, 7.9 Hz, C(=O)CH$_A$*H*$_B$CH(CH$_3$)), 0.97 (3H, d, J = 6.7 Hz, CHC*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 187.0, 159.2, 130.5, 129.3, 113.8, 81.7, 78.4, 74.3, 72.7, 55.4, 49.9, 30.3, 16.9; **IR** (film, cm^{-1}) 3258, 2959, 2932, 2856, 2091, 1680, 1612, 1513, 1462, 1362, 1302, 1247, 1174, 1091, 1034, 819; **HRESIMS** calculated for $C_{15}H_{18}O_3Na^+$: 269.1148; found: 269.1153.



(3*S*,5*R*)-6-(4-methoxybenzyl)oxy-3-hydroxy-5-methylhex-1-yne (62), synthesised according to the procedure of Trost *et al*.[10] To a stirred solution of ketone **63** (2.71

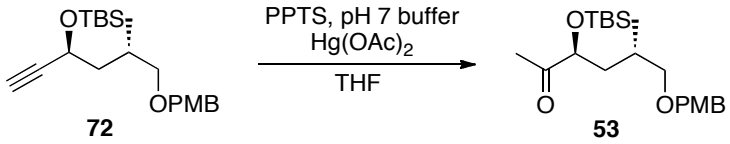
g; 11.0 mmol) in THF (55 mL) at -30 °C was added (*S*)-2-methyl-CBS-oxazaborolidine (1 M in toluene; 12.1 mL; 12.1 mmol), followed by borane-dimethylsulfide complex (5.50 mL; 55.0 mmol) dropwise over 2 min. The reaction mixture was stirred at -30 °C for 2 h and quenched by addition of EtOH (40 mL). The mixture was warmed to rt and diluted with H_2O (40 mL) and Et_2O (40 mL). Layers were separated and the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 10% Et_2O/CH_2Cl_2) gave the alcohol **62** (2.65 g; 97%, 98% ds) as a yellow oil. **R*f*** = 0.32 (10% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = -15.7 (c 1.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.4 Hz, Ar*H*), 6.89 (2H, d, J = 8.4 Hz, Ar*H*), 4.45 (2H, s, OC*H*$_2$PMP), 4.44 (1H, m, C*H*OH), 3.82 (3H, s, OC*H*$_3$), 3.38 (1H, dd, J = 9.6, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.36 (1H, d, J = 4.2 Hz, O*H*), 3.28 (1H, dd, J = 9.6, 8.4 Hz, CH$_A$*H*$_B$OPMB), 2.45 (1H, d, J = 2.4 Hz, C*H*CCOH), 2.03 (1H, m, C*H*CH$_3$), 1.85 (1H, ddd, J = 16.2, 14.4, 7.2 Hz, CH(OH)C*H*$_A$H$_B$), 1.75-1.71 (1H, m, CH(OH)CH$_A$*H*$_B$), 0.97 (3H, d, J = 7.2 Hz, CHC*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 129.7, 129.4, 113.8, 85.4, 75.5, 72.8, 72.0, 61.1, 55.1, 43.1, 30.8, 17.5; **IR** (film, cm^{-1}) 3308, 2955, 2856, 1613, 1513, 1463, 1442, 1361, 1302, 1248, 1172, 1089, 1038, 1174, 1073, 1034, 820, 756, 637; **HRESIMS** calculated for $C_{15}H_{20}O_3Na^+$: 271.1305; found: 271.1308.



62 **72**

(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methylhex-1-yne (72). To a stirred solution of alcohol **62** (1.35 mg; 5.42 mmol) in CH_2Cl_2 (54 mL) at -78 °C was added 2,6-lutidine (1.26 mL; 10.8 mmol) followed by TBSOTf (1.87 mL; 8.13 mmol). The resulting solution was stirred at -78 °C for 7.5 h before warming to 0 °C for 10 min. The reaction was quenched by addition of 5% $NaHCO_3$ (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave TBS ether **72** (1.94 mg; 99%) as a colourless oil. **R*f*** = 0.53 (100%, CH_2Cl_2); **$[\alpha]^{20}_D$** = -23.2 (c 1.34, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.4 Hz, Ar*H*), 6.89

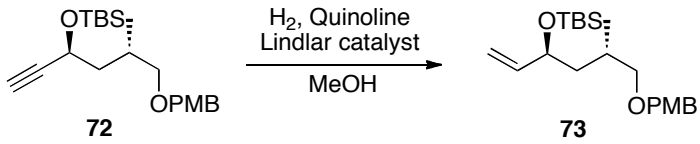
(2H, d, J = 8.4 Hz, Ar*H*), 4.47 (1H, ddd, J = 7.8, 6.0, 2.4 Hz, C*H*OTBS), 4.44 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 3.81 (3H, s, OCH_3), 3.33 (1H, dd, J = 9.0, 6.0 Hz, CH_AH$_B$OPMB), 3.27 (1H, dd, J = 9.0, 6.6 Hz, CH$_A$$H_B$OPMB), 2.39 (1H, d, J = 1.8 Hz, C*H*CCH(OTBS)), 2.07 (1H, m, C*H*CH$_3$), 1.86 (1H, ddd, J = 13.8, 8.4, 5.4 Hz, CH(OTBS)CH_AH$_B$), 1.49 (1H, ddd, J = 13.2, 7.8, 5.4 Hz, CH(OTBS)CH$_A$$H_B$), 0.97 (3H, d, J = 6.6 Hz, CHCH_3), 0.91 (9H, s, SiC(CH_3)$_3$), 0.14 (3H, s, Si(CH_3)CH$_3$), 0.11 (3H, s, Si(CH$_3$)CH_3); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 159.0, 130.7, 113.7, 85.9, 75.5, 72.5, 72.1, 60.9, 55.3, 42.7, 29.7, 25.8, 18.2, 17.0, -4.8, -5.1; **IR** (film, cm^{-1}) 3395, 3289, 2956, 2933, 2859, 1612, 1513, 1463, 1362, 1302, 1247, 1005, 938, 902, 837, 778, 663, 629; **HRESIMS** calculated for $C_{21}H_{34}O_3SiNa^+$: 385.2169; found: 385.2175.



72 **53**

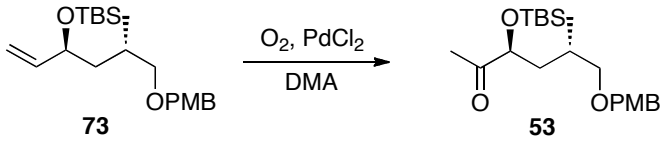
(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-hexan-2-one (53), synthesised according to a procedure modified from Paterson and Tudge.[11] To a stirred solution of alkyne **72** (50.0 mg; 138 µmol) in THF (2.8 mL) was added sequentially pyridinium *p*-toluenesulfonate (52.0 mg; 207 µmol), pH 7 buffer (20 µL) and mercury (II) acetate (13.2 mg; 41.4 µmol). After 5 h at 45 ^{o}C the reaction mixture was treated with sat. aq. NaHCO$_3$ (3 mL). The organic phase was separated and the aqueous phase was extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH$_2$Cl$_2$) gave methyl ketone **53** (41.2 mg; 76%) as a colourless oil. **R*f*** = 0.56 (100% CH$_2$Cl$_2$); **[α]$^{20}_{D}$** = -20.8 (c 1.06, CHCl$_3$); **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.24 (2H, d, J = 8.6 Hz, Ar*H*), 6.87 (2H, d, J = 8.6 Hz, Ar*H*), 4.42 (2H, ABq, J = 11.8 Hz, OCH_2PMP), 4.07 (1H, dd J = 9.6, 4.2 Hz, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.26 (2H, apt dd, J = 6.1, 2.6 Hz, CH_2OPMB), 2.14 (3H, s, CH_3C=O), 2.00-1.91 (1H, m, C*H*CH$_3$), 1.75 (1H, ddd, J = 13.5, 9.0, 4.3 Hz, CH(OTBS)CH_AH$_B$), 1.30 (1H, ddd, J = 13.5, 9.1, 4.2 Hz, CH(OTBS)CH$_A$$H_B$), 0.95 (2H, d, J = 6.7 Hz, CHCH_3), 0.91 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, Si(CH_3)CH$_3$), 0.04 (3H, s, Si(CH$_3$)CH_3); **^{13}C NMR** (151

MHz, $CDCl_3$) δ 212.3, 159.4, 131.0, 129.3, 114.0, 77.5, 75.6, 72.7, 55.5, 38.7, 29.6, 26.0, 24.9, 18.3, 17.1, -4.6, -4.8; **IR** (film, cm^{-1}) 3414, 2955, 2930, 2856, 1715, 1612, 1586, 1513, 1463, 1389, 1360, 1301, 1249, 1172, 1092, 1036, 1006, 900, 837, 777, 669; **HRESIMS** calculated for $C_{21}H_{36}O_3SiNa^+$: 403.2275; found: 403.2278.



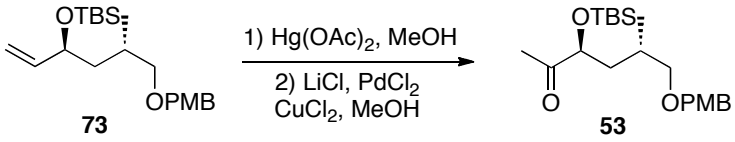
72 **73**

(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-hex-1-ene (73). To a stirred solution of alkyne **72** (250 mg; 690 µmol) in MeOH (3 mL) at rt was successively added quinoline (2.5 µL; 20.7 µmol) and Lindlar catalyst (25 mg; 10% w/w). The reaction mixture was stirred at rt under an atmosphere of H_2 for 1 h and then filtered through a pad of celite. The solution was concentrated *in vacuo* and the residue diluted with Et_2O (5 mL), washed with 10% HCl (5 mL), H_2O (5 mL), $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave alkene **73** (250 mg; 99%) as a colourless oil. **R*f*** = 0.53 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 9.0 Hz, Ar*H*), 6.88 (2H, d, J = 8.4 Hz, Ar*H*), 5.81 (1H, ddd, J = 16.8, 10.2, 6.6 Hz, $CH_2CHCHOTBS$), 5.13 (1H, ddd, J = 16.8, 1.2, 1.2 Hz, $CH_AH_BCHCHOTBS$), 5.01 (1H, m, $CH_AH_BCHCHOTBS$), 4.43 (2H, s, OCH_2PMP), 4.20 (1H, m, C*H*OTBS), 3.81(3H, s, OCH_3), 3.32 (1H, dd, J = 9.0, 5.4 Hz, CH_AH_BOPMB), 3.23 (1H, dd, J = 9.0, 6.6 Hz, CH_AH_BOPMB), 2.01-1.93 (1H, m, $CHCH_3$), 1.64 (1H, ddd, J = 13.2, 8.4, 4.8 Hz, $CH(OTBS)CH_AH_B$), 1.21 (1H, ddd, J = 13.8, 9.0, 4.8 Hz, $CH(OTBS)CH_AH_B$), 0.96 (3H, d, J = 6.6 Hz, $CHCH_3$), 0.90 (9H, d, $OSi(CH_3)_3$), 0.06 (3H, s, $OSi(CH_3)CH_3$), 0.03 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) δ 159.2, 142.4, 131.1, 129.2, 113.8, 113.7, 76.1, 72.6, 72.1, 55.4, 42.5, 29.7, 26.1, 18.4, 17.4, -4.0, -4.7.



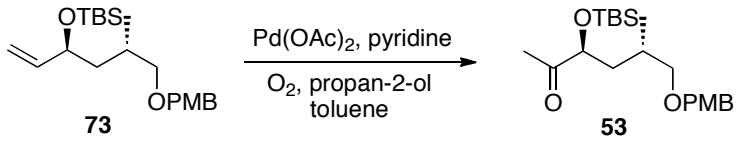
73 53

(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-hexan-1-one (53), synthesis attempted according to the procedure of Mitsudome *et al*.[12] A solution of $PdCl_2$ (0.5 mg; 2.82 μmol), DMA (1.4 mL) and H_2O (82 μL) was heated at 80 °C under an atmosphere of O_2 for 4 h. Alkene **73** (50.0 mg; 137 μmol) was then added and the mixture stirred vigorously at 80 °C for 6 h. The mixture was then cooled to room temperature, diluted with H_2O (10 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. NMR analysis of the crude residue showed decomposition products only.



73 53

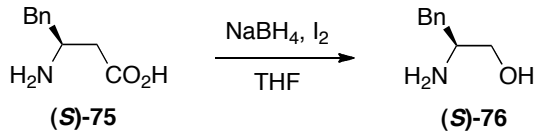
(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-hexan-1-one (53), synthesis attempted according to the modified procedure of Crimmins *et al*.[13] A solution of alkene **73** (30.5 mg; 146 μmol) and mercury (II) acetate (55.7 mg; 175 μmol) in MeOH (1 mL) was stirred at rt for 12 h. The reaction mixture was then transferred to a solution of LiCl (12.3 mg; 291 μmol), $PdCl_2$ (25.8 mg; 146 μmol) and $CuCl_2$ (58.7 mg; 437 μmol) in MeOH (0.5 mL) *via* cannula and the resultant mixture stirred at 55 °C for 3 h. Sat. aq. $NaHCO_3$ (5 mL) was added to quench the reaction and the product was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave the methyl ketone **53** (15.9 mg; 52%) as a clear, colourless oil. **NMR** data as for compound **53** (p. 201).



73 53

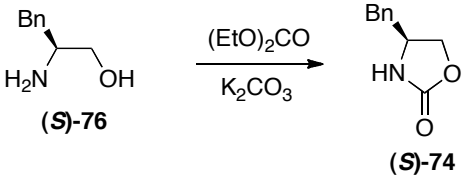
(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-hexan-1-one (53), synthesis attempted according to the procedure of Nishimura *et al*.[14] To a stirred suspension of $Pd(OAc)_2$ (5.6 mg; 24.8 μmol) in toluene (2.5 mL) was added pyridine (8 μL; 99.2 μmol) under an atmosphere of O_2. The mixture was then warmed to 60°C and propan-2-ol (0.5 mL) was added. After 5 min, alkene **73** (181 mg; 496 μmol) in propan-2-ol (2 mL) was added and the mixture was stirred at 60 °C under O_2 for 6 h. The reaction mixture was cooled to room temperature and passed through Florisil. Purification by column chromatography (buffered silica, 20% X4/CH_2Cl_2) gave methyl ketone **53** (80.5 mg; 43%) as a colourless oil. **NMR** data as for compound **53** (p. 201).

4.2.2 Model Aldehyde Synthesis



(***S***)-75 (***S***)-76

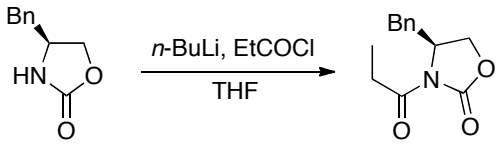
(*S*)-phenylalanol [(*S*)-76], synthesised according to the procedure of McKennon and Meyers.[15] To a stirred suspension of sodium borohydride (11.0 g; 291 mmol) in THF (160 mL) was added (*S*)-phenylalanine [**(*S*)-75**] (20.0 g; 121 mmol) in one portion and the resulting mixture was cooled to 0 ^{o}C. A solution of iodine (28.5 g; 121 mmol) in THF (80 mL) was added dropwise over 30 min, resulting in vigorous evolution of hydrogen. After addition of iodine was complete and gas evolution had ceased, the solution was heated to reflux for 18 h, then cooled to rt and MeOH was added cautiously until the mixture became clear. After stirring for 30 min the solvent was removed *in vacuo* leaving a white paste which was dissolved by addition of 20% aq. KOH (240 mL). The solution was stirred for 4 h and extracted with CH_2Cl_2 (3 x 200 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a white semi-solid which was recrystallised from toluene to give (*S*)-phenylalanol [**(*S*)-76**] (16.2 g; 88%) as white crystals. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30-7.27 (2H, m, Ar*H*), 7.23-7.20 (1H, m, Ar*H*), 7.19-7.17 (2H, m, Ar*H*), 3.63 (1H, dd, J = 10.8, 3.6 Hz, CH_AH$_B$OH), 3.40 (1H, dd, J = 10.8, 7.2 Hz, CH$_A$$H_B$OH), 3,13 (1H, m, C*H*NH$_2$), 2.78 (1H, dd, J = 13.8, 5.4 Hz, CH_AH$_B$Ph), 2.72 (3H, br s, NH_2 and O*H*), 2.55 (1H, dd, J = 13.2, 8.4 Hz, CH$_A$$H_B$Ph); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 129.3, 128.7, 126.6, 65.9, 54.3, 40.5.



(***S***)-76 (***S***)-74

(4*S*)-4-(phenylmethyl)-2-oxazolidinone [(*S*)-74], synthesised according to the procedure of Gage and Evans.[16] To a round bottom flask fitted with a Vigreux

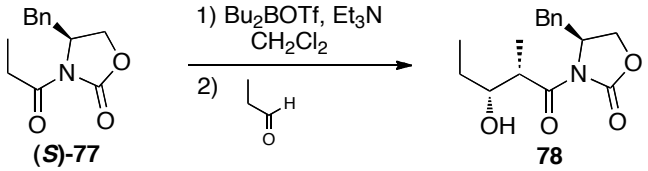
column and a distillation head was added (*S*)-phenylalanol [**(*S*)-76**] (5.60 g; 37.0 mmol), anhydrous K_2CO_3 (511 mg; 3.70 mmol) and diethyl carbonate (9.41 mL; 77.7 mmol). The mixture was heated to 135 ^{o}C until dissolution was achieved and the mixture was then heated to reflux for approx. 2 h until ethanol ceased to collect in the receiver flask. The resulting solution was cooled to room temperature, diluted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid which was recrystallised from 2:1 EtOAc/X4 to give **(*S*)-74** (5.22 g; 80%) as white plates. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.24 (1H, m, Ar*H*), 7.19-7.16 (2H, m, Ar*H*), 5.92 (1H, br s, N*H*), 4.22 (1H, dd, J = 8.0, 7.6 Hz, CHCH_AH$_B$O), 4.14 (1H, dd, J = 8.4, 5.6 Hz, CH$_A$$H_B$O), 4.14-4.05 (1H, m, C*H*CH$_2$Ph), 2.90 (1H, dd, J = 14.0, 7.2 Hz, CH_AH$_B$Ph), 2.85 (1H, dd, J = 13.2, 6.0 Hz, CH$_A$$H_B$Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ159.7, 136.2, 129.2, 129.2, 127.4, 69.8, 54.0, 41.6.



(*S*)-74 (*S*)-77

(4*S*)-4-(phenylmethyl)-2-oxazolidinone [(*S*)-77], synthesised according the procedure of Gage and Evans.[16] To a stirred solution of auxiliary **(*S*)-74** (1.47 g; 8.27 mmol) in THF (14 mL) at -78 ^{o}C was added *n*-BuLi (6.07 mL; 1.5 M in hexanes, 9.10 mmol) dropwise, followed immediately by propionyl chloride (795 µL; 9.10 mmol). The resulting mixture was stirred at -78 ^{o}C for 30 min and then allowed to warm to room temperature over 30 min. The reaction was quenched by addition of NH_4Cl (14 mL) and the volatiles removed *in vacuo.* The resulting slurry was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with 1M NaOH (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (50% Et_2O/X4) gave oxazolidinone **(*S*)-77** (1.65 g; 86 %) as white plates. **R*f*** = 0.37 (50% Et_2O/X4); **[α]$^{20}_{D}$** = +55.5 (c 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m, Ar*H*), 7.29-7.24 (1H, m, Ar*H*), 7.22-7.18 (2H, m, Ar*H*), 4.67 (1H, m, C*H*CH$_2$Ph), 4.22-4.14 (2H, m, CHCH_2O), 3.29 (1H, dd, J = 13.4, 3.3

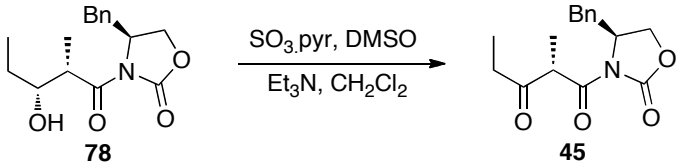
Hz, C*H*$_A$H$_B$Ph), 3.02 (1H, dq, J = 18.0, 7.2 Hz, C*H*$_A$H$_B$CH$_3$), 2.98 (1H, dq, J = 18.0, 7.2 Hz, CH$_A$*H*$_B$CH$_3$), 2.77 (1H, dd, J = 13.4, 9.6 Hz, CH$_A$*H*$_B$Ph), 1.20 (3H, t, J = 7.4 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3, 153.7, 135.5, 129.6, 129.1, 127.5, 66.4, 55.4, 38.1, 29.4, 8.5.



(***S***)-77 **78**

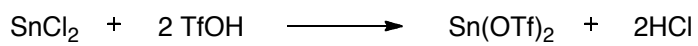
[[3-(2*S*,3*R*)-4*S*]-3-(3-hydroxy-2-methyl-1-oxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (78), synthesised according to the procedure of Evans *et al.*[17] To a stirred solution of oxazolidine **(*S*)-77** (10.0 g; 42.9 mmol) in CH_2Cl_2 (86 mL) at 0 ^oC was added Bu_2BOTf (51.4 mL; 1M in CH_2Cl_2; 51.4 mmol) dropwise giving a red solution. After 30 min Et_3N (7.77 mL; 55.7 mmol) was added and the resulting yellow solution was stirred for a further 30 min before cooling to -78 ^oC. Propanal (6.18 mL; 85.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise *via* cannula and the reaction mixture stirred at -78 ^oC for 30 min and then at 0 ^oC for 4 h, at which time the reaction was quenched by addition of pH 7 buffer (30 mL) and MeOH (30 mL). A solution of 2:1 MeOH/H_2O_2 (60 mL) was then added and the mixture stirred at room temperature for 1 h. The volatiles were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave aldol adduct **78** (10.8 g; 86%) as white crystals. **R*f*** = 0.40 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +43.5 (c 4.33, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35-7.32 (2H, m, Ar*H*), 7.29-7.27 (1H, m, Ar*H*), 7.21-7.20 (2H, m, Ar*H*), 4.70 (1H, dddd, J = 9.0, 7.8, 3.6, 3.0 Hz, C*H*CH$_2$Ph), 4.23 (1H, dd, J = 9.0, 7.8 Hz, CHC*H*$_A$H$_B$O), 4.18 (1H, dd, J = 9.0, 4.8 Hz, CHCH$_A$*H*$_B$O), 3.87 (1H, ddd, J = 7.8, 5.2, 2.4 Hz, C*H*OH), 3.78 (1H, dq, J = 7.2, 2.4 Hz, CH(OH)C*H*(CH$_3$)C=O), 3.25 (1H, dd, J = 13.2, 3.0 Hz, C*H*$_A$H$_B$Ph), 2.79 (1H, dd, J = 13.2, 9.0 Hz, CH$_A$*H*$_B$Ph), 2.25 (1H, br s, O*H*), 1.58 (1H, ddq, J = 15.0, 7.8, 7.2 Hz, C*H*$_A$H$_B$CH$_3$), 1.46 (1H, ddq, J = 15.0, 7.8, 5.4 Hz, CH$_A$*H*$_B$CH$_3$) 1.25 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.98 (3H, t,

J = 7.8 Hz, CH_2CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.8, 153.2, 135.1, 129.6, 129.1, 127.6, 73.1, 66.3, 55.2, 41.8, 37.9, 26.9, 10.6, 10.4.



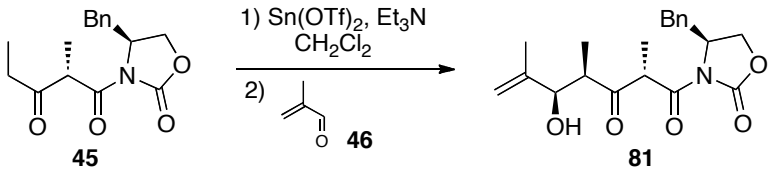
78 **45**

[[3-(2*S*)-4*S*]-3-(2-methyl-1,3-dioxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (45), synthesised according to the procedure of Evans *et al.*[17] To a stirred solution of oxazolidinone **78** (4.00 g; 13.7 mmol) in 1:1 CH_2Cl_2/DMSO (137 mL) at −5 °C was added Et_3N (5.74 mL; 41.2 mmol) dropwise, followed by a solution of sulphur trioxide-pyridine complex (6.56 g; 41.2 mmol) in DMSO (69 mL) *via* cannula over 30 min. The reaction mixture was then warmed to rt for 3 h, before being diluted with Et_2O (300 mL) and washed with 1 M $NaHSO_4$ (300 mL), sat. aq. $NaHCO_3$ (300 mL), and brine (300 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow solid. Recrystallisation from 1:1 Et_2O/pentane gave β-ketoimide **45** a white solid (3.01 g; 76%). **R*f*** = 0.38 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +129.0 (c 1.93, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.20-7.18 (2H, m, Ar*H*), 4.74 (1H, m, C*H*CH_2Ph), 4.60 (1H, q, J = 7.2 Hz, C(=O)C*H*(CH_3)C=O), 4.26-4.15 (2H, m, CHC*H*$_2$O), 3.30 (1H, dd, J = 13.2, 8.0 Hz, C$H_A$$H_B$Ph), 2.77 (1H, dd, J = 13.2, 9.6 Hz, C$H_A$$H_B$Ph), 2.69 (1H, dq, J = 14.4.0, 7.2 Hz, C$H_A$$H_B$$CH_3$), C$H_A$$H_B$$CH_3$), 2.60 (1H, dq, J = 18.0, 7.2 Hz, C$H_A$$H_B$$CH_3$), 1.43 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)C=O), 1.07 (3H, t, J = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.3, 170.2, 153.9, 135.2, 129.5, 129.1, 127.5, 66.6, 55.3, 52.8, 38.0, 34.1, 13.0, 7.6.



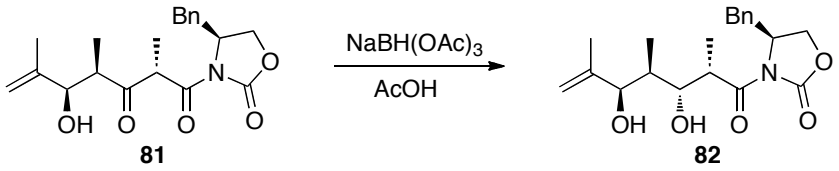
Tin triflate, synthesised according to the procedure of Evans *et al*.[17] $SnCl_2$ (8.00 g; 47.2 mmol) was dried at 120 °C on a high vacuum pump for 2 h. TfOH (20 mL) was added and the resulting mixture heated to 85 °C for 16 hours. The product was isolated *via* Schlenk tube under a heavy flow of argon and rinsed with anhydrous

Et_2O until neutral to litmus. The resulting white powder was then dried under high vacuum for 24 h before use, with transferral to reaction flask carried out in an argon glove bag.



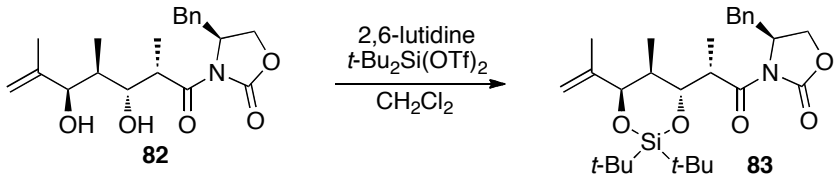
[[3-(2*S*,4*R*,5*R*)-4*S*]-3-(5-hydroxy-2,4,6-trimethyl-1,3-dioxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (81), synthesised according to the procedure of Evans *et al.*[17] To a stirred suspension of $Sn(OTf)_2$ (1.87 g; 4.49 mmol) in CH_2Cl_2 (17 mL) at 0 ^oC under an atmosphere of argon was added Et_3N (626 μL; 4.49 μmol) dropwise and the resulting suspension was cooled to -20 ^oC for 10 min. β-ketoimide **45** (1.00 mg; 3.46 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* cannula and the resulting solution stirred at -20 ^oC for 1 h before cooling to -78 ^oC. Methacrolein (**46**) (573 μL; 6.92 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* cannula and the reaction mixture was stirred at -78 ^oC for 30 min, then transferred *via* cannula to a vigorously stirred cooled (0 ^oC) mixture of CH_2Cl_2/1 M $NaHSO_4$ (20 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts washed with sat. aq. $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude NMR showed a 0.3:1 mixture of diastereomers which were able to be separated by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) to give aldol adduct **81** (803 mg; 65%) as a white solid. **R*f*** = 0.23 (5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = +74.8 (c 1.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, Ar*H*), 7.28-7.23 (1H, m, Ar*H*), 7.19-7.15 (2H, m, Ar*H*), 5.08 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.94 (1H, m, CH$_A$$H_B$C($CH_3$)CHOH), 4.87 (1H, q, J = 7.2 Hz, C(=O)C*H*(CH_3)C=O), 4.74 (1H, m, C*H*CH_2Ph), 4.43 (1H, m, C*H*OH), 4.25 (1H, dd, J = 9.2, 8.8 Hz, CHCH_AH$_B$O), 4.17 (1H, dd, J = 8.8, 2.8 Hz, CHCH$_A$$H_B$O), 3.28 (1H, dd, J = 13.6, 3.6 Hz, CH_AH$_B$Ph), 2.92 (1H, dq, J = 7.2, 3.2 Hz, CH(OH)C*H*(CH_3)C=O), 2.77 (1H, dd, J = 13.2, 9.2 Hz, CH$_A$$H_B$Ph), 2.64 (1H, br s, O*H*), 1.69 (3H, s, CH_2C(CH_3)CHOH), 1.47 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)C=O), 1.16 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)C=O);

^{13}C NMR (100 MHz, $CDCl_3$) 211.2, 170.3, 153.7, 143.7, 135.1, 129.5, 129.0, 127.5, 112.1, 73.8, 66.6, 55.4, 51.8, 46.8, 37.9, 19.4, 13.1, 9.8.

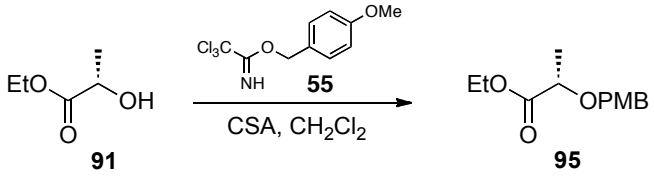


81 **82**

[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(3,5-dihydroxy-2,4,6-trimethyl-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (82). To a stirred solution of aldol adduct **81** (194 mg; 540 μmol) in a 1:1 mixture of AcOH/CH_3CN (10 mL) at 5 ^{o}C was added $NaBH(OAc)_3$ (572 mg; 2.70 mmol) and the mixture stirred at 5 ^{o}C for 3 h. The reaction was cooled to 0 ^{o}C and quenched by slow addition of sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 20% Et_2O/CH_2Cl_2) gave 1,3-diol **82** (166 mg; 85%, 88% ds) as a white foam. **R*f*** = 0.19 (20% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = +42.7 (c 3.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.32 (2H, m, Ar*H*), 7.31-7.27 (1H, m, Ar*H*), 7.21-7.19 (2H, m, Ar*H*), 5.03 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.95 (1H, m, CH$_A$$H_B$C($CH_3$)CHOH), 4.70 (1H, m, C*H*CH_2Ph), 4.49 (1H, br s, CH_2C(CH_3)C*H*OH), 4.20 (2H, m, , CHCH_2O), 4.01-3.98 (1H, m, CH(OH)C*H*(CH_3)C=O), 3.99-3.95 (1H, m, CH(OH)C*H*(CH_3)C=O), 3.53 (1H, br s, O*H*), 3.25 (1H, dd, J = 13.2, 3.2 Hz, CH_AH$_B$Ph), 2.80 (1H, dd, J = 13.6, 9.6 Hz, CH$_A$$H_B$Ph), 2.13 (1H, br s, O*H*), 1.91-1.80 (1H, m, CH(OH)C*H*(CH_3)CHOH), 1.69 (3H, s, CH_2C(CH_3)CHOH), 1.30 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)C=O), 0.82 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) 178.0, 153.1, 146.4, 135.2, 129.7, 129.2, 127.7, 110.5, 74.3, 73.7, 66.5, 55.4, 40.2, 38.0, 37.5, 20.3, 10.9, 9.8.

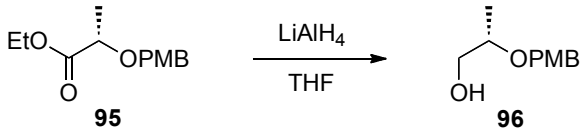


[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(2,4,6-trimethyl-3,5-[(bis-(1,1-dimethylethyl)-silylene)dioxy]-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (83). To a stirred solution of 1,3-diol **82** (166 mg; 459 μmol) in CH_2Cl_2 (0.9 mL) at rt was added 2,6-lutidine (160 μL; 1.38 mmol), followed by *t*-$Bu_2Si(OTf)_2$ (300 μL; 918 μmol). The resulting solution was stirred at rt for 5 h before diluting with CH_2Cl_2 (5 mL) and quenching by addition of sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H showed that no protection had occurred and only starting material **82** was recovered.



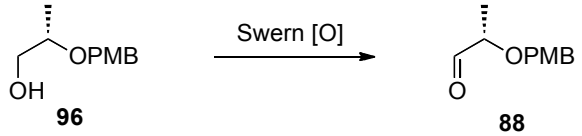
(2*S*)-ethyl-2-(4-methoxybenzyl)oxy-propionate (95), synthesised according to the procedure of Yu *et al.*[18] To a stirred solution of ethyl (*S*)-lactate (**91**) (5.00 mL; 44.1 mmol) in CH_2Cl_2 (60 mL) was added PMB imidate **55** (16.2 g; 57.3 mmol), followed by CSA (1.06 g; 4.59 mmol). The resulting mixture was stirred at rt for 4 days, during which time addition PMB imidiate **55** and CSA were added as appropriate by TLC. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (70 ml), the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentratrated *in vacuo*. The resulting slurry was triturated (25% CH_2Cl_2/X4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave PMB ether **95** (7.87 g; 75%) as a clear, colourless oil. **R*f*** = 50% (5% Et_2O/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 8.4 Hz, Ar*H*), 6.88 (2H, d, J = 8.4 Hz, Ar*H*), 4.63 (1H, d, J = 11.2 Hz, OC$H_A$$H_B$PMP), 4.40 (1H, d, J = 11.2 Hz, OC$H_A$$H_B$PMP), 4.22 (1H, dq, J = 7.2, 2.4 Hz, OC$H_2$$CH_3$), 4.03 (1H, q, J = 7.2 Hz, C*H*(CH_3)OPMB), 3.80 (3H, s, OCH_3), 1.42

(3H, d, J = 7.2 Hz, CH(C*H*$_3$)OPMB), 1.30 (3H, t, J = 7.2 Hz, OCH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 159.6, 130.7, 129.8, 129.6, 114.0, 74.0, 71.8, 55.5, 18.9, 14.4.



95 **96**

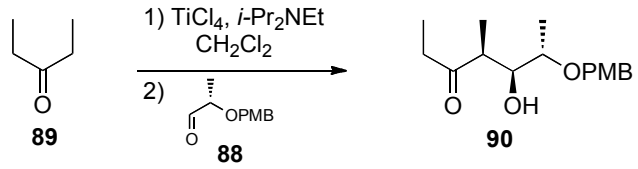
(2*S*)-2-(4-methoxyphenyl)oxy-propan-1-ol (96). The previous procedure used for the preparation of alcohol **58** was followed with ester **95** (7.87 g; 33.0 mmol), $LiAlH_4$ (1.42 g; 37.3 mmol) and THF (120 mL). Purification by column chromatography (buffered silica, 15% Et_2O/CH_2Cl_2) gave alcohol **96** (4.15 g; 70%) as a clear, colourless oil. **R*f*** = 0.27 (15% Et_2O/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.8 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.58 (1H, d, J = 11.2 Hz, OC*H*$_A$H$_B$PMP), 4.42 (1H, d, J = 11.2 Hz, OCH$_A$*H*$_B$PMP), 3.80 (3H, s, OC*H*$_3$), 3.66 (1H, ddq, J = 6.4 Hz, 3.6, 3.6 Hz, C*H*(CH$_3$)OPMB), 3.58 (1H, ddd, J = 11.6, 8.0, 3.6 Hz, C*H*$_A$H$_B$OH), 3.48 (1H, ddd, J = 11.6, 7.2, 4.4 Hz, CH$_A$*H*$_B$OH), 2.15 (1H, dd, J = 8.0, 7.2 Hz, O*H*), 1.16 (3H, d, J = 6.4 Hz, CH(C*H*$_3$)OPMB); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 130.7, 129.4, 114.0, 75.4, 70.6, 66.5, 55.4, 16.0.



96 **88**

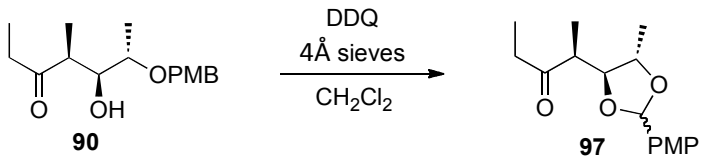
(2*S*)-2-(4-methoxybenzyl)oxy-propanal (88), synthesised according to the procedure of Mancuso *et al.*[19] To a stirred solution of DMSO (1.68 mL; 23.7 mmol) in CH_2Cl_2 (70 mL) at -78 ^oC was added $(COCl)_2$ (5.93 mL; 2M in CH_2Cl_2; 11.9 mmol) dropwise and the resulting solution was stirred at -78 ^oC for 30 min. Alcohol **96** (1.55 g; 7.91 mmol) was added dropwise *via* cannula (CH_2Cl_2, 10 mL) and the mixture stirred at -78 ^oC for 45 min before Et_3N (6.62 mL; 47.4 mmol) was added dropwise. The mixture was stirred at -78 ^oC for a further 30 min before warming to 0 ^oC for 30 min and the reaction was quenched by addition of sat. aq. NH_4Cl (160

mL). The product was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts dried (Na_2SO_4) and concentratrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **88** (1.34 g; 87%) as a colourless oil. **R*f*** = 0.37 (100% CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.63 (1H, d, J = 2.0 Hz, C*H*O), 7.28 (2H, d, J = 8.8 Hz, Ar*H*), 6.89 (2H, d, J = 8.4 Hz, Ar*H*), 4.55 (1H, ABq, J = 11.6 Hz, OC*H*$_2$PMP), 3.86 (1H, dq, J = 7.2, 2.0 Hz, C*H*(CH_3)OPMB, 3.80 (3H, s, OC*H*$_3$), 1.30 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)OPMB); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.6, 159.7, 129.7, 129.5, 114.1, 79.2, 71.8, 55.4, 15.4.

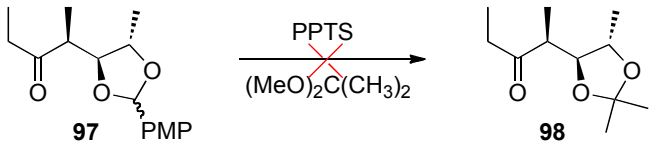


(4*S*,5*S*,6*S*)-5-hydroxy-6-(4-methoxyphenyl)oxy-4,6-dimethyl-heptan-3-one (90), synthesised according to the procedure of Evans *et al.*[17] To a stirred solution of diethyl ketone (**89**) (710 μL; 6.69 mmol) in CH_2Cl_2 (15 mL) at -78 ^{o}C was added $TiCl_4$ (8.03 mL; 1 M in CH_2Cl_2) dropwise and the resulting yellow solution stirred at -78 ^{o}C for 30 min. *i*-Pr_2NEt (1.63 mL; 9.36 mmol) was added dropwise and the resulting red solution was stirred for an additional 1 h before being cooled to -90 ^{o}C and aldehyde **88** (1.30 g; 6.69 mmol) added dropwise *via* cannula (CH_2Cl_2, 3 mL). The reaction mixture was stirred at -90 ^{o}C for 1.5 h, then warmed to 0 ^{o}C and quenched by addition of pH 7 phosphate buffer solution (30 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% Et_2O/CH_2Cl_2) gave aldol adduct **90** (1.66 g; 88%; 86% ds) as a white solid, which could be separated from the minor isomer. **R*f*** = 0.19 (5% Et_2O/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.8 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.55 (1H, d, J = 11.2 Hz, OC*H*$_A$H$_B$PMP), 4.35 (1H, d, J = 11.2 Hz, OCH$_A$*H*$_B$PMP), 3.83 (1H, ddd, J = 7.2, 4.4, 2.8 Hz, C*H*OH), 3.80 (3H, s, OC*H*$_3$), 3.42 (1H, dq, J = 7.2, 6.4 Hz, C*H*(CH_3)OPMB), 2.91 (1H, dq, J = 7.6, 4.4 Hz, C(=O)C*H*(CH_3)CHOH), 2.81 (1H, d, J = 2.8 Hz, O*H*), 2.48 (2H, ABdq, J = 17.6, 7.2 Hz, C(=O)C*H*$_2$CH$_3$), 1.24 (3H,

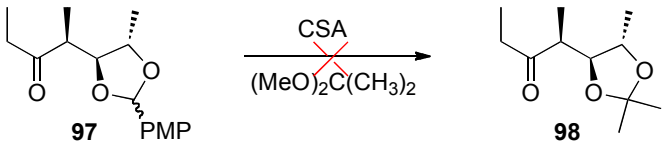
d, J = 6.4 Hz, CH(C*H*$_3$)OPMB), 1.07 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CHOH), 1.02 (3H, t, J = 7.2 Hz, C(=O)CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 216.5, 159.4, 130.6, 129.7, 129.6, 114.0, 74.5, 73.9, 70.4, 55.4, 46.6, 34.9, 15.7, 11.0, 7.8.



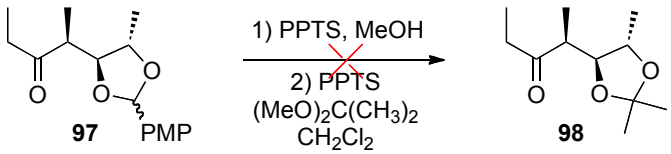
(4*S*,5*S*,6*S*)-4-[2-(4-methyoxyphenyl)-4-methyl-[1,3]dioxan-3-yl]-4-methyl-pentan-3-one (97), synthesised according to the procedure of Paquette *et al*.[20] To a stirred solution of alcohol **90** (106 mg; 378 μmol) in CH_2Cl_2 (6 mL) at 0 °C was added 4 Å molecular sieves (0.9 g), followed by DDQ (453 mg; 103 μmol). The resulting slurry was stirred at 0 °C for 5 h, then filtered through a pad of celite. The filtrate was washed with 1 M NaOH (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% CH_2Cl_2) gave a 2:1 mixture of diastereomers of PMP acetal **97** (80.1 mg; 76%) as a yellow solid. **R*f*** = 0.23 (100% CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) **major isomer:** δ 7.40 (2H, d, J = 8.8 Hz, Ar*H*), 6.90 (2H, d, J = 8.8 Hz, Ar*H*), 6.00 (1H, s, C*H*PMP), 4.43 (1H, dq, J = 6.4, 6.4 Hz, C(-O-)C*H*(CH$_3$)C(-O-)), 4.36 (1H, dd, J = 9.6, 6.4 Hz, CH(CH$_3$)C*H*(-O-)CH(CH$_3$)), 3.81 (3H, s, OC*H*$_3$), 2.84 (1H, dq, J = 9.6, 7.2 Hz, C(=O)C*H*(CH$_3$)CHOH), 2.63 (1H, dq, J = 18.0, 7.2 Hz, C(=O)C*H*$_A$H$_B$CH$_3$), 2.43 (1H, dq, J = 18.0, 7.2 Hz, C(=O)CH$_A$*H*$_B$CH$_3$), 1.32 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)C(-O-)), 1.12 (3H, d, J = 6.0 Hz, C(=O)CH(C*H*$_3$)CHOH), 1.07 (3H, t, J = 7.2 Hz, C(=O)CH$_2$C*H*$_3$); **minor isomer:** δ 7.37 (2H, d, J = 8.8 Hz, Ar*H*), 6.89 (2H, d, J = 8.8 Hz, Ar*H*), 5.17 (1H, s, C*H*PMP), 4.52 (1H, dq, J = 6.4, 5.6 Hz, C(-O-)C*H*(CH$_3$)C(-O-)), 4.37 (1H, dd, J = 9.6, 5.2 Hz, CH(CH$_3$)C*H*(-O-)CH(CH$_3$)), 3.80 (3H, s, OC*H*$_3$), 2.82 (1H, dq, J = 9.6, 7.2 Hz, C(=O)C*H*(CH$_3$)CHOH), 2.62 (1H, dq, J = 18.0, 7.2 Hz, C(=O)C*H*$_A$H$_B$CH$_3$), 2.43 (1H, dq, J = 18.0, 7.2 Hz, C(=O)CH$_A$*H*$_B$CH$_3$), 1.33 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)C(-O-)), 1.10 (3H, d, J = 6.8 Hz, C(=O)CH(C*H*$_3$)CHOH), 1.07 (3H, t, J = 7.2 Hz, C(=O)CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.4, 160.7, 130.1, 128.4, 128.3, 127.7, 114.0, 102.8, 101.7, 80.2, 79.4, 74.3, 74.2, 55.5, 47.1, 46.6, 34.60, 34.57, 16.4, 15.9, 15.8, 14.9, 7.94, 7.91.



(4*S*,5*S*,6*S*)-4,6-dimethyl-5,6-[(bis-dimethyl-methylene)dioxy]-heptan-3-one (98). To a stirred solution of PMP acetal **97** (46.4 mg; 167 μmol) in 2,2-dimethoxypropane (8.3 mL) at rt was added PPTS (8.4 mg; 33.3 μmol) and resulting mixture heated to 60 ^{o}C for 20 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed PMB aldehyde, but no product **98** or starting material **97**.

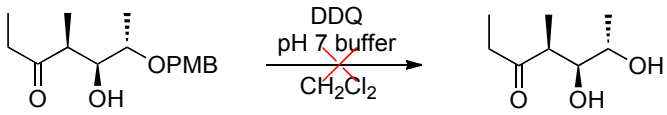


(4*S*,5*S*,6*S*)-4,6-dimethyl-5,6-[(bis-dimethyl-methylene)dioxy]-heptan-3-one (98). To a stirred solution of PMP acetal **97** (55.0 mg; 199 μmol) in 2,2-dimethoxypropane (2 mL) at rt was added CSA (4.6 mg; 19.8 μmol) and resulting mixture was stirred at rt for 1 h. The reaction was quenched with Et_3N (a few drops) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed PMB aldehyde, but no product **98** or starting material **97**.



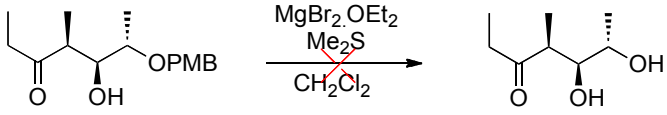
(4*S*,5*S*,6*S*)-4,6-dimethyl-5,6-[(bis-dimethyl-methylene)dioxy]-heptan-3-one (98). To a stirred solution of PMP acetal **97** (37.7 mg; 135 μmol) in MeOH (7 mL) was added PPTS (8.5 mg; 33.9 μmol) and the resulting solution stirred at 70 ^{o}C for 30 min. The mixture was cooled to rt and the solvent removed under a stream of N_2.

The resultant solid was dissolved in CH_2Cl_2 (2.5 mL) and $(MeO)_2C(CH_3)_2$ (2.5 mL) was added, followed by a few crystals of PPTS. The solution was stirred at rt for 15 h before diluting with CH_2Cl_2 (5 mL) and washing with sat. aq. $NaHCO_3$ (5 mL) and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^1H NMR showed PMB aldehyde, but no product **98** or starting material **97**.



90 **99**

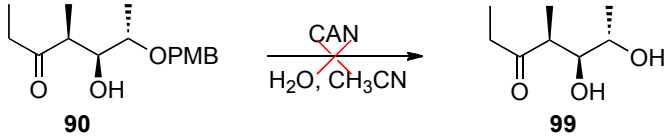
(4*S*,5*S*,6*S*)-5,6-dihydroxy-4,6-dimethyl-heptan-3-one (99), synthesis attempted according to the procedure of Tanemura *et al*.[21] To a stirred solution of PMB ether **90** (104 mg; 372 µmol) in CH_2Cl_2 (19 mL) at 0 ^oC was added pH 7 buffer (3.7 mL), followed by DDQ (127 mg; 559 µmol) and the resulting slurry was stirred at 0 ^oC for 3 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (60 mL). The layers were separated and the organic phase was washed with $NaHCO_3$ (60 mL), H_2O (60 mL) and brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^1H NMR showed that deprotection had not occurred, and instead PMB acetal **97** was produced.



90 **99**

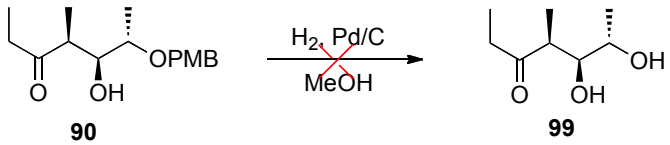
(4*S*,5*S*,6*S*)-5,6-dihydroxy-4,6-dimethyl-heptan-3-one (99), synthesis attempted according to the procedure of Iwasaki *et al*.[22] To a stirred solution of PMB ether **90** (106 mg; 378 µmol) in CH_2Cl_2 (6.3 mL) at rt was added Me_2S (278 µL; 3.78 mmol) and powdered $MgBr_2.OEt_2$ (293 mg; 1.13 mmol) and mixture was stirred at rt for 24 h. The reaction was quenched by addition of sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and

concentrated *in vacuo*. Crude ^{1}H NMR showed a complex mixture of products that could not be separated.



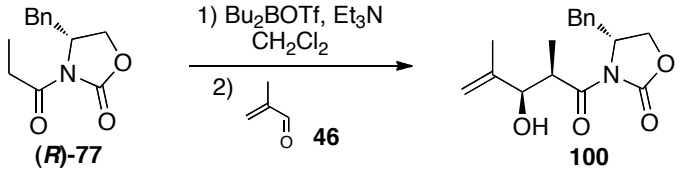
90 **99**

(4*S*,5*S*,6*S*)-5,6-dihydroxy-4,6-dimethyl-heptan-3-one (99), synthesis attempted according to a procedure modified from Wang *et al*.[23] To a stirred solution of PMB ether **90** (60.0 mg; 214 μmol) in a 5:1 solution of CH_3CN/H_2O (3 mL) at rt was added CAN (352 mg; 642 μmol) and the mixture was stirred at rt for 12 h. The reaction was cooled to 0 ^oC, quenched by addition of 1 M HCl (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed that no reaction had occurred, returning PMB ether **90**.

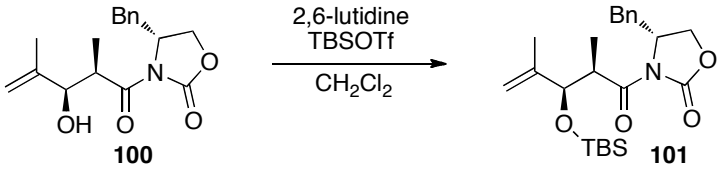


90 **99**

(4*S*,5*S*,6*S*)-5,6-dihydroxy-4,6-dimethyl-heptan-3-one (99). A solution of PMB ether **90** (32.3 mg; 115 μmol) and 10% Pd/C (3.2 mg; 10% w/w) in MeOH (1.2 mL) under an atmosphere of H_2 was stirred at rt for 12 h. The reaction micture was then filtered through celite (Et_2O) and concentrated *in vacuo*. Crude ^{1}H NMR showed that no reaction had occurred, returning PMB ether **90**.

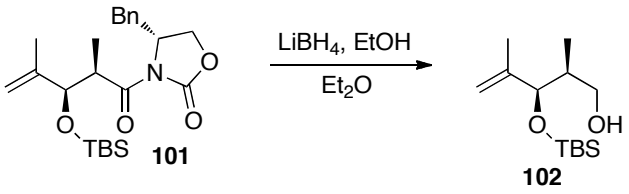


[[3-(2*R*,3*R*)-4*R*]-3-(3-hydroxy-2,4-dimethyl-1-oxo-pent-4-enyl)-4-(phenylmethyl)]-2-oxazolidinone (100). The previous procedure used for the preparation of aldol adduct **78** was followed with oxazolidinone **(*R*)-77** (2.05 g; 8.78 mmol), Bu_2BOTf (10.5 mL; 1 M in CH_2Cl_2; 10.5 mmol), Et_3N (1.59 mL; 11.4 mmol), methacrolein (**46**) (1.45 mL; 17.6 mmol) and CH_2Cl_2 (18 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **100** (2.61 g; 98%, >98% ds) as a white solid. **R*f*** = 0.31 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = -19.6 (c 1.12, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*) 7.22-7.19 (2H, m, Ar*H*), 5.12 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.97 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.71 (1H, m, C*H*CH_2O), 4.42 (1H, s, C*H*OH), 4.23 (1H, dd, J = 9.6, 9.2 Hz, CHCH_AH$_B$O), 4.19 (1H, dd, J = 8.8, 3.2 Hz, CHCH_A*H*$_B$O), 3.98 (1H, dq, J = 7.2, 3.2 Hz, CH(OH)C*H*(CH_3)C=O), 3.27 (1H, dd, J = 13.6, 3.6 Hz, CH_AH$_B$Ph), 2.94 (1H, br s, O*H*), 2.80 (1H, dd, J = 13.2, 9.2 Hz, CH_A*H*$_B$Ph), 1.74 (3H, s, CH_2C(CH_3)CHOH), 1.19 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.2, 153.1, 143.9, 135.2, 129.6, 129.1, 127.6, 111.9, 74.1, 66.4, 55.4, 40.3, 37.9, 19.5, 10.2.

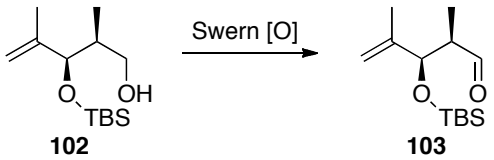


[[3-(2*R*,3*R*)-4*R*]-3-(3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-1-oxo-pent-4-enyl)-4-(phenylmethyl)]-2-oxazolidinone (101). The previous procedure used for the preparation of TBS ether **72** was followed with alcohol **100** (2.67 g; 8.79 mmol), 2,6-lutidine (2.05 mL; 17.6 mmol), TBSOTf (3.03 mL; 13.2 mmol) and CH_2Cl_2 (88 mL). Purification by column chromatography (buffered silica, 20% X4/CH_2Cl_2) gave TBS ether **101** (3.66 g; 100%) as a while solid. **R*f*** = 0.55 20% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = -48.1 (c 1.85, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar*H*), 7.26-7.22 (1H, m,

Ar*H*) 7.21-7.18 (2H, m, Ar*H*), 4.94 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CHOH), 4.83 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CHOH), 4.56 (1H, m, C*H*CH$_2$O), 4.36 (1H, d, J = 6.4 Hz, C*H*OTBS), 4.15-4.08 (2H, m, J = 9.6, 9.2 Hz, CHC*H*$_2$O), 4.03 (1H, dq, J = 6.8, 6.8 Hz, CH(OTBS)C*H*(CH$_3$)C=O), 3.25 (1H, dd, J = 13.6, 3.2 Hz, C*H*$_A$H$_B$Ph), 2.76 (1H, dd, J = 13.6, 9.6 Hz, CH$_A$*H*$_B$Ph), 1.72 (3H, s, CH$_2$C(C*H*$_3$)CHOTBS), 1.21 (3H, d, J = 6.8 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.02 (3H, s, OSi(C*H*$_3$)CH$_3$), -0.01 (3H, s, OSi(CH$_3$)C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 174.9, 153.2, 145.8, 135.5, 129.6, 129.0, 127.5, 112.7, 77.1, 66.1, 55.8, 42.6, 37.8, 25.9, 18.3, 17.9, 12.5, -4.6, -5.2.

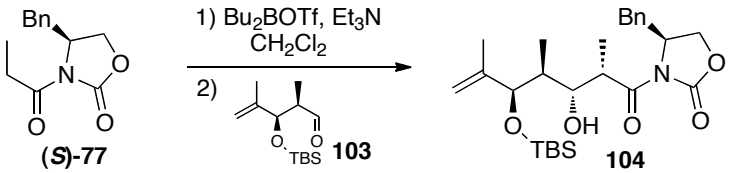


(2*S*,3*R*)-3-(tert-butyldimethylsilyloxy)-2,4-dimethyl-pent-4-en-1-ol (102), synthesised according to the procedure of Penning *et al*.[24] To a stirred solution of oxazolidinone **101** (2.71 g; 6.48 mmol) in Et$_2$O (80 mL) at -10 ^{o}C was added EtOH (911 μL; 15.6 mmol) and LiBH$_4$ (15.6 mL; 1 M in THF; 15.6 mmol) and the resulting mixture was stirred at -10 ^{o}C for 4 h. The reaction mixture was warmed to 0 ^{o}C and quenched by addition of 1 M NaOH (50 mL). The mixture was poured into brine (50 mL) and extracted with Et$_2$O (4 x 50 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et$_2$O/CH$_2$Cl$_2$) gave alcohol **102** (1.24 g; 78%) as a colourless oil. **R*f*** = 0.47 (5% Et$_2$O/CH$_2$Cl$_2$); **[α]$^{20}_D$** = +17.9 (c 1.45, CHCl$_3$); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 4.93 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CHOH), 4.87 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CHOH), 4.05 (1H, d, J = 5.6 Hz, C*H*OTBS), 3.57 (1H, dd, J = 10.4, 6.8 Hz, C*H*$_A$H$_B$OH), 3.47 (1H, dd, J = 10.8, 5.2 Hz, CH$_A$*H*$_B$OH), 2.01 (1H, br s, O*H*), 1.89-1.80 (1H, m, C*H*(CH$_3$)CH$_2$OH), 1.70 (3H, s, CH$_2$C(C*H*$_3$)CHOTBS), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.86 (3H, d, J = 6.8Hz, CH(C*H*$_3$)CH$_2$OH), 0.06 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.00 (3H, s, OSi(CH$_3$)C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 146.6, 112.1, 78.3, 66.0, 39.7, 26.0, 18.8, 18.3, 12.1, -4.5, -5.1.



102 103

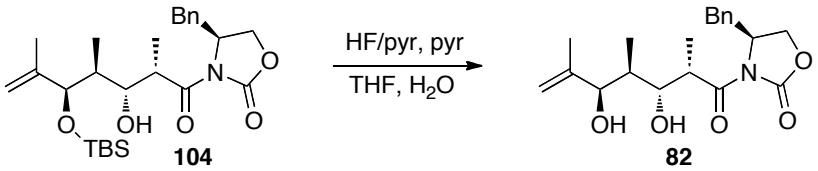
(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-pent-4-enal (103). The previous procedure used for the preparation of aldehyde **88** was followed with alcohol **102** (1.17 g; 4.77 mmol), DMSO (1.02 mL; 14.3 mmol), $(COCl)_2$ (3.58 mL; 7.16 mmol), Et_3N (3.99 mL; 28.6 mmol) and CH_2Cl_2 (48 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **103** as a colourless oil. **R*f*** = 0.40 (100% CH_2Cl_2); **[α]$^{20}_{D}$** = +32.9 (c 1.10, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.69 (1H, d, J = 1.6 Hz, C*H*O), 4.97 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.91 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.40 (1H, d, J = 4.8 Hz, C*H*OTBS), 2.47 (1H, ddq, J = 6.8, 4.8, 1.6, C*H*(CH_3)CHO), 1.68 (3H, s, CH_2C(CH_3)CHOTBS), 1.04 (3H, d, J = 6.8 Hz, CH(CH_3)CHO), 0.87 (9H, s, OSiC(CH_3)$_3$), 0.03 (3H, s, OSi(CH_3)CH_3), 0.00 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 115.0, 113.1, 76.0, 53.6, 50.7, 25.9, 18.6, 8.5, -4.4, -5.1.



(*S*)-77 103 104

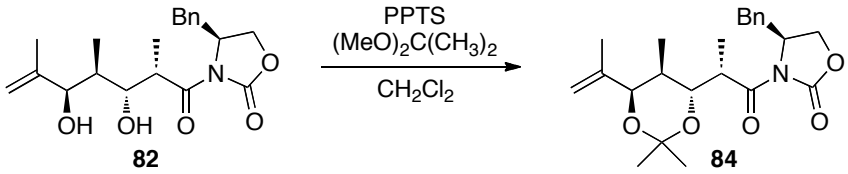
[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4,6-trimethyl-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (104). The previous procedure used for the preparation of aldol adduct **78** was followed with oxazolidinone **(*S*)-77** (1.62 mg; 6.93 mmol), Bu_2BOTf (8.32 mL; 1 M in CH_2Cl_2; 8.32 mmol), Et_3N (1.26 mL; 9.01 mmol), aldehyde **103** (1.41 g; 5.82 mmol) and CH_2Cl_2 (15 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldol adduct **104** (1.81 g; 65%, >98% ds) as a clear, colourless oil. **R*f*** = 0.40 (100% CH_2Cl_2); **[α]$^{20}_{D}$** = +32.9 (c 1.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.35-7.31 (2H, m, Ar*H*), 7.29-7.24 (1H, m, Ar*H*), 7.22-7.19 (2H, m, Ar*H*), 5.02 (1H, m, (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.91 (1H, m, CH_AH$_B$C(CH_3)CHOH), 4.72 (1H, m, $CHCH_2O$), 4.48

(1H, d, s, C*H*OTBS), 4.23-4.15 (2H, m, CHCH_2O), 3.90-3.87 (1H, m, C*H*OH), 3.86 (1H, dq, J = 7.2, 2.0 Hz, CH(OH)C*H*(CH_3)C=O), 3.53 (1H, br s, O*H*), 3.27 (1H, dd, J = 13.6, 3.6 Hz, C$H_A$$H_B$Ph), 2.79 (1H, dd, J = 13.6, 9.6 Hz, $CH_A$$H_B$Ph), 1.70 (3H, s, CH_2C(CH_3)CHOTBS), 1.24 (3H, d, J = 6.8 Hz, CH(OTBS)CH(CH_3)COH), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.77 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)C=O), 0.09 (3H, s, OSi(CH_3)CH_3), 0.01 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) 178.1, 153.0, 146.1, 135.3, 129.6, 129.1, 127.6, 111.8, 75.0, 72.0, 66.4, 55.4, 40.1, 39.2, 38.0, 26.2, 20.3, 18.4, 9.5, -4.4, -5.1; **IR** (film, cm^{-1}) 3534, 3064, 3029, 2928, 2884, 2856, 1785, 1681, 1498, 1471, 1454, 1386, 1286, 1243, 1209, 1116, 1068, 1021, 967, 937, 854, 835, 775, 738, 701, 673, 653.

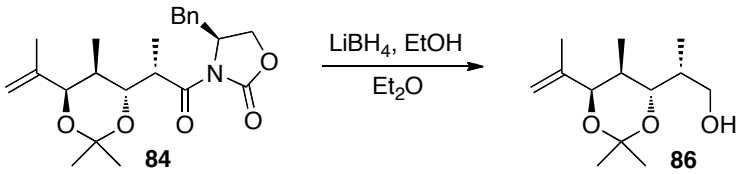


[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(3,5-dihydroxy-2,4,6-trimethyl-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (82). To a Teflon cylinder containing TBS ether **104** (37.7 mg; 79.3 μmol) was added buffered pyridinium hydrofluoride (570 μL from a stock solution containing dry THF (10 mL), pyridine (5 mL), pyridinium hydrofluoride (2.1 g)) and H_2O (61 μL). The resulting solution was stirred at rt for 5 days, then diluted with Et_2O (15 mL), washed with sat. aq. $CuSO_4$ (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 20% Et_2O/CH_2Cl_2) gave diol **82** (27.0 mg; 94%) as a white foam. **R*f*** = 0.19 (20% Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = +38.5 (c 1.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.21-7.18 (2H, m, Ar*H*), 5.03 (1H, m, C$H_A$$H_B$C($CH_3$)CHOH), 4.94 (1H, m, $CH_A$$H_B$C($CH_3$)CHOH), 4.69 (1H, m, C*H*CH_2Ph), 4.48 (1H, br s, CH_2C(CH_3)C*H*OH), 4.24-4.16 (2H, m, CHCH_2O), 3.99-3.96 (1H, m, CH(OH)C*H*(CH_3)C=O), 3.94 (1H, dd, J = 6.8, 3.6 Hz, C*H*(OH)CH(CH_3)C=O), 3.59 (1H, br s, O*H*), 3.25 (1H, dd, J = 13.6, 4.8 Hz, C$H_A$$H_B$Ph), 2.80 (1H, dd, J = 13.6, 9.6 Hz, $CH_A$$H_B$Ph), 2.51 (1H, br s, O*H*), 1.84 (1H, ddq, J = 7.6, 7.2, 2.4 Hz, CH(OH)C*H*(CH_3)CHOH), 1.68 (3H, s, CH_2C(CH_3)CHOH), 1.30

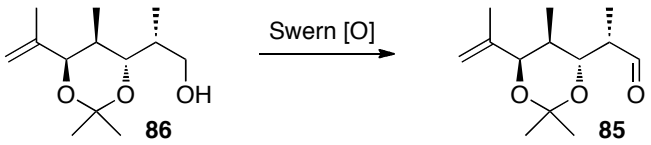
(3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)C=O), 0.82 (3H, d, J = 6.8 Hz, CH(OH)CH(C*H*$_3$)C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) 178.0, 153.1, 146.4, 135.2, 129.7, 129.2, 127.7, 110.5, 74.3, 73.7, 66.5, 55.4, 40.2, 38.0, 37.5, 20.3, 10.9, 9.8; **IR** (film, cm^{-1}) 3446, 3087, 3063, 3028, 2974, 2920, 1779, 1694, 1604, 1497, 1454, 1387, 1289, 1210, 1107, 1048, 1009, 983, 900, 844, 762, 702, 667.



[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (84). To a stirred solution of 1,3-diol **82** (199 mg; 551 μmol) in CH_2Cl_2 (9 mL) was added 2,2-dimethoxypropane (9 mL) and a few crystals of PPTS and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave acetonide **84** (219 mg; 99%) as a clear, colourless oil. **R*f*** = 0.48 (100% CH_2Cl_2); **[α]$^{20}_D$** = +75.7 (c 1.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.28-7.26 (1H, m, Ar*H*), 7.25-7.21 (2H, m, Ar*H*), 4.99 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CH(-O-)), 4.86 (1H, m, CH$_A$*H*$_B$C(CH$_3$)CH(-O-)), 4.64 (1H, m, C*H*CH$_2$Ph), 4.21 (1H, d, J = 4.0 Hz, CH$_2$C(CH$_3$)C*H*(-O-)), 4.19-4.14 (2H, m, CHC*H*$_2$O), 4.07 (1H, dq, J = 6.8, 4.8 Hz, CH(-O-)C*H*(CH$_3$)C=O), 3.63 (1H, dd, J = 6.8, 4.8 Hz, C*H*(-O-)CH(CH$_3$)C=O), 3.32 (1H, dd, J = 13.6, 12.8 Hz, C*H*$_A$H$_B$Ph), 2.77 (1H, dd, J = 13.6, 10.0 Hz, CH$_A$*H*$_B$Ph), 2.04 (1H, m, CH(-O-)C*H*(CH$_3$)CH(-O-)), 1.65 (3H, s, CH$_2$C(C*H*$_3$)CHOH), 1.34 (3H, s, C(C*H*$_3$)CH$_3$), 1.32 (3H, s, C(CH$_3$)C*H*$_3$), 1.30 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.81 (3H, d, J = 6.8 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.0, 153.3, 142.3, 135.5, 129.6, 129.1, 127.5, 110.4, 100.8, 75.6, 71.6, 66.2, 55.9, 41.4, 37.9, 35.6, 25.3, 24.0, 19.9, 12.6, 12.0.

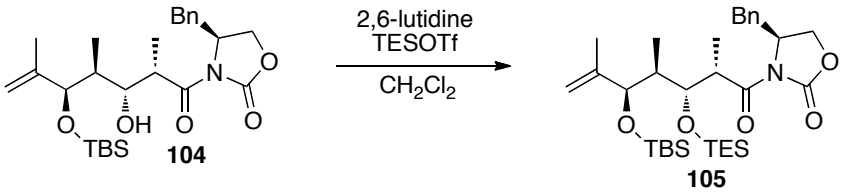


(2*R*,3*S*,4*S*,5*R*)-2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-hept-6-en-1-ol (86). The previous procedure used for the preparation of alcohol **102** was followed with oxazolidinone **84** (91.9 mg; 229 μmol), EtOH (47 μL; 802 μmol), $LiBH_4$ (401 μL; 2 M in THF; 802 mmol) and Et_2O (3 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **86** (44.5 mg; 85%) as a white solid. **R*f*** = 0.52 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = +35.3 (c 1.11, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.98 (1H, s, C*H*$_A$H$_B$C(CH_3)CH(-O-)), 4.86 (1H, m, CH$_A$*H*$_B$C(CH_3)CH(-O-)), 4.17 (1H, d, J = 4.4 Hz, CH_2C(CH_3)C*H*(-O-)), 3.68 (1H, dd, J = 10.4, 6.0 Hz, C*H*$_A$H$_B$OH), 3.63 (1H, dd, J = 10.8, 4.4 Hz, CH$_A$*H*$_B$OH), 3.51 (1H, dd, J = 7.6, 2.8 Hz, C*H*(-O-)CH(CH_3)CH_2OH), 2.51 (1H, br s, O*H*), 1.99 (1H, ddq, J = 7.2, 6.8, 4.8 Hz, CH(-O-)C*H*(CH_3)CH(-O-)), 1.89-1.82 (1H, m, C*H*(CH_3)CH_2OH), 1.65 (3H, s, CH_2C(C*H*$_3$)CH(-O-)), 1.36 (3H, s, C(C*H*$_3$)CH_3), 1.31 (3H, s, C(CH_3)C*H*$_3$), 0.99 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2OH), 0.70 (3H, d, J= 6.8 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.2, 110.3, 100.9, 77.1, 71.8, 67.1, 37.8, 34.8, 25.3, 23.8, 20.0, 12.8, 10.9; **IR** (film, cm^{-1}) 3394, 3094, 2968, 2927, 2875, 1651, 1459, 1381, 1296, 1273, 1241, 1225, 1199, 1176, 1142, 1121, 1100, 1030, 1008, 955, 931, 904, 849, 806, 761, 747, 734, 657.



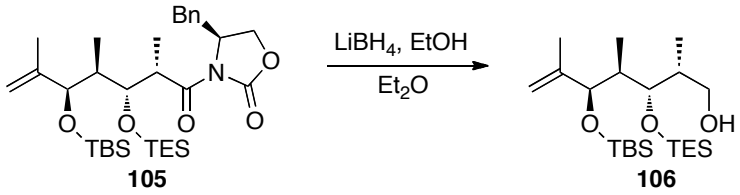
(2*S*,3*R*,4*S*,5*R*)-2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-hept-6-enal (85). The previous procedure used for the preparation of aldehyde **88** was followed with alcohol **86** (55.1 mg; 241 μmol), DMSO (51 μL; 724 μmol), $(COCl)_2$ (31 μL; 362 μmol), Et_3N (202 μL; 1.45 mmol) and CH_2Cl_2 (2.4 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **85** (54.6 mg; 100%) as a colourless oil. **R*f*** = 0.47 (100% CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (1H, d, J =

0.8 Hz, C*H*O), 4.99 (1H, m, CH_AH$_B$CH(CH$_3$)CH(-O-)), 4.87 (1H, m, CH$_A$$H_B$CH(CH$_3$)CH(-O-)), 4.19 (1H, d, J = 4.8 Hz, CH$_2$C(CH$_3$)C*H*(-O-)), 3.77 (1H, dd, J = 7.6, 3.6 Hz, C*H*(-O-)CH(CH$_3$)CHO), 2.44 (1H, ddq, J = 7.2, 3.2 1.2 Hz, C*H*(CH$_3$)CHO), 2.02 (1H, ddd, J = 8.0, 6.8, 4.8 Hz, CH(-O-)C*H*(CH$_3$)CH(-O-)), 1.65 (3H, m, CH$_2$CH(CH_3)CH(-O-)), 1.34 (3H, s, C(CH_3)CH$_3$), 1.29 (3H, s, C(CH$_3$)CH_3), 1.16 (3H, d, J = 7.2 Hz, CH(CH_3)CHO), 0.75 (3H, d, J = 6.4 Hz, CH(-O-)CH(CH_3)CH(-O-)); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 204.2, 141.9, 110.5, 101.1, 73.9, 71.6, 49.2, 35.2, 24.9, 23.7, 19.9, 12.5, 8.0.



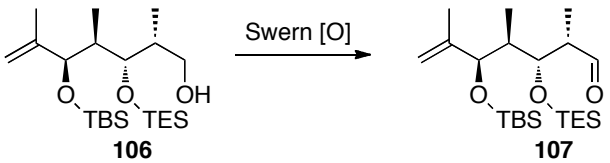
[[3-(2*S*,3*R*,4*S*,5*R*)-4*S*]-3-(5-(*tert*-butyldimethylsilyloxy)-3-triethylsilyloxy-2,4,6-trimethyl-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (105). The previous procedure used for the preparation of TBS ether **72** was followed with alcohol **104** (474 mg; 997 mmol), 2,6-lutidine (232 μL; 1.99 mmol), TESOTf (338 μL; 1.50 μmmol) and CH$_2$Cl$_2$ (10 mL). Purification by column chromatography (buffered silica, 20% CH$_2$Cl$_2$/X4) gave TES ether **105** (548 mg; 93%) as a colourless oil. **R*f*** = 0.66 (20% CH$_2$Cl$_2$/X4); **[α]$^{20}_D$** = +32.5 (c 0.96, CHCl$_3$); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.22-7.20 (2H, m, Ar*H*), 4.79 (2H, br s, CH_2C(CH$_3$)CHOTBS), 4.64 (1H, m, C*H*CH$_2$Ph), 4.17-4.13 (2H, m, CHCH_2O), 4.09 (1H, dd, J = 4.4, 3.6 Hz, C*H*OTES), 3.94-3.87 (CH(OTBS)C*H*(CH$_3$)CHOTBS), 3.92 (1H, d, J = 8.0 Hz, C*H*OTBS), 3.24 (1H, dd, J = 13.2, 3.2 Hz, CH_AH$_B$Ph), 2.75 (1H, dd, J = 13.6, 9.6 Hz, CH$_A$$H_B$Ph), 1.82-1.77 (1H, dq, J = 6.8, 3.6 Hz, CH(OTES)C*H*(CH$_3$)C=O), 1.67 (3H, s, CH$_2$C(CH_3)CHOTBS), 1.22 (3H, d, J = 6.8 Hz, CH(OTBS)CH(CH_3)CHOTES), 1.03 (3H, d, J = 8.0 Hz, CH(OTES)CH(CH_3)C=O), 1.00 (9H, t, J = 8.4 Hz, OSi(CH$_2$CH_3)$_3$), 0.88 (9H, s, OSi(CH_3)$_3$), 0.68 (6H, q, J = 8.4 Hz, , OSi(CH_2CH$_3$)$_3$), 0.04 (3H, s, OSi(CH_3)CH$_3$), -0.02 (3H, s, OSi(CH$_3$)CH_3); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 176.7, 152.9, 147.5, 135.4, 129.6, 129.1, 127.5, 112.9, 78.0, 73.0, 66.1, 55.4, 44.2, 40.4, 37.9, 26.0, 18.4, 17.3, 14.5, 12.8, 7.2, 6.9, 6.6, 5.6, -4.4, -4.8; **IR** (film, cm^{-1}) 3067, 3029, 2877, 2360, 1782, 1701,

1652, 1498, 1456, 1386, 1349, 1288, 1209, 1056, 1005, 970, 939, 903, 868, 836, 739, 702, 669.



105 **106**

(2*R*,3*S*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-3-triethylsilyloxy-2,4,6-trimethyl-1-hept-6-en-1-ol (106). The previous procedure used for the preparation of alcohol **102** was followed with oxazolidinone **105** (109 mg; 185 μmol), EtOH (26 μL; 445 μmol), $LiBH_4$ (222 μL; 2 M in THF; 445 mmol) and Et_2O (2.3 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave alcohol **106** (46.3 mg; 60%) as a white solid. **R*f*** = 0.50 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -14.9 (c 1.01, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.86-4.84 (2H, m, C*H*$_2$C(CH_3)CHOTBS), 3.84 (1H, d, J = 8.4 Hz, C*H*OTBS), 3.69 (1H, dd, J = 4.4, 1.2 Hz, C*H*OTES), 3.45 (1H, dd, J = 6.0, 4.4 Hz, C*H*$_A$H$_B$OH), 3.40 (1H, dd, J = 10.4, 6.4 Hz, CH$_A$*H*$_B$OH), 1.84 (1H, m, C*H*(CH_3)CH_2OH), 1.78 (1H, ddq, J = 13.6, 6.8, 2.4 Hz, CH(OTBS)C*H*(CH_3)CHOTES), 1.71 (3H, m, CH_2C(C*H*$_3$)CHOTBS), 1.44 (1H, br s, O*H*), 1.00 (3H, d, J = 6.8 Hz, CH(OTBS)CH(C*H*$_3$)CHOTES), 0.96 (9H, t, J = 8.0 Hz, OSi(CH_2C*H*$_3$)$_3$), 0.93 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CH_2OH), 0.88 (9H, s, OSi(C*H*$_3$)$_3$), 0.60 (6H, q, J = 8.0 Hz, OSi(C*H*$_2$$CH_3$)$_3$), 0.05 (3H, s, OSi(C*H*$_3$)$CH_3$), -0.01 (3H, s, OSi($CH_3$)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.2, 113.1, 79.5, 72.0, 68.0, 44.2, 37.3, 26.0, 18.4, 17.0, 11.9, 11.8, 7.1, 5.5, -4.3, -4.8.

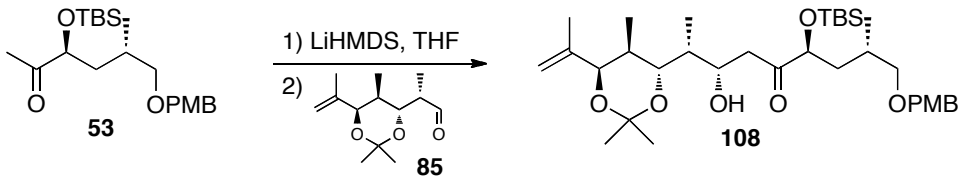


106 **107**

(2*S*,3*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-3-triethylsilyloxy-2,4,6-trimethyl-1-hept-6-en-1-ol (107). The previous procedure used for the preparation of aldehyde

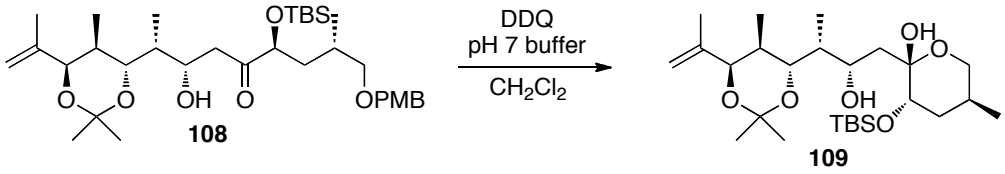
88 was followed with alcohol **106** (46.3 mg; 111 μmol), DMSO (24 μL; 333 μmol), $(COCl)_2$ (83 μL; 2M in CH_2Cl_2; 167 μmol), Et_3N (93 μL; 666 μmol) and CH_2Cl_2 (1.2 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **107** (46.1 mg; 100%) as a colourless oil. **R*f*** = 0.81 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +11.0 (c 2.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.57 (1H, d, J = 1.2 Hz, C*H*O), 4.87 (1H, m, CH_AH$_B$C(CH_3)CHOTBS), 4.81 (1H, m, CH$_A$$H_B$C($CH_3$)CHOTBS), 4.16 (1H, dd, J = 4.8, 2.4 Hz, C*H*OTES), 3.83 (1H, d, J = 7.6 Hz, C*H*OTBS), 2.44 (1H, ddq, J = 7.6, 2.4, 0.8 Hz, C*H*(CH_3)CHO), 1.88 (1H, ddq, J = 7.6, 7.2, 4.4 Hz, CH(OTBS)C*H*(CH_3)CHOTES), 1.72 (3H, m, CH_2C(CH_3)CHOTBS), 1.13 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CHOTES), 0.99 (3H, d, J = 7.6 Hz, CH(CH_3)CHO), 0.93 (9H, t, J = 7.6 Hz, OSi(CH_2CH_3)$_3$), 0.89 (9H, s, OSi(CH_3)$_3$), 0.56 (6H, q, J = 8.0 Hz, OSi(C$H_2$$CH_3$)$_3$), 0.04 (3H, s, OSi(C$H_3$)$CH_3$), -0.01 (3H, s, OSi($CH_3$)C$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 146.6, 113.3, 78.9, 70.0, 48.9, 44.2, 26.0, 18.4, 17.3, 11.5, 8.9, 7.0, 5.3, -4.3, -4.8.

4.2.3 Model Aldol Coupling



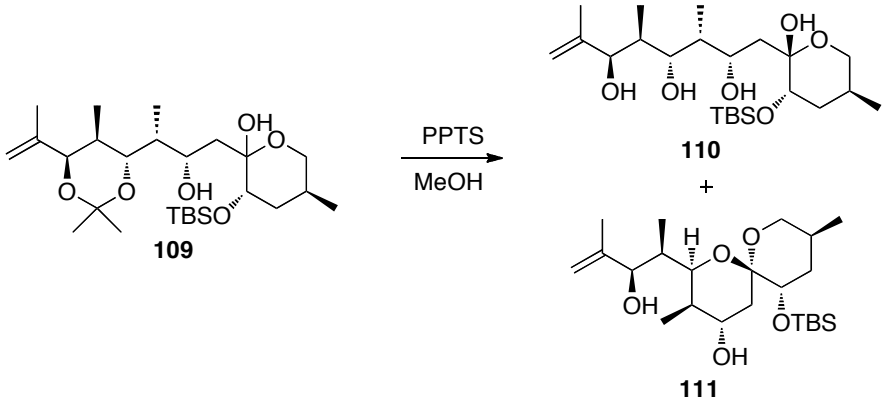
(2*S*,4*S*,7*S*,8*R*,9*S*,10*S*,11*R*)-4-(*tert*-butyldimethylsilyloxy)-1-(4-methoxyphenyl)oxy-7-hydroxy-2,8,10,12-tetramethyl-9,11-[(bis-dimethyl-methylene)dioxy]-tridec-12-en-5-one (108). To a stirred solution of ketone **53** (16.1 mg; 42.3 μmol) in THF (0.5 mL) at -78 ^oC was added LiHMDS (64 μL; 1M in THF; 64 μmol) dropwise and the mixture stirred at -78 ^oC for 1 h. Aldehyde **85** (12.5 mg; 55 μmol) was added dropwise *via* cannula and the reaction mixture was stirred at -78 ^oC for 5 h. The reaction mixture was diluted with Et_2O (5 mL) and quenched with $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 30% Et_2O/X4) gave aldol

adduct **108** (8.7 mg; 34%, 75% ds). **R*f*** = 0.15 (30% Et_2O/X4); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.98 (1H, s $CH_AH_BCCH_3$), 4.86 (1H, s, $CH_AH_BCCH_3$), 4.41 (2H, ABq, J = 12 Hz, OCH_2PMP), 4.23 (1H, m, C*H*OH), 4.16 (1H, d, J = 4.2 Hz, $CH_2C(CH_3)CH$(-O-)$CHCH_3$), 4.11 (1H, dd, J = 9.0, 4.2 Hz, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.53 (1H, dd, J = 7.8, 2.4 Hz, $CH(CH_3)CH$(-O-)$CH(CH_3)$CHOH), 3.30 (1H, d, J = 0.6 Hz, O*H*), 3.28 (1H, dd, J = 9.6, 6.0 Hz, CH_AH_BOPMB), 3.25 (1H, dd, J = 9.6, 6.6 Hz, CH_AH_BOPMB), 2.77 (1H, dd, J = 18.0, 8.4 Hz, CH(OH)CH_AH_BC=O), 2.69 (1H, dd, J = 13.2, 4.8 Hz, CH(OH)CH_AH_BC=O), 2.01-1.95 (1H, m, CH(-O-)$CH(CH_3)$CH(-O-)), 1.99-1.93 (1H, m, $CH(CH_3)CH_2$OPMB), 1.73 (1H, ddd, J = 13.8, 9.0, 4.8 Hz, CH_AH_BCH$(CH_3)CH_2$OPMB), 1.66 (3H, s, $CH_2C(CH_3)$CH(-O-)), 1.66-1.62 (1H, m, CH(-O-)$CH(CH_3)$CHOH), 1.38 (3H, s, $C(CH_3)CH_3$), 1.34 (1H, ddd, J = 13.8, 9.0, 4.2 Hz, CH_AH_BCH$(CH_3)CH_2$OPMB), 1.31 (3H, s, $C(CH_3)CH_3$), 1.00 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOH), 0.95 (3H, d, J = 7.2 Hz, $CH(CH_3)CH_2$OPMB), 0.92 (9H, s, $OSiC(CH_3)_3$), 0.72 (3H, d, J = 6.6 Hz, CH(-O-)CH(CH_3)CH(-O-)), 0.06 (3H, s, $OSi(CH_3)CH_3$), 0.03 (3H, s, $OSi(CH_3)CH_3$).



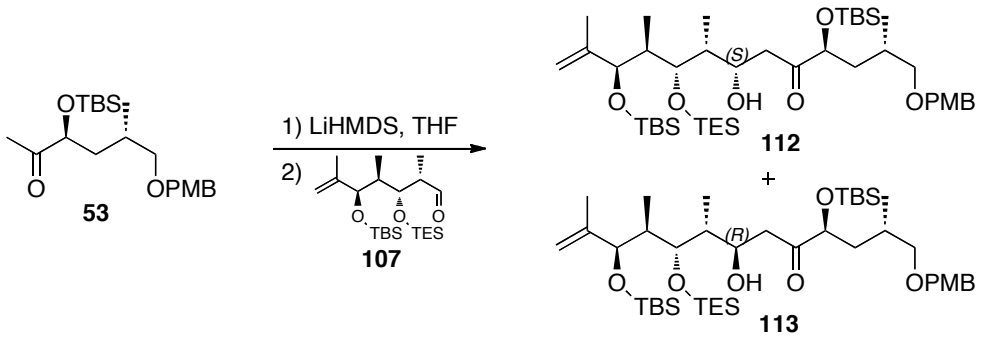
(2*S*,3*S*,5*S*)-2-[(2*S*,3*R*,4*S*,5*S*,6*R*)-2-hydroxy-3,5,7-trimethyl-oct-7-enyl]-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-4-methyl-4,6-[(bis-dimethyl-methylene)dioxy]-tetrahydro-2*H*-pyran-4-ol (109). The previous procedure used for the attempted preparation of alcohol **99** was followed with PMB ether **108** (8.7 mg; 14.3 μmmol), DDQ (4.9 mg; 35.6 μmol), pH 7 buffer (181 μL) and CH_2Cl_2 (0.7 mL). Purification by column chromatography (buffered silica, 2.5% Et_2O/CH_2Cl_2) gave hemiacetal **109** (3.9 mg; 56%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.51 (1H, s, $CH_2C(OH)$(-O-)CHOTBS), 4.98 (1H, s, $CH_AH_BCCH_3$), 4.87 (1H, m, $CH_AH_BCCH_3$), 4.48 (1H, d, J = 11.4 Hz, CH_2CCH_3CH(-O-)$CHCH_3$), 4.15 (1H, d, J = 4.2 Hz, CHO*H*), 3.64-3.59 (1H, m, CH(OTBS)$CH_2CH(CH_3)CH_AH_B$O), 3.62-3.58 (1H, m, $CH(CH_3)CH$(OH)CH_2C(OH)(-O-)), 3.56 (1H, dd, J = 3.6, 2.4 Hz, C*H*OTBS), 3.54 (1H, ddd, J = 10.2, 4.8, 1.8 Hz,

CH(OTBS)CH_2CH(CH_3)CH_AH_BO), 2.14-2.05 (1H, m, CH(OTBS)CH_2C*H*(CH_3)CH_2O), 2.02-1.97 (1H, m, CH(-O-)C*H*(CH_3)CH(-O-)), 1.90 (1H, m, CH(OTBS)CH_AH_BCCH_3), 1.73 (1H, ddd, J = 13.8, 12.6, 2.4 Hz, CH(OTBS)CH_AH_BCCH_3), 1.65 (3H, s, CH_2CCH_3), 1.63 (1H, dd, J = 14.4, 11.4 Hz, CH(CH_3)C*H*(-O-)CH(CH_3)CHOH), 1.42 (3H, s, C(CH_3)CH_3), 1.32 (3H, s, C(CH_3)CH_3), 1.01 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOH), 0.90 (9H, s, OSiC(CH_3)$_3$), 0.78 (3H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(CH_3)CH_2O), 0.69 (3H, d, J = 6.6 Hz, CH(-O-)CH(CH_3)CH(-O-)), 0.07 (3H, s, OSi(CH_3)CH_3), 0.06 (3H, s, OSi(CH_3)CH_3).



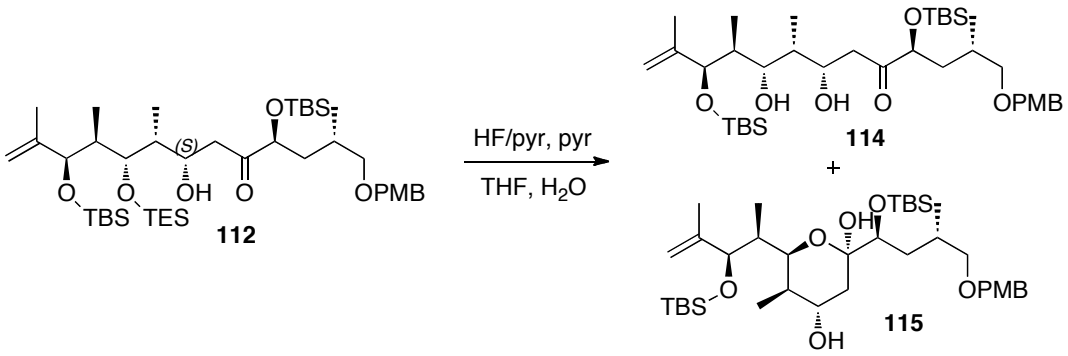
(2*S*,3*S*,5*S*)-2-[(2*S*,3*R*,4*S*,5*S*,6*R*)-4-(3-(*tert*-butyldimethylsilyloxy)-2,4,6-trihydroxy-3,5,7-trimethyl-oct-7-enyl]-2-hydroxy-4-methyl-tetrahydro-2*H*-pyran-4-ol (110) and **(2*S*,3*R*,4*S*,7*R*,9*S*,11*S*)-2-[(1*R*,2*R*)-2-hydroxy-1,3-dimethyl-but-3-enyl]-11-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,9-dimethyl-1,7-dioxaspiro[6,6]undecane (111).** To a stirred solution of acetonide **109** (3.3mg; 6.8 μmol) in MeOH (1 mL) at rt was added a few crystals of PPTS and the mixture stirred at rt for 14 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue (2.9 mg) was a 1:1 mixture of hemiacetal **110**/spiroacetal **111**. **Spiroacetal 111: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.00 (1H, m, CH_AH_BCCH_3), 4.93 (1H, m, CH_AH_BCCH_3), 4.34 (1H, d, J = 11.4 Hz, CH_2CCH_3C*H*(-O-)CHCH_3), 4.06 (1H, ddd, J = 9.6, 1.8, 1.2 Hz, CH(-O-)CH(CH_3)C*H*(OH)CH_2), 3.93 (1H, dd, J = 10.2, 2.4 Hz, CH(CH_3)C*H*(-O-)CH(CH_3)CHOH), 3.54 (1H, m, C*H*OTBS), 3.51 (1H, ddd, J = 10.8, 4.8, 2.4 Hz, CH(OTBS)CH_2CH(CH_3)CH_AH_BO), 3.17 (1H, m, CH(OTBS)CH_2CH(CH_3)CH_AH_BO), 2.31 (1H, dd, J = 15.0, 9.0 Hz, CH(-O-)CH(CH_3)CH(OH)CH_AH_B), 2.17-2.10 (1H, m,

CH(OTBS)CH_2C*H*(CH_3)CH_2O), 1.86-1.82 (1H, m, CH_2C(CH_3)CH(OH)C*H*(CH_3)CH(-O-)), 1.81 (1H, s, CH_2CCH_3CH(O*H*)CCH_3), 1.71 (3H, s, CH_2C(C*H*$_3$)CHOH), 1.65-1.62 (1H, m, CH(OTBS)C*H*$_A$H$_B$CHCH_3), 1.57 (1H, m, CH(OTBS)CH_A*H*$_B$CHCH_3), 1.38 (1H, m, CH(-O-)CH(CH_3)CH(OH)C*H*$_A$H$_B$), 1.38 (1H, s, CH(-O-)CH(CH_3)CH(O*H*)CH_2), 1.32 (1H, m, CH(-O-)C*H*(CH_3)CH(OH)CH_2), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.87 (3H, d, J = 6.6 Hz, CH(-O-)CH(C*H*$_3$)CH(OH)CH_2), 0.74 (3H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(C*H*$_3$)CH_2O), 0.70 (3H, d, J = 7.2 Hz, CH_2C(CH_3)CH(-O-)CH(C*H*$_3$)CH(-O-)), 0.13 (3H, s, OSi(C*H*$_3$)CH_3), 0.06 (3H, s, OSi(CH_3)C*H*$_3$); **Hemiacetal 110: ^{1}H NMR** (600MHz, $CDCl_3$) δ 5.09 (1H, s, CH_2C(O*H*)(-O-)CHOTBS), 5.00 (1H, m, C*H*$_A$H$_B$CCH_3), 4.93 (1H, m, CH_A*H*$_B$CCH_3), 4.64 (1H, ddd, J = 10.8, 1.8, 1.8 Hz, CH(CH_3)C*H*(OH)CH_2), 4.34 (1H, m, CH_2CCH_3C*H*(OH)CHCH_3), 3.98 (1H, dd, J = 9.6, 1.8 Hz, CH(OH)CH(CH_3)C*H*(OH)CH(CH_3)CHOH), 3.70 (1H, dd, J = 3.0, 2.4 Hz, C*H*OTBS), 3.56-3.53 (2H, m, CH(OTBS)CH_2CH(CH_3)C*H*$_2$O), 2.12-2.05 (1H, m, CH(OTBS)CH_2C*H*(CH_3)CH_2O), 2.00 (1H, d, J = 5.4 Hz, CH_2C(CH_3)CHO*H*), 1.88-1.84 (1H, m, CH(OH)C*H*$_A$H$_B$C(OH)(-O-)), 1.86-1.82 (1H, m, CH_2C(CH_3)CH(OH)C*H*CH_3), 1.69 (3H, s, CH_2C(C*H*$_3$)CHOH), 1.69-1.66 (1H, m, CH(OH)CH_A*H*$_B$C(OH)(-O-)), 1.67-1.64 (1H, m, CH(OTBS)C*H*$_A$H$_B$CH(CH_3)CH_2O), 1.57 (1H, m, CH(OTBS)CH_A*H*$_B$CH(CH_3)CH_2O), 1.55 (1H, s, CH(OH)CH(CH_3)CH(O*H*)CH(CH_3)CHOH), 1.38 (1H, m, CH(OH)C*H*(CH_3)CH(OH)CH_2C(OH)(-O-)), 1.37 (1H, s, CH(O*H*)CH_2C(OH)(-O-)), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.87 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH(OH)CH_2C(OH)(-O-)), 0.77 (3H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(C*H*$_3$)CH_2O), 0.68 (3H, d, J = 7.2 Hz, CH_2C(CH_3)CH(OH)CH(C*H*$_3$)CHOH), 0.07 (3H, s, OSi(C*H*$_3$)CH_3), 0.06 (3H, s, OSi(CH_3)C*H*$_3$).



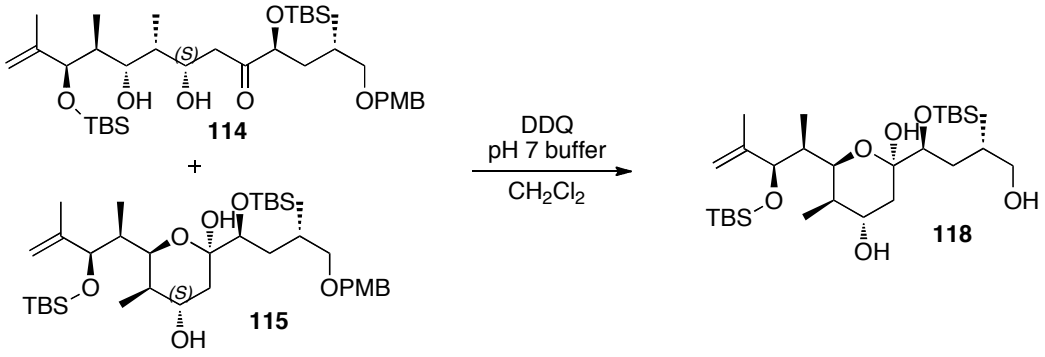
(2*S*,4*S*,7*S*,8*R*,9*S*,10*S*,11*R*)-4,11-bis(*tert*-butyldimethylsilyloxy)-9-triethylsilyloxy-7-hydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-tridec-12-en-5-one (112) and **(2*S*,4*S*,7*R*,8*R*,9*S*,10*S*,11*R*)-4,11-bis(*tert*-butyldimethylsilyloxy)-9-triethylsilyloxy-7-hydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-tridec-12-en-5-one (113).** The previous procedure used for the preparation of aldol adduct **118** was followed with ketone **53** (42.3 mg; 111 µmol), aldehyde **107** (46.1 mg; 111 µmol), LiHMDS (167 µL; 167 µmol) and THF (0.5 mL). Purification by column chromatography (buffered silica, 15% Et_2O/X4) gave aldol adduct **112** (21.8 mg; 25%) and aldol adduct **113** (8.8 mg; 10%). **Major isomer 112: R*f*** = 0.28 (15% Et_2O/X4); **$[\alpha]^{20}_D$** = -22.1 (c 1.04, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz, Ar*H*), 6.86 (2H, d, J = 8.4 Hz, Ar*H*), 4.86 (2H, s, CH_2C(CH)$_3$CHOTBS), 4.41 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.10 (1H, dd, J = 9.0, 4.8 Hz, C(=O)C*H*OTBS), 4.05 (1H, m, C*H*OH), 3.80 (1H, d, J = 9.0 Hz, CH_2C(CH_3)C*H*OTBS), 3.80 (3H, s, OCH_3), 3.78 (1H, dd, J = 4.2, 2.4 Hz, C*H*OTES), 3.28 (1H, dd, J = 9.0, 6.0 Hz, CH_AH$_B$OPMB), 3.25 (1H, dd, J = 9.0, 6.6 Hz, CH$_A$$H_B$OPMB), 2.95 (1H, d, J = 1.8 Hz, O*H*), 2.65-2.64 (2H, m, CH(OH)CH_2C(=O)), 1.94-1.89 (1H, m, C*H*(CH_3)CH_2OPMB), 1.89-1.85 (1H, m, CH(OTBS)C*H*(CH_3)CHOTES), 1.71 (1H, ddd, J = 13.8, 9.0, 4.8 Hz, CH_AH$_B$CH(CH_3)CH_2OPMB), 1.70 (3H, s, CH_2C(CH_3)CHOTBS), 1.67-1.64 (1H, m, CH(OTES)C*H*(CH_3)CHOH), 1.31 (1H, ddd, J = 13.8, 9.0, 4.2 Hz, CH$_A$$H_B$CH($CH_3$)$CH_2$OPMB), 0.99 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CHOTES), 0.96 (9H, t, J = 7.8 Hz, OSi(CH_2CH_3)$_3$), 0.95 (3H, d, J = 6.6 Hz, CH(CH_3)CH_2OPMB), 0.93 (3H, d, J = 7.2 Hz, CH(OTES)CH(CH_3)CHOH), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.87 (9H, s, OSiC(CH_3)$_3$), 0.62 (6H, q, J = 8.8 Hz, OSi($CH_2$$CH_3$)$_3$), 0.05 (3H, s, OSi(C$H_3$)$CH_3$), 0.04 (3H, s, OSi($CH_3$)C$H_3$), 0.03 (3H, s, OSi(C$H_3$)$CH_3$), -0.02 (3H, s, OSi($CH_3$)C$H_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 213.5, 159.2, 146.4, 130.8, 113.8, 79.2, 75.5, 72.6, 71.7, 55.4,

43.9, 42.1, 38.7, 38.4, 34.8, 31.7, 29.5, 27.1, 26.0, 25.9, 25.4, 22.8, 20.8, 18.4, 18.3, 17.0, 16.8, 14.3, 12.5, 8.6, 7.1, 5.6, -4.4, -4.6, -4.8, -4.9; **IR** (film, cm^{-1}) 3539, 2955, 2857, 1711, 1613, 1513, 1463, 1408, 1361, 1302, 1249, 1171, 1093, 1057, 1005, 939, 905, 837, 776, 741, 671; **HRESIMS** calculated for $C_{43}H_{82}O_7Si_3Na^+$: 817.5261; found: 817.5265. **Minor isomer 113: R*f*** = 0.22 (15% Et_2O/X4); **$[\alpha]^{20}_D$** = 0.00 (c 0.44, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 4.90 (1H, s, C$H_A$$H_B$C($CH_3$)CHOTBS), 4.84 (1H, s, C$H_A$$H_B$C($CH_3$)CHOTBS), 4.41 (2H, ABq, J = 12.0 Hz, OCH_2PMP), 4.10 (1H, dd, J = 9.0, 4.2 Hz, C(=O)C*H*OTBS), 4.03 (1H, dd, J = 5.4, 4.8 Hz, C*H*OTES), 3.87 (1H, d, J = 7.2 Hz, CH_2C(CH_3)C*H*OTBS), 3.80 (3H, s, OCH_3), 3.77 (1H, ddd, J = 8.4, 4.8, 1.8 Hz, C*H*OH), 3.27 (1H, dd, J = 9.6, 6.0 Hz, C$H_A$$H_B$OPMB), 3.24 (1H, dd, J = 9.0, 6.0 Hz, C$H_A$$H_B$OPMB), 3.09 (1H, d, J = 4.8 Hz, O*H*), 2.75 (1H, dd, J = 18.0, 2.4 Hz, CH(OH)C$H_A$$H_B$C(=O)), 2.59 (1H, dd, J = 18.0, 9.0 Hz, CH(OH)C$H_A$$H_B$C(=O)), 1.97-1.91 (1H, m, C*H*(CH_3)CH_2OPMB), 1.83-1.77 (1H, m, CH(OTBS)C*H*(CH_3)CHOTES), 1.74 (1H, ddd, J = 13.2, 9.0, 4.8 Hz, C$H_A$$H_B$CH($CH_3$)$CH_2$OPMB), 1.70 (3H, s, CH_2C(CH_3)CHOTBS), 1.70-1.66 (1H, m, CH(OTES)C*H*(CH_3)CHOH), 1.31 (1H, ddd, J = 13.8, 9.0, 4.8 Hz, C$H_A$$H_B$CH($CH_3$)$CH_2$OPMB), 0.95 (9H, t, J = 10.8 Hz, OSi(CH_2CH_3)$_3$), 0.95 (3H, d, J = 6.6 Hz, CH(CH_3)CH_2OPMB), 0.94 (3H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CHOTES), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.88 (9H, s, OSiC(CH_3)$_3$), 0.84 (3H, d, J = 6.6 Hz, CH(OTES)CH(CH_3)CHOH), 0.62 (6H, q, J = 7.8 Hz, OSi(C$H_2$$CH_3$)$_3$), 0.05 (6H, s, OSi(C$H_3$)$_2$), 0.03 (3H, s, OSi(C$H_3$)$CH_3$), -0.01 (3H, s, OSi($CH_3$)C$H_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 215.4, 159.2, 146.8, 130.8, 129.3, 113.8, 129.3, 113.8, 113.0, 78.4, 75.4, 72.6, 71.1, 70.4, 55.4, 43.9, 41.2, 39.6, 38.5, 29.5, 26.1, 25.9, 18.4, 18.2, 17.6, 16.9, 11.6, 11.2, 7.2, 5.6, -4.1, -4.6, -4.7, -4.9; **IR** (film, cm^{-1}) 3526, 3072, 2955, 2857, 1706, 1652, 1613, 1587, 1513, 1462, 1408, 1387, 1361, 1302, 1249, 1171, 1090, 939, 904, 836, 776, 741, 669, 407; **HRESIMS** calculated for $C_{43}H_{82}O_7Si_3Na^+$: 817.5261; found: 817.5258.



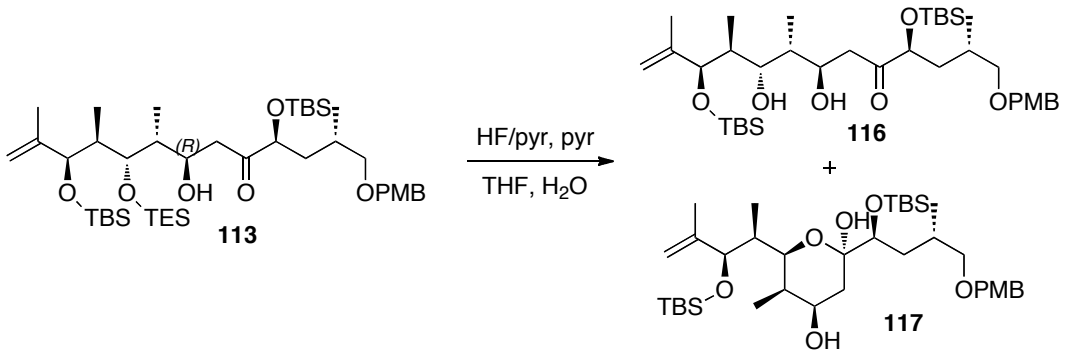
(2*S*,4*S*,7*S*,8*R*,9*S*,10*S*,11*R*)-4,11-bis(*tert*-butyldimethylsilyloxy)-7,9-dihydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-tridec-12-en-5-one (114) and **(2*R*,4*S*,5*R*,6*S*)-2-[(1*S*,3*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(4-methoxyphenyl)oxy-3-methyl-butanyl]-5-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylbut-3-enyl]-2,4-dihydroxy-4-methyl-tetrahydro-2*H*-pyran (115).** The previous procedure used for the preparation of **82** was followed with TES ether **112** (20.8 mg; 26.2 µmol), HF/pyr/pyr (300 µL) and H_2O (20 µL) at rt for 4 h. Purification by column chromatography (buffered silica, 2.5% Et_2O/CH_2Cl_2) gave a 2:1 mixture of hemiacetal **115**/diol **114** (6.8 mg). **R*f*** = 0.29 (2.5% Et_2O/CH_2Cl_2); **Hemiacetal 115: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 4.98 (1H, m, C*H*$_A$H$_B$C(CH$_3$)CHOTBS), 4.86 (1H, m, CH$_A$*H*$_B$C(CH$_3$)CHOTBS), 4.43 (2H, ABq, J = 11.4 Hz, OC*H*$_2$PMP), 4.41 (1H, s, CH$_2$C(-O-)(O*H*)CHOTBS), 4.13 (1H, dd, J = 10.2, 2.4 Hz, CH(CH$_3$)C*H*(-O-)CH(CH$_3$)CHOH), 3.92 (1H, dddd, J = 6.6, 3.0, 3.0, 3.0 Hz, C*H*OH), 3.82 (1H, d, J = 1.2 Hz, CH$_2$C(CH$_3$)C*H*OTBS), 3.81 (3H, s, OC*H*$_3$), 3.55 (1H, dd, J = 7.8, 3.6 Hz, C*H*(OTBS)CH$_2$CH(CH$_3$)CH$_2$OPMB), 3.39 (1H, d, J = 7.2 Hz, CHO*H*), 3.26 (1H, dd, J = 9.0, 6.0 Hz, C*H*$_A$H$_B$OPMB), 3.22 (1H, dd, J = 9.0, 6.6 Hz, CH$_A$*H*$_B$OPMB), 2.05-1.99 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.89 (1H, ddd, J = 13.8, 3.0, 0.6 Hz, CH(OH)C*H*$_A$H$_B$C(-O-)OH), 1.81-1.76 (1H, m, CH(-O-)C*H*(CH$_3$)CHOH), 1.64 (3H, s, CH$_2$C(C*H*$_3$)CHOTBS), 1.63 (1H, ddd, J = 13.8, 3.0, 1.2 Hz, CH(OH)CH$_A$*H*$_B$C(-O-)OH), 1.62-1.59 (1H, m, CH(OTBS)C*H*(CH$_3$)CH(-O-)), 1.52 (1H, ddd, J = 14.4, 9.6, 4.2 Hz, C*H*$_A$H$_B$CH(CH$_3$)CH$_2$OPMB), 1.47 (1H, ddd, J = 13.8, 7.2, 4.8 Hz, CH$_A$*H*$_B$CH(CH$_3$)CH$_2$OPMB), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.90 (3H, d, J = 7.8 Hz, CH(C*H*$_3$)CH$_2$OPMB), 0.89 (9H, s, OSiC(C*H*$_3$)$_3$), 0.84 (3H, d, J = 6.6 Hz, CH(-O-)CH(C*H*$_3$)CHOH), 0.73 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH(-O-)), 0.10 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.09 (3H, s, OSi(CH$_3$)C*H*$_3$), 0.08 (3H, s, OSi(C*H*$_3$)CH$_3$), -0.03 (3H, s,

OSi(CH_3)C*H*$_3$); **Diol 114: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (3H, d, J = 8.4 Hz, Ar*H*), 4.98 (1H, m, C*H*$_A$H$_B$C(CH_3)CHOTBS), 4.91 (1H, m, CH$_A$*H*$_B$C(CH_3)CHOTBS), 4.41 (2H, ABq, J = 12.0 Hz, OC*H*$_2$PMP), 4.40 (1H, s, O*H*), 4.26 (1H, d, J = 10.2 Hz, C*H*(OH)CH_2C=O), 4.12 (1H, dd, J = 13.2, 4.2 Hz, C(=O)C*H*OTBS), 4.00 (1H, s, O*H*), 3.80 (3H, s, OC*H*$_3$), 3.77 (1H, d, J = 9.6 Hz, C*H*(OTBS)CH(CH_3)CHOH), 3.69 (1H, d, J = 1.2 Hz, CH(CH_3)C*H*(OH)CHCH_3), 3.26-2.25 (2H, m, C*H*$_2$OPMB), 2.80 (1H, dd, J = 18.0, 9.6 Hz, CH(OH)C*H*$_A$H$_B$C=O), 2.65 (1H, dd, J = 18.0, 3.0 Hz, CH(OH)CH$_A$*H*$_B$C=O), 1.98-1.93 (1H, m, C*H*(CH_3)CH_2OPMB), 1.75 (1H, ddd, J = 13.8, 9.0, 4.8 Hz, CH(OTBS)C*H*$_A$H$_B$CHCH_3), 1.72 (3H, s, CH_2C(C*H*$_3$)CHOTBS), 1.68 (1H, m, CH(OTBS)C*H*(CH_3)CHOH), 1.54 (1H, m, CH(OH)C*H*(CH_3)CHOH), 1.34 (1H, ddd, J = 13.8, 9.6, 4.8 Hz, CH(OTBS)CH$_A$*H*$_B$CHCH_3), 0.95 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH_2OPMB), 0.92 (9H, s, OSiC(C*H*$_3$)$_3$), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.89 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)CHOH), 0.66 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CHOH), 0.09 (3H, s, OSi(C*H*$_3$)CH_3), 0.06 (3H, s, OSi(CH_3)C*H*$_3$), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), 0.00 (3H, s, OSi(CH_3)C*H*$_3$); **Mixture: ^{13}C NMR** (151 MHz, $CDCl_3$) δ 215.2, 159.2, 159.1, 147.1, 146.2, 130.9, 130.7, 129.3, 129.2, 113.9, 113.8, 111.8, 110.9, 99.1, 76.3, 76.0, 75.6, 75.4, 73.1, 73.0, 72.6, 71.8, 67.1, 55.4, 42.4, 39.9, 38.7, 38.3, 38.2, 37.6, 36.1, 30.0, 29.5, 26.3, 26.2, 26.1, 25.9, 20.5, 20.3, 18.5, 18.4, 18.2, 17.3, 17.0, 10.5, 10.2, 7.9, 4.8, -3.3, -3.7, -4.4, -4.5, -4.6, -4.6, -4.8, -5.1.



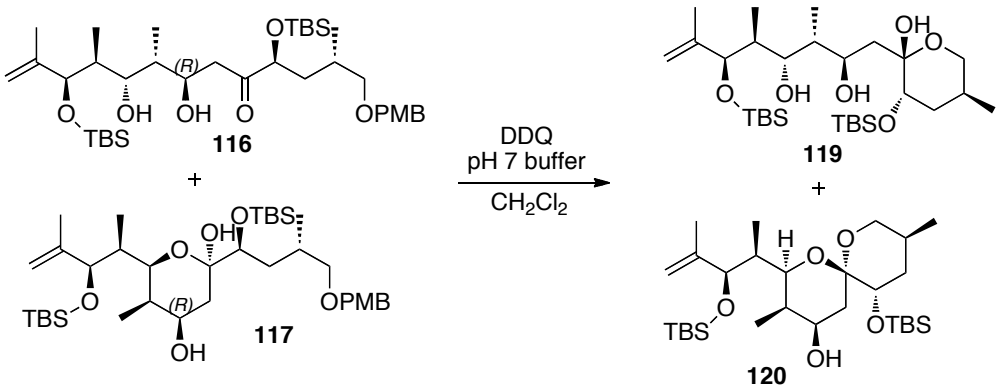
(2*R*,4*S*,5*R*,6*S*)-2-[(1*S*,3*S*)-1-(*tert*-butyldimethylsilyloxy)-3methyl-butan-4-ol]-5-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethyl-but-3-enyl]-2,4-dihydroxy-4-methyl-tetrahydro-2*H*-pyran (118). The previous procedure used for the preparation of hemiacetal **109** was followed with hemiacetal **115**/diol **114** mixture

(6.8 mg), DDQ (3.4 mg; 15.0 µmol), pH 7 buffer (120 µL) and CH_2Cl_2 (0.5 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave hemiacetal **118** (5.1 mg). **R*f*** = 0.41 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.82 (1H, s, $CH_2C(OH)$(-O-)CHOTBS), 4.98 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.90 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.56 (1H, s, $CH(CH_3)CH(OH)CH_2C(OH)$(-O-)), 4.54 (1H, d, J = 10.8 Hz, $CH(CH_3)CH(OH)CH_2C(OH)$(-O-)), 4.51 (1H, s, CH_2OH), 4.21 (1H, d, J = 3.6 Hz, $CH_2C(CH_3)CH$OTBS), 3.93 (1H, d, J = 10.2 Hz, $CH(CH_3)CH$(-O-)$CHCH_3$), 3.62 (1H, dd, J = 11.4, 11.4 Hz, CH_AH_BOH), 3.56 (1H, m, CH(OTBS)$CH_2CH(CH_3)CH_2OH$), 3.54 (1H, ddd, J = 11.4, 10.8, 1.2 Hz, CH_AH_BOH), 2.11-2.06 (1H, m, $CH(CH_3)CH_2OH$), 1.92-1.88 (1H, m, CH(OTBS)$CH(CH_3)$CH(-O-)), 1.83 (1H, d, J = 13.8 Hz, CH(OH)$CH_AH_BC(OH)$(-O-)), 1.79 (3H, s, $CH_2C(CH_3)$CHOTBS), 1.73 (1H, ddd, J = 14.4, 13.8, 2.4 Hz, CH(OTBS)$CH_AH_BCH(CH_3)CH_2OH$), 1.66 (1H, dd, J = 13.8, 11.4 Hz, $CH(OH)CH_AH_BC(OH)$(-O-)), 1.58 (1H, m, CH(OTBS)$CH_AH_BCH(CH_3)CH_2OH$), 1.37 (1H, m, CH(-O-)$CH(CH_3)$CHOH), 0.90 (3H, d, J = 6.6 Hz, CH(-O-)$CH(CH_3)$CHOH), 0.89 (9H, s, $OSiC(CH_3)_3$), 0.89 (9H, s, $OSiC(CH_3)_3$), 0.78 (3H, d, J = 6.6 Hz, $CH(CH_3)CH_2OH$), 0.69 (3H, d, J = 6.6 Hz, CH(OTBS)$CH(CH_3)$CH(-O-)), 0.08 (3H, s, $OSi(CH_3)CH_3$), 0.07 (3H, s, $OSi(CH_3)CH_3$), 0.06 (3H, s, $OSi(CH_3)CH_3$), 0.03 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.4, 114.1, 97.0, 81.4, 79.7, 73.7, 71.2, 67.1, 40.7, 39.1, 35.5, 29.9, 24.3, 22.9, 20.1, 18.2, 18.2, 17.2, 14.3, 13.4, 4.2, -4.5, -4.5, -4.8, -5.3; **HRESIMS** calculated for $C_{29}H_{60}O_6Si_2Na^+$: 583.3821; found: 583.3820.



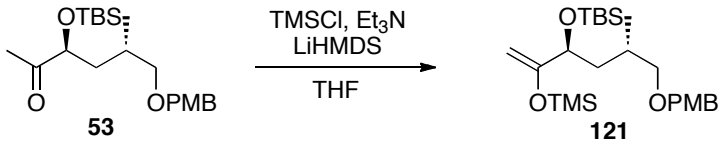
(2*S*,4*S*,7*R*,8*R*,9*S*,10*S*,11*R*)-4,11-bis(*tert*-butyldimethylsilyloxy)-7,9-dihydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-tridec-12-en-5-one (116) and **(2*R*,4*R*,5*R*,6*S*)-2-[(1*S*,3*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(4-methoxyphenyl)oxy-3-methyl-butanyl]-5-[(1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethyl-but-3-enyl]-2,4-dihydroxy-4-methyl-tetrahydro-2*H*-pyran (117).** The previous procedure used for the preparation of alcohol **82** was followed with TES ether **113** (8.7 mg; 10.9 μmol), HF/pyr/pyr (80 μL) and H_2O (9 μL) at rt for 4 h. Purification by column chromatography (buffered silica, 10% Et_2O/CH_2Cl_2) gave a a 1:2 mixture of hemiacetal **117**/diol **116** (3.7 mg). **R*f*** = 0.29 (10% Et_2O/CH_2Cl_2); **Hemiacetal 117: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.98 (1H, s, CH_AH$_B$C(CH_3)CHOTBS), 4.91 (1H, s, CH$_A$$H_B$C($CH_3$)CHOTBS), 4.40 (2H, ABq, J = 12.0 Hz, OCH_2PMP), 4.40 (1H, s, CH_2C(-O-)(O*H*)CHOTBS), 4.11 (1H, dd, J = 8.4, 4.2 Hz, CH(CH_3)C*H*(-O-)CH(CH_3)CHOH), 4.09 (1H, dddd, J = 7.8, 3.6, 3.6, 3.6 Hz, C*H*OH), 3.93 (1H, d, J = 9.6 Hz, CH_2C(CH_3)C*H*OTBS), 3.80 (3H, s, OCH_3), 3.57 (1H, m, C*H*(OTBS)CH_2CH(CH_3)CH_2OPMB), 3.51 (1H, d, J = 3.6 Hz, CHO*H*), 3.28 (1H, dd, J = 9.0, 6.0 Hz, CH_AH$_B$OPMB), 3.26 (1H, m, CH$_A$$H_B$OPMB), 1.94 (1H, m, C*H*(CH_3)CH_2OPMB), 1.74 (1H, ddd, J = 13.2, 9.0, 4.2 Hz, CH_AH$_B$CH(CH_3)CH_2OPMB), 1.73 (3H, s, CH_2C(CH_3)CHOTBS), 1.67 (1H, m, CH(-O-)C*H*(CH_3)CHOH), 1.54 (1H, m, CH(OTBS)C*H*(CH_3)CH(-O-)), 1.54 (1H, m, CH(OH)CH_AH$_B$C(-O-)OH) 1.46 (1H, dd, J = 9.0, 4.2 Hz, CH(OH)CH$_A$$H_B$C(-O-)OH), 1.33 (1H, ddd, J = 13.2, 8.4, 4.2 Hz, CH$_A$$H_B$CH($CH_3$)$CH_2$OPMB), 0.98 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CH(-O-)), 0.96 (3H, d, J = 7.8 Hz, CH(CH_3)CH_2OPMB), 0.92 (9H, s, OSiC(CH_3)$_3$), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.66 ((3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOH), 0.08 (3H, s, OSi(CH_3)CH_3), 0.05 (3H, s, OSi(CH_3)CH_3), 0.02 (3H, s, OSi(CH_3)CH_3), 0.01 (3H, s, OSi(CH_3)CH_3); **Diol 116: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 9.0 Hz, Ar*H*),

6.87 (3H, d, J = 8.4 Hz, Ar*H*), 4.97 (1H, s, C*H*$_A$H$_B$C(CH$_3$)CHOTBS), 4.83 (1H, s, CH$_A$*H*$_B$C(CH$_3$)CHOTBS), 4.43 (2H, ABq, J = 12.0 Hz, OC*H*$_2$PMP), 4.40 (1H, s, CH(OTBS)CH(CH$_3$)CH(O*H*)CHCH$_3$), 4.31 (1H, s, CH(O*H*)CH$_2$C=O), 4.22 (1H, m, CH$_2$C(CH$_3$)C*H*OTBS), 4.12 (1H, dd, J = 8.4, 4.2 Hz, C*H*(OH)CH$_2$C=O), 3.80 (3H, s, OC*H*$_3$), 3.75 (1H, dd, J = 10.2, 1.8 Hz, CH(OTBS)CH(CH$_3$)C*H*(OH)CHCH$_3$), 3.58 (1H, dd, J = 7.2, 3.6 Hz, C(=O)C*H*OTBS), 3.26 (1H, dd, J = 12.6, 6.6 Hz, C*H*$_A$H$_B$OPMB), 3.22 (1H, dd, J = 9.0, 6.0 Hz, CH$_A$*H*$_B$OPMB), 2.78 (2H, m, CH(OH)C*H*$_2$C=O), 2.03 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.94 (1H, m, CH(OTBS)C*H*(CH$_3$)CHOH), 1.60 (1H, m, CH(OH)C*H*(CH$_3$)CHOH), 1.64 (3H, s, CH$_2$C(C*H*$_3$)CHOTBS), 1.53-1.46 (2H, m, CH(OTBS)C*H*$_2$CHCH$_3$), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.89 (9H, s, OSiC(C*H*$_3$)$_3$), 0.88 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH$_2$OPMB), 0.81 (3H, d, J = 7.2 Hz, CH(OTBS)C*H*(CH$_3$)CHOH), 0.74 (3H, d, J = 6.6 Hz, CH(OH)CH(C*H*$_3$)CHOH), 0.10 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.08 (3H, s, OSi(CH$_3$)C*H*$_3$), 0.03 (3H, s, OSi(C*H*$_3$)CH$_3$), -0.05 (3H, s, OSi(CH$_3$)C*H*$_3$).

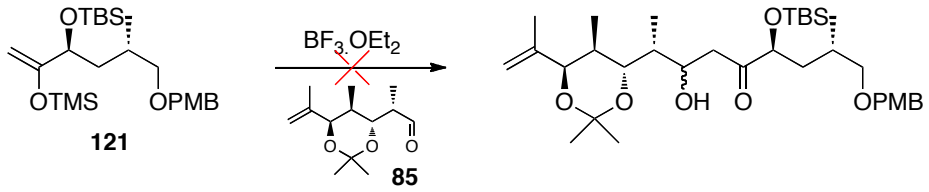


(2*S*,3*S*,5*S*)-2-[(2*S*,3*R*,4*S*,5*S*,6*R*)-4-(6-(*tert*-butyldimethylsilyloxy)-2,4-dihydroxy-3,5,7-trimethyl-oct-7-enyl]-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-4-methyl-tetrahydro-2*H*-pyran-4-ol (119) and **(2*S*,3*R*,4*R*,7*R*,9*S*,11*S*)-2-[(1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethyl-but-3-enyl]-11-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,9-dimethyl-1,7-dioxaspiro[6,6]undecane (120).** The previous procedure used for the preparation of hemiacetal **109** was followed with hemiacetal **117**/diol **116** mixture (3.7 mg), DDQ (1.8 mg; 8.15 µmol), pH 7 buffer (65 µL) and CH_2Cl_2 (0.3 mL). Purification by column chromatography (buffered silica, 10% Et_2O/X4) gave a 1:1 mixture of hemiacetal **119**/spiroacetal **120** (1.8 mg). **Hemiacetal 119: ^{1}H NMR**

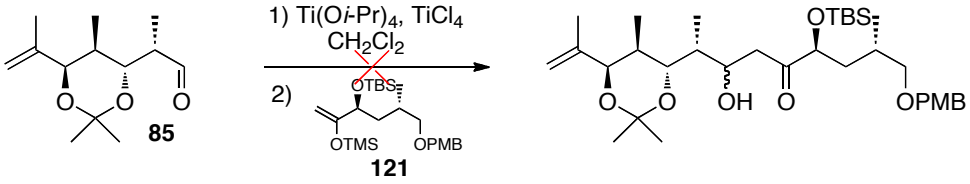
(600 MHz, $CDCl_3$) δ 5.21 (1H, s, $CH_2C(OH)$(-O-)CHOTBS), 4.96 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.91 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.52 (1H, s, CH(OTBS)$CH(CH_3)CH(OH)CHCH_3$), 4.47 (1H, d, J = 7.8 Hz, $CH(CH_3)CH(OH)CH_2C(OH)$(-O-)), 4.25 (1H, d, J = 3.6 Hz, $CH_2C(CH_3)CH$OTBS), 4.07 (1H, d, J = 9.6 Hz, CH(OTBS)$CH(CH_3)CH(OH)CHCH_3$), 3.85 (1H, m, $CH(CH_3)CH(OH)CH_2C(OH)$(-O-)), 3.75 (1H, m, C(OH)(-O-)C*H*(OTBS)CH_2CHCH_3), 3.60 (1H, dd, J = 11.4, 11.4 Hz, CH(OTBS)$CH_2CH(CH_3)CH_AH_BO$), 3.55 (1H, ddd, J = 10.8, 4.8, 1.8 Hz, CH(OTBS)$CH_2CH(CH_3)CH_AH_BO$), 2.10 (1H, m, CH(OTBS)$CH_2CH(CH_3)CH_2O$), 2.04 (1H, d, J = 13.8 Hz, CH(OH)$CH_AH_BC(OH)$(-O-)), 1.92-1.87 (1H, m, CH(OTBS)$CH(CH_3)CHOH$), 1.86 (1H, dd, J = 7.2, 2.4 Hz, $CH(OH)CH_AH_BC(OH)$(-O-)), 1.79 (1H, m, CH(OTBS)$CH_AH_BCH(CH_3)CH_2O$), 1.78 (3H, s, $CH_2C(CH_3)$CHOTBS), 1.65 (1H, m, CH(OTBS)$CH_AH_BCH(CH_3)CH_2O$), 1.04 (3H, d, J = 6.6 Hz, $CH(OH)CH(CH_3)CHOH$), 0.90 (9H, s, $OSiC(CH_3)_3$), 0.88 (9H, s, $OSiC(CH_3)_3$), 0.79 (3H, d, J = 6.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH_2O$), 0.66 (3H, d, J = 6.6 Hz, $CH(OTBS)CH(CH_3)CHOH$), 0.08 (3H, s, $OSi(CH_3)CH_3$), 0.08 (3H, s, $OSi(CH_3)CH_3$), 0.03 (3H, s, $OSi(CH_3)CH_3$), 0.02 (3H, s, $OSi(CH_3)CH_3$); **Spiroacetal 120: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.96 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.92 (1H, s, $CH_AH_BC(CH_3)$CHOTBS), 4.37 (1H, s, $CH_2C(CH_3)CH$OTBS), 4.18 (1H, m, CH(-O-)$CH(CH_3)CH(OH)CH_2$), 4.03 (1H, dd, J = 11.4, 3.6 Hz, CH(OTBS)$CH_2CH(CH_3)CH_AH_BO$), 3.96 (1H, d, J = 9.6 Hz, $CH(CH_3)CH$(-O-)$CH(CH_3)CHOH$), 3.70 (1H, dd, J = 9.6, 4.2 Hz, C*H*(OTBS)$CH_2CH(CH_3)CH_2O$), 3.48 (1H, d, J = 6.6 Hz, O*H*), 3.22 (1H, dd, J = 11.4, 2.4 Hz, CH(OTBS)$CH_2CH(CH_3)CH_AH_BO$), 2.06 (1H, dd, J = 13.2, 10.2 Hz, CH(-O-)$CH(CH_3)CH(OH)CH_AH_B$), 1.99-1.93 (1H, m, CH(OTBS)$CH_2CH(CH_3)CH_2O$), 1.92-1.88 (1H, m, CH(OTBS)$CH_AH_BCH(CH_3)CH_2O$), 1.81 (1H, dd, J = 14.4, 12.6 Hz, $CH(-O-)CH(CH_3)CH(OH)CH_AH_B$), 1.80-1.74 (1H, m, CH(OTBS)$CH(CH_3)CH$(-O-)), 1.74 (3H, s, $CH_2C(CH_3)$CHOTBS), 1.56-1.51 (1H, m, CH(OTBS)$CH_AH_BCH(CH_3)CH_2O$), 1.49-1.45 (1H, m, CH(-O-)$CH(CH_3)CHOH$), 1.05 (3H, d, J = 7.2 Hz, $CH(-O-)CH(CH_3)CHOH$), 1.03 (3H, d, J = 6.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH_2O$), 0.92 (9H, s, $OSi(CH_3)_3$), 0.91 (9H, s, $OSi(CH_3)_3$), 0.66 (3H, d, J = 6.6 Hz, CH(OTBS)$CH(CH_3)CH$(-O-)), 0.10 (3H, s, $OSi(CH_3)CH_3$), 0.10 (3H, s, $OSi(CH_3)CH_3$), 0.09 (3H, s, $OSi(CH_3)CH_3$), 0.02 (3H, s, $OSi(CH_3)CH_3$).



(3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyl)oxy-5-methyl-2-trimethylsilyloxy-hex-1-ene (121), synthesised according to the procedure of Paterson *et al*.[25] To a solution of methyl ketone **53** (19.3 mg; 50.7 μmol) in THF (1.7 mL) at -78 ^{o}C was added a mixture of TMSCl/Et_3N (67.5 μL; 507 μmol; 1:1 molar ratio) and LiHMDS (1M in THF; 101 μL; 101 μmol). The mixture was stirred at -78 ^{o}C for 20 min before another portion of LiHMDS (1M in THF; 172 μL; 172 μmol) and TMSCl/Et_3N (34 μL; 254 μmol) were added and the resulting mixture stirred at -78 ^{o}C for a further 1 h. The reaction mixture was treated with pH 7 phosphate buffer solution (5 mL), diluted with Et_2O (5 mL) and warmed to rt. Layers were separated and the aqueous layer extracted with Et_2O (4 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (buffered silica, 100% CH_2Cl_2) to give silyl enol ether **121** (22.3 mg; 97%) as a colourless oil. **R*f*** = 0.34 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -10.8 (c 1.12, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 4.42 (2H, s, OCH_2PMP), 4.33 (1H, s, CH_AH$_B$C(OTMS)CHOTBS), 4.08 (1H, m, CH$_A$$H_B$C(OTMS)CHOTBS), 3.94 (1H, dd, J = 7.8, 3.6 Hz, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.22 (1H, dd, J = 9.0, 5.4 Hz, CH_AH$_B$OPMB), 3.19 (1H, dd, J = 9.0, 7.2 Hz, CH$_A$$H_B$OPMB), 2.01-1.92 (1H, m, C*H*(CH_3)CH_2OPMB), 1.60 (1H, ddd, J = 12.6, 8.4, 4.2 Hz, CH(OTBS)CH_AH$_B$CHCH$_3$), 1.36 (1H, ddd, J = 13.2, 9.0, 3.6 Hz, CH(OTBS)CH$_A$$H_B$CHCH$_3$), 0.95 (2H, d, J = 7.2 Hz, CH(CH_3)CH_2OPMB), 0.90 (9H, s, OSiC(CH_3)$_3$), 0.20 (9H, s, OSi(CH_3)$_3$), 0.05 (3H, s, OSi(CH_3)CH_3), 0.04 (1H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.1, 159.1, 131.1, 129.2, 113.8, 88.9, 76.2, 55.4, 40.1, 29.6, 26.1, 18.3, 17.4, 5.6, 0.3, -4.4, -4.8; **IR** (film, cm^{-1}) 2956, 2929, 2856, 1717, 1613, 1513, 1463, 1361, 1301, 1251, 1171, 1094, 1038, 1006, 911, 839, 776.

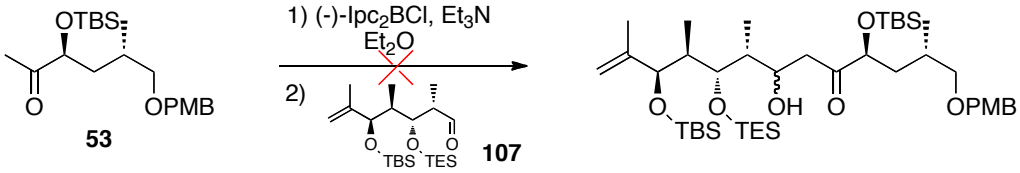


(2*S*,4*S*,8*R*,9*S*,10*S*,11*R*)-4-(*tert*-butyldimethylsilyloxy)-7-hydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-9,11-[(bis-dimethyl-methylene)dioxy]-tridec-12-en-5-one, synthesis attempted according to the procedure of Paterson *et al*.[25] To a stirred solution of silyl enol ether **121** (20.2 mg; 44.6 μmol) in CH_2Cl_2 (1.5 mL) at -78 °C was added aldehyde **85** (51.9 mg; 229 μmol) dropwise *via* cannula. $BF_3.OEt_2$ (32.5 μL; 229 μmol) was then added dropwise and the resulting mixture was sittred at -78 °C for 1.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) returned only methyl ketone **53**.



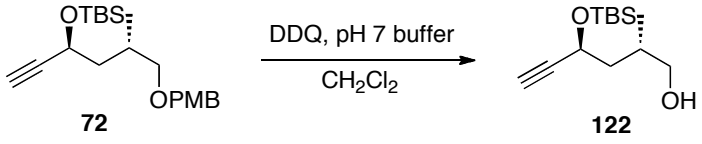
(2*S*,4*S*,8*R*,9*S*,10*S*,11*R*)-4-(*tert*-butyldimethylsilyloxy)-7-hydroxy-1-(4-methoxyphenyl)oxy-2,8,10,12-tetramethyl-9,11-[(bis-dimethyl-methylene)dioxy]-tridec-12-en-5-one. To a stirred solution of $TiCl_4$ (101 μL; 1M in CH_2Cl_2; 101 μmol) in CH_2Cl_2 (0.6 mL) at 0 °C was added Ti(O*i*-Pr)$_4$ (10 μL; 33.6 μmol) dropwise and the resulting mixture was stirred at 0 °C for 10 min before warming to rt for 10 min. The mixture was then cannulated into a solution of aldehyde **85** (13.6 mg; 60.1 μmol) in CH_2Cl_2 (0.6 mL) at -78 °C. After 2 min silyl enol ether **121** (27.2 mg; 60.1 μmol) was added dropwise *via* cannula and the mixture stirred at -78 °C for 3 h before quenching with sat. aq. NH_4Cl (2 mL). The mixture was poured into H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried

(Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatograpy (buffered silica, 100% CH_2Cl_2) returned only methyl ketone **53**.



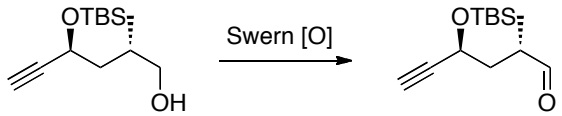
(2*S*,4*S*,8*R*,9*S*,10*S*,11*R*)-1-(4-methoxyphenyl)oxy-4,11-bis(*tert*-butyldimethylsilyloxy)-9-triethylsilyloxy-7-hydroxy-2,8,10,12-tetramethyl-tridec-12-en-5-one, synthesis attempted according to the procedure of Paterson *et al*.[26,27] To a stirred solution of (-)-Ipc_2BCl (17.0 mg; 60.4 μmol) in Et_2O (0.6 mL) at 0 ^oC was added ketone **53** (23.0 mg; 60.4 μmol) dropwise *via* cannula, followed by Et_3N (9 μL; 66.4 μmol) dropwise. The resulting mixture was stirred at 0 ^oC for 1.5 h before cooling to -78 ^oC. Aldehyde **107** (29.6 mg; 71.3 μmol) was added dropwise *via* cannula and the mixture was stirred at -78 ^oC for 3 h before placing in the freezer (-20 ^oC) overnight. The reaction was quenched at 0 ^oC by addition of MeOH/pH 7 buffer/H_2O_2 (1 mL: 1 mL: 1 mL) and stirring continued at rt for 1 h. The mixture was partitioned between H_2O (5 mL) and CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^1H NMR showed that no reaction had occurred and only starting materials remained.

4.2.4 Ketone Fragment Synthesis



(3*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-2-methyl-hex-5-ynyl-1-ol (122). To a stirred solution of PMB ether **72** (481 mg; 1.33 mmol) in CH_2Cl_2 (66 mL) at 0 ^oC was added pH 7 phosphate buffer (13 mL), followed by DDQ (452 mg; 1.99 mmol) and the

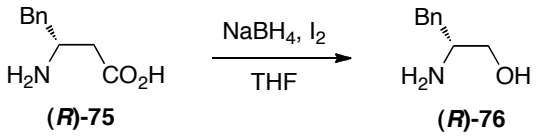
resultant slurry was stirred at 0 °C for 3 h. The mixture was diluted with CH_2Cl_2 (75 mL) and quenched with sat. aq. $NaHCO_3$ (120 mL). The layers were separated and the organic phase was washed with sat. aq. $NaHCO_3$ (150 mL), H_2O (150 mL) and brine (150 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **122** (313 mg; 97%) as a colourless oil. **R*f*** = 0.31 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = -56.4 (c 1.46, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.45 (1H, ddd, J = 8.3, 5.1, 2.1 Hz, C*H*OTBS), 3.46 (2H, d, J = 5.9 Hz, CH_2OH), 2.38 (1H, d, J = 2.1 Hz, CH(OTBS)CC*H*), 2.28 (1H, br s, O*H*), 1.88 (1H, m, C*H*(CH_3)CH_2OH), 1.82 (1H, ddd, J = 13.8, 8.3, 5.6 Hz, CH_AH_BCHOTBS), 1.49 (1H, ddd, J = 13.7, 7.6, 5.1 Hz, CH_AH_BCHOTBS), 0.93 (3H, d, J = 6.8 Hz, CH(CH_3)CH_2OH), 0.88 (9H, s, SiC(CH_3)$_3$), -0.13 (3H, s, Si(CH_3)CH_3), -0.10 (3H, s, Si(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 85.9, 72.5, 68.1, 61.2, 42.5, 32.5, 25.8, 18.3, 16.9, -4.4, -5.0; **IR** (film, cm^{-1}) 3311, 2956, 2930, 2858, 2361, 2338, 1472, 1463, 1388, 1361, 1252, 1088, 1040, 1005, 939, 898, 838, 808, 778, 655, 627; **HRESIMS** calculated for $C_{21}H_{36}O_3SiH^+$: 243.1775; found: 243.1783.



122 **49**

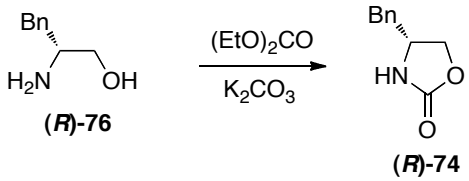
(3*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-2-methyl-hex-5-ynal (49). The previous procedure used for the preparation of aldehyde **88** was followed with DMSO (423 µL; 4.92 mmol), $(COCl)_2$ (1.23 mL; 2.46 mmol), alcohol **122** (399 mg; 1.64 mmol), Et_3N (1.37 mL; 9.84 mmol) and CH_2Cl_2 (10 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **49** (395 mg; 99%) as a colourless oil. **R*f*** = 0.56 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -40.5 (c 1.61, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.63 (1H, d, J = 1.6 Hz, C*H*O), 4.46 (1H, ddd, J = 7.6, 5.2, 2.0 Hz, C*H*OTBS), 2.62 (1H, m, C*H*(CH_3)CHO), 2.41 (1H, d, J = 2.0 Hz, CH(OTBS)CC*H*), 2.21 (1H, ddd, J = 14.4, 7.6, 6.4 Hz, CH_AH_BCHOTBS), 1.64 (1H, ddd, J = 13.6, 6.4, 5.2 Hz, CH_AH_BCHOTBS), 1.13 (3H, d, J = 7.2 Hz, CH(CH_3)CHO), 0.89 (9H, s, SiC(CH_3)$_3$), 0.14 (3H, s, Si(CH_3)CH_3), 0.11 (3H, s, Si(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.3, 85.0,

73.2, 60.8, 43.3, 39.4, 25.9, 18.3, 13.8, -4.4, -5.0; **IR** (film, cm^{-1}) 3309, 2930, 2885, 2858, 2712, 1727, 1472, 1463, 1390, 1361, 1343, 1254, 1098, 1005, 937, 900, 838, 810, 779, 737, 661, 631.



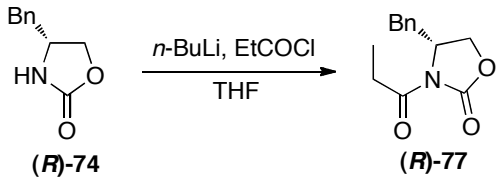
(***R***)-75 (***R***)-76

(*R*)-phenylalanol [(*R*)-76]. The previous procedure used for the preparation of **(*S*)-76** was followed with (*R*)-phenylalanine [**(*R*)-75**] (20.0 g; 121 mmol), $NaBH_4$ (11.00 g; 291 mmol), I_2 (28.5 g; 121 mmol) and THF (240). Recrystallisation from toluene gave (*R*)-phenylalanol **(*R*)-76** (16.2 g; 88%) as white crystals. **$[\alpha]^{20}_{D}$** = +55.5 (c 1.05, $CHCl_3$); **NMR** data as for the enantiomer **(*S*)-76.**



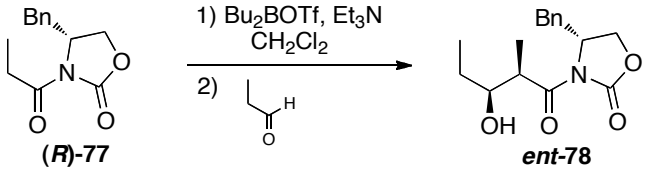
(***R***)-76 (***R***)-74

(4*R*)-4-(phenylmethyl)-2-oxazolidinone [(*R*)-74]. The previous procedure used for the preparation of auxiliary **(*S*)-74** was followed with (*R*)-phenylalanol [**(*R*)-76**] (15.1 g; 99.7 mmol), anhydrous K_2CO_3 (1.38 g; 9.97 mmol) and diethyl carbonate (24.7 mL; 209 mmol). Purification by recrystallisation from 2:1 EtOAc/X4 gave auxiliary **(*R*)-74** (13.8 g; 78%) as white plates. **$[\alpha]^{20}_{D}$** = +58.3 (c 1.12, $CHCl_3$); **NMR** data as for the enantiomer **(*S*)-74**.



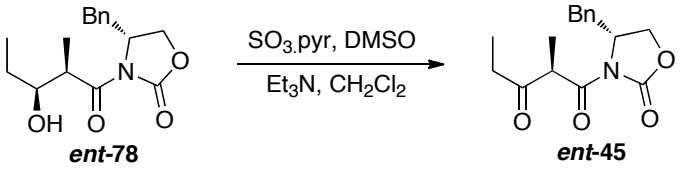
(*R*)-74 (*R*)-77

(4*R*)-4-(phenylmethyl)-2-oxazolidinone [(*R*)-77]. The previous procedure used for the preparation of oxazolidinone **(*S*)-77** was followed with (*R*)-auxiliary **(*R*)-74** (1.47 g; 8.27 mmol), *n*-BuLi (6.07 mL; 1.5 M in hexanes, 9.10 mmol), propionyl chloride (795 µL; 9.10 mmol) and THF (14 mL). Purification by column chromatography (50% Et_2O/X4) gave (*R*)-oxazolidinone **(*R*)-77** (1.93 g; 86%) as a white plates. **R*f*** = 0.37 (50% Et_2O/X4); **[α]$^{20}_{D}$** = +55.5 (c 1.05, $CHCl_3$); **NMR** data as for the enantiomer **(*S*)-77.**



(*R*)-77 *ent*-78

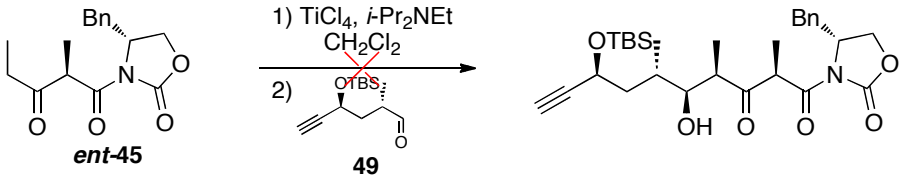
[[3-(2*R*,3*S*)-4*R*]-3-(3-hydroxy-2-methyl-1-oxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone [*ent*-78]. The previous procedure used for the preparation of aldol adduct **78** was followed with (*R*)-oxazolidine **(*R*)-77** (3.00 g; 12.9 mmol), Bu_2BOTf (15.4 mL; 1M in CH_2Cl_2; 15.4 mmol), Et_3N (2.34 mL; 16.8 mmol), propanal (1.86 mL; 25.8 mmol) and CH_2Cl_2 (26 mL). Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave aldol adduct ***ent*-78** (2.60 g; 70%) as white crystals. **Rf** = 0.40 (100% CH_2Cl_2); **[α]$^{20}_{D}$** = -48.1 (c 1.19, $CHCl_3$); **NMR** data as for the enantiomer **78***.*



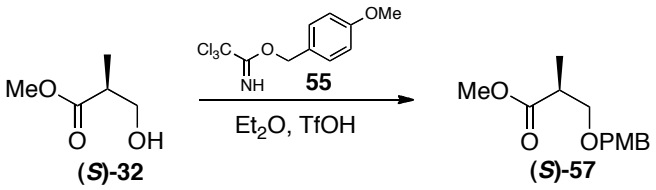
ent-78 *ent*-45

[[3-(2*R*)-4*R*]-3-(2-methyl-1,3-dioxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone [*ent*-45]. The previous procedure used for the preparation of β-ketoester **45** was

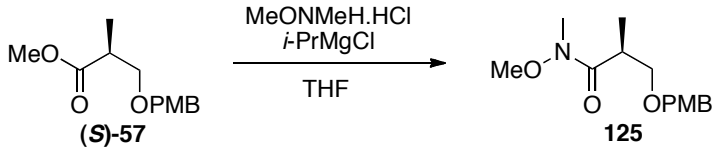
followed with oxazolidinone ***ent*-45** (2.47 g; 8.48 mmol), Et_3N (3.55 mL; 25.5 mmol), sulphur trioxide-pyridine complex (4.06 g; 25.5 mmol) in DMSO (45 mL) and 1:1 CH_2Cl_2/DMSO (89 mL). Purification by recrystallisation from 1:1 Et_2O/pentane gave β-ketoimide ***ent*-45** a white solid (1.82 g; 74%). **Rf** = 0.38 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -124.2 (c 1.10, $CHCl_3$); **NMR** data as for the enantiomer **45**.



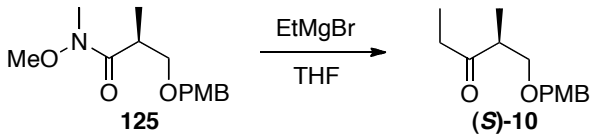
[[3-(2*R*,4*R*,5*S*,6*S*,8*S*)-4*R*]-3-(8-[*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6-trimethyl-1,3-dioxo-dec-9-ynyl)-4-(phenylmethyl)]-2-oxazolidinone. To a stirred solution of β-ketoimide ***ent*-45** (55.8 mg; 193 μmol) in CH_2Cl_2 (0.8 mL) at -5 °C was added $TiCl_4$ (212 μL; 1 M in CH_2Cl_2; 212 μmol) and the resulting dark yellow solution was treated immediately with *i*-Pr_2NEt (37 μL; 212 μmol). The resulting deep red solution was stirred at -5 °C for 1 h before cooling to -78 °C. A solution of aldehyde **49** (46.4 mg; 193 μmol) in CH_2Cl_2 (1 mL) was added dropwise *via* cannula and the mixture stirred at -78 °C for 1.5 h before placing the freezer (-20 °C) overnight. To the resultant brown solution was added pH 7 buffer (2 mL) and the mixture stirred vigorously as it warmed to ambient temperature. The mixture was partitioned between sat. aq. NH_4Cl (10 mL) and Et_2O (3 x 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed no product or aldehyde **49**, only β-ketoimide ***ent*-45**.



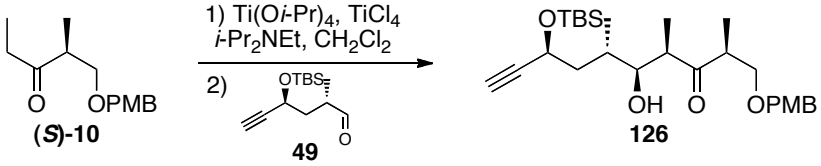
(2*S*)-methyl-3-(4-methoxybenzyl)oxy-2-methyl-propionate [(*S*)-57]. The previous procedure used for the preparation of **(*R*)-57** was followed with (*S*)-Roche ester [**(*S*)-32**] (1.15 mL; 10.4 mmol), PMB-imidate (**55**) (4.42 g; 15.6 mmol), TfOH (3 μL; 31.2 μmol) and Et_2O (52 mL). Purification by column chromatography (33% EtOAc/X4) gave PMB ether **(*S*)-57** (2.48 g; 100%) as a colourless oil. **R*f*** = 0.47 (5% Et_2O/CH_2Cl_2); **NMR** data as for the enantiomer **(*R*)-57**.



(2*S*)-3-(4-methoxybenzyl)oxy-2-methyl-*N*-methoxy-*N*-methylpropionamide (125). To a stirred slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (1.52 g; 15.6 mmol) and semi-crude ester **(*S*)-57** (2.48 g; 10.4 mmol) in THF (17 mL) at -15 ^oC was added *i*-PrMgCl (15.6 mL; 2 M in THF; 31.2 mmol) at such a rate that the reaction temperature remained below -15 ^oC. The resulting mixture was stirred at -15 ^oC for 30 min, then partitioned between NH_4Cl (20 mL) and Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* and the residue was purified by column chromatography (33% EtOAc/X4) to give Weinreb amide **125** (2.27 g; 82%) as a yellow oil. **R*f*** = 0.19 (33% EtOAc/X4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (2H, d, J = 8.3 Hz, Ar*H*), 6.85 (2H, d, J = 8.5 Hz, Ar*H*), 4.43 (2H, ABq, J = 11.7 Hz, OC*H*$_2$PMP), 3.79 (1H, m, C*H*CH_3), 3.78 (3H, s, ArOC*H*$_3$), 3.68 (3H, s, NOC*H*$_3$), 3.67 (1H, dd, J = 15.0, 6.2 Hz, C*H*$_A$H$_B$OPMB), 3.39 (1H, dd, J = 8.9, 5.8 Hz, CH$_A$*H*$_B$OPMB), 3.19 (3H, s, NC*H*$_3$), 1.09 (3H, d, J = 6.9 Hz, CHC*H*$_3$; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 130.7, 129.3, 128.8, 73.1, 72.5, 61.7, 55.4, 14.4.

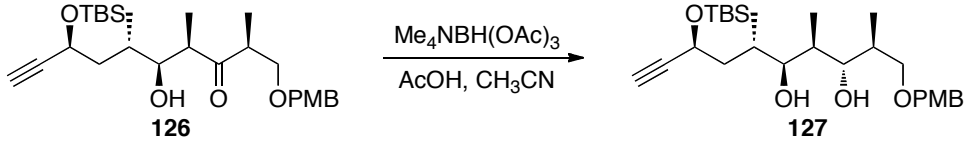


(4*S*)-5-(4-methoxybenzyl)oxy-4-methyl-pentan-2-one [(*S*)-10]. To a stirred solution of Weinreb amide **125** (1.00 g; 3.74 mmol) in THF (31 mL) at 0 ^{o}C was added EtMgBr (2.37 mL; 3 M in Et_2O; 7.11 mmol) dropwise. The resultant mixture was stirred at 0 ^{o}C for 2 h then partitioned between NH_4Cl (40 mL) and Et_2O (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (33% EtOAc/X4) gave ethyl ketone **(*S*)-10** (807 mg; 91%) as a colourless oil. **R*f*** = 0.47 (33% EtOAc/X4); **[α]$^{20}_{D}$** = +21.2 (c 1.37, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.8 Hz, Ar*H*), 6.89 (2H, d, J = 8.8 Hz, Ar*H*), 4.44 (2H, ABq, J = 11.6 Hz, OC*H*$_2$PMP), 3.82 (3H, s, OC*H*$_3$), 3.62 (1H, dd, J = 9.2, 8.0 Hz, C*H*$_A$H$_B$OPMB), 3.46 (1H, dd, J = 9.2, 5.6 Hz, CH$_A$*H*$_B$OPMB), 2.89 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 2.53 (2H, q, J = 7.2 Hz, CH$_3$C*H*$_2$), 1.09 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH$_2$OPMB) 1.07 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.8, 159.3, 130.4, 129.3, 113.9, 73.0, 72.2, 55.4, 46.3, 35.4, 13.7, 7.7.



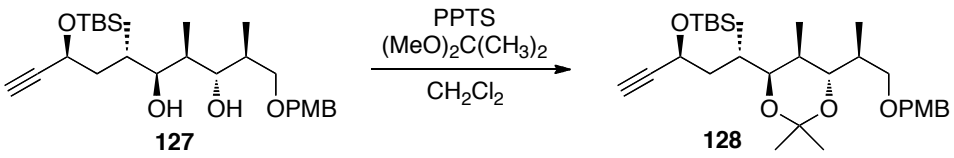
(3*S*,5*S*,6*S*,7*R*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-6-hydroxy-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-8-oxo-dec-1-yne (126), synthesised according to the procedure of Solsona *et al*.[28] Titanium(IV) isopropoxide (135 μL; 456 μmol) was added dropwise to a solution of $TiCl_4$ (1.37 mL; 914 μmol) in CH_2Cl_2 (3.3 mL) at 0 ^{o}C. The mixture was stirred for 10 min at 0 ^{o}C and 10 min at rt and diluted with CH_2Cl_2 (3.3 mL). The resulting colourless solution was added *via* cannula to a solution of ketone **(*S*)-10** (385 mg; 1.63 mmol) in CH_2Cl_2 (5 mL) at -78 ^{o}C. The pale yellow solution was stirred for 2 min and *i*-Pr_2NEt (312 μL; 1.79 mmol) was added dropwise. The resulting red-orange solution was stirred for 30 min at -78 ^{o}C before aldehyde **49** (392 mg; 1.63 mmol) was added *via* cannula. After 3 h at -78 ^{o}C the

reaction was quenched by addition of sat. aq. NH_4Cl (30 mL) and vigorously stirred at rt. The mixture was diluted with Et_2O (40 mL) and washed with H_2O (30 mL), sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). The aqueous layers were extracted with Et_2O (3 x 40 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude NMR showed a 0.15:1 mixture of diastereomers, which were able to be separated by column chromatography (buffered silica, 3% Et_2O/CH_2Cl_2) to give aldol adduct **126** (627 mg; 81%, 87% ds) as a white amorphous solids. **R*f*** = 0.28 (3% Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = -13.8 (c 1.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 8.4 Hz, Ar*H*), 6.86 (2H, d, J = 8.8 Hz, Ar*H*), 4.55 (1H, ddd, J = 8.0, 5.6, 2.0 Hz, C*H*OTBS), 4.38 (2H, ABq, J = 11.6 Hz, OCH_2PMP), 3.79 (3H, s, OCH_3), 3.72 (1H, dd, J = 9.6, 2.0 Hz, C*H*OH), 3.59 (1H, dd, J = 9.2 Hz, CH_AH$_B$OPMB), 3.41 (1H, dd, J = 8.8, 4.8 Hz, CH$_A$$H_B$OPMB), 3.17-3.10 (1H, ddq, J = 9.2, 6.8, 4.1 Hz, C*H*(CH$_3$)CH$_2$OPMB), 2.96 (1H, br s, O*H*), 2.82 (1H, dq, J = 7.2, 2.4 Hz, CH(OH)C*H*(CH$_3$)C(=O)), 2.37 (2H, d, J = 2.0 Hz, CH(OTBS)CC*H*), 2.18 (1H, ddd, J = 13.2, 8.0, 4.0 Hz, CH_AH$_B$CH(OTBS)CCH), 1.86-1.75 (1H, m, CH$_2$C*H*(CH$_3$)CHOH), 1.40 (1H, ddd, J = 13.6, 8.0, 5.6 Hz, CH$_A$$H_B$CH(OTBS)CCH), 1.05 (3H, d, J = 7.2 Hz, CH(CH_3)CH$_2$OPMB), 1.00 (3H, d, J = 6.8 Hz, CH(OH)CH(CH_3)C(=O)), 0.89 (9H, s, SiC(CH_3)$_3$) 0.84 (3H, d, J = 6.8 Hz, CH$_2$CH(CH_3)CHOH), 0.13 (3H, s, Si(CH_3)CH$_3$), 0.11 (3H, s, Si(CH$_3$)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 218.0, 159.5, 129.8, 129.4, 114.0, 86.3, 74.5, 73.3, 73.1, 72.1, 61.6, 55.3, 48.6, 44.4, 42.8, 31.9, 25.9, 18.3, 16.4, 13.9, 7.8, -4.3, -4.9; **IR** (film, cm^{-1}) 3505, 3307, 2933, 2857, 1711, 1613, 1586, 1513, 1462, 1407, 1361, 1302, 1249, 1174, 1090, 1036, 1004, 977, 940, 908, 837, 778, 736, 625, 460; **HRESIMS** calculated for $C_{27}H_{44}O_5SiCl^-$: 511.2652; found: 511.2655.



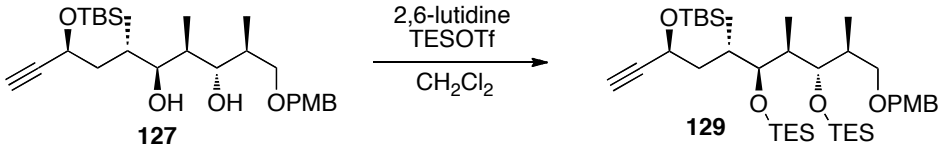
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-6,8-dihydroxy-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-dec-1-yne (127), synthesised according to the procedure of Evans *et al*.[29] To a stirred solution of β-hydroxyketone **126** (52.5 mg;

110 μmol) in a 1:1 mixture of AcOH/CH_3CN (4.4 mL) was added tetramethylammonium triacetoxyborohydride (467 mg; 2.20 mmol) and the resulting mixture stirred at rt for 4 days. The mixture was diluted with Et_2O (10 mL) and quenched by careful addition of sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4 x 15 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 10% Et_2O/CH_2Cl_2) to give 1,3-diol **127** (45.8 mg; 87%, 87% ds) as a yellow oil. **R*f*** = 0.48 (10% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = -23.0 (c 2.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.56 (1H, ddd, J = 8.4, 5.2, 2.0Hz, C*H*OTBS), 4.45 (2H, ABq, J = 11.2 Hz, OC*H*$_2$PMP), 3.80 (3H, s, OC*H*$_3$), 3.61 (1H, dd, J = 4.0 Hz, C*H*(OH)CH(CH_3)CH_2OPMB), 3.60 (1H, dd, J = 9.2 Hz, CH_AH_BOPMB), 3.54 (1H, dd, J = 9.2, 2.8 Hz, CH(OTBS)CH_2CH(CH_3)C*H*(OH)), 3.47 (1H, dd, J = 8.4 Hz, CH$_A$*H*$_B$OPMB), 2.38 (1H, d, J = 2.0 Hz, CH(OTBS)CC*H*), 2.21 (1H, ddd, J = 13.6, 8.8, 4.4 Hz, CH_AH_BCHOTBS), 2.16-2.10 (1H, m, C*H*(CH_3)CH_2OPMB), 1.86-1.78 (1H, m, CH(OTBS)CH_2C*H*(CH_3)), 1.82-1.78 (1H, m, CH(OH)C*H*(CH_3)CH(OH)), 1.43 (1H, ddd, J = 13.6, 7.6, 5.2 Hz, CH$_A$*H*$_B$CHOTBS), 1.25 (1H, br s, O*H*), 1.03 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CH_2OPMB), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.84 (3H, d, J = 6.8 Hz, CH(OH)CH(C*H*$_3$)CH(OH)), 0.80 (3H, d, J = 6.8 Hz, CH(OTBS)CH_2CH(C*H*$_3$)), 0.15 (3H, s, Si(C*H*$_3$)CH_3), 0.12 (3H, s, Si(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 129.7, 129.5, 114.0, 86.3, 82.7, 76.1, 75.4, 73.3, 72.2, 61.8, 55.4, 42.9, 35.9, 34.8, 32.9, 25.9, 18.3, 16.6, 14.3, 10.7, -4.3, -4.9; **IR** (film, cm^{-1}) 3423, 3309, 2958, 2931, 2856, 1613, 1513, 1463, 1379, 1360, 1302, 1249, 1173, 1084, 1037, 1004, 937, 941, 908, 837, 778, 402; **HRESIMS** calculated for $C_{27}H_{46}O_5SiNa^+$: 501.3007; found: 501.3009.



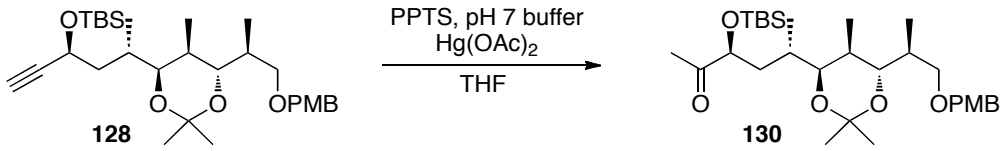
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-dec-1-yne (128). The previous

procedure used for the preparation of acetonide **84** was followed with diol **127** (24.3 mg; 50.9 μmol), PPTS, 2,2-dimethoxypropane (0.85 mL) and CH_2Cl_2 (0.85 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave acetonide **128** (24.5 mg; 93%) as a clear, colourless oil. **R*f*** = 0.55 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -7.3 (c 1.23, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.8 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.49 (1H, ddd, J = 8.4, 6.0, 2.0 Hz, C*H*OTBS), 4.42 (2H, ABq, J = 7.2 Hz, OCH_2PMP), 3.80 (3H, s, OCH_3), 3.55 (1H, dd, J = 9.2, 4.8 Hz, CH_AH$_B$OPMB), 3.32 (1H, dd, J = 8.8, 6.8 Hz, CH$_A$$H_B$OPMB), 3.29 (1H, dd, J = 10.8, 5.2 Hz, C*H*(-O-)CH(CH$_3$)CH$_2$OPMB), 3.22 (1H, dd, J = 6.8, 5.6 Hz, CH(OTBS)CH$_2$CH(CH$_3$)C*H*(-O-)), 2.37 (1H, d, J = 2.0 Hz, CH(OTBS)CC*H*), 2.11 (1H, ddd, J = 13.2, 8.8, 4.4 Hz, CH_AH$_B$CHOTBS), 1.96-1.85 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.93-1.86 (1H, m, CH(-O-)C*H*(CH$_3$)CH(-O)), 1.83-1.74 (1H, m, CH(OTBS)CH$_2$C*H*(CH$_3$)), 1.27 (1H, m, CH$_A$$H_B$CHOTBS), 1.27 (6H, s, C(CH_3)$_2$), 1.00 (3H, d, J = 6.8 Hz, CH(CH_3)CH$_2$OPMB), 0.90 (9H, s, SiC(CH_3)$_3$), 0.84 (3H, d, J = 6.8 Hz, CH(-O-)CH(CH_3)CH(-O-)), 0.83 (3H, d, J = 6.8 Hz, CH(OTBS)CH$_2$CH(CH_3)), 0.14 (3H, s, Si(CH_3)CH$_3$), 0.11 (3H, s, Si(CH$_3$)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 131.0, 129.3, 113.8, 100.4, 76.6, 74.0, 72.9, 72.2, 72.0, 61.6, 55.4, 42.8, 38.0, 35.3, 29.1, 25.9, 25.4, 23.7, 18.3, 15.8, 14.4, 12.5, -4.2, -4.9; **IR** (film, cm^{-1}) 3309, 2959, 2932, 2856, 1613, 1586, 1513, 1463, 1378, 1361, 1301, 1248, 1225, 1181, 1093, 1039, 1023, 1004, 939, 910, 882, 837, 808, 777, 625; **HRESIMS** calculated for $C_{30}H_{50}O_5SiH^+$: 519.3500; found: 519.3505.



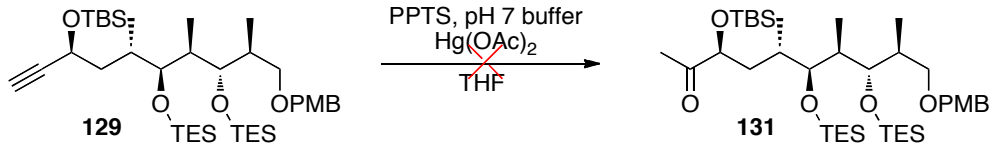
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-6,8-bis(triethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyldec-1-yne (129). The previous procedure used for the preparation of silyl ether **72** was followed with 1,3-diol **127** (133 mg; 279 μmol), 2,6-lutidine (131 μL; 1.12 mmol), TESOTf (189 μL; 836 μmol) and CH_2Cl_2 (2.8 mL). Purification by column chromatography (buffered silica, 40% X4/CH_2Cl_2) gave *di*-TES ether **129** (117 mg; 90%) as a clear, colourless oil. **R*f*** = 0.33 (40% X4/CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 7.8 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.40 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.38 (1H, m, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.64 (1H, dd, J = 9.6, 4.2 Hz, CH_AH$_B$OPMB), 3.60 (1H, m, $CH_2CH(CH_3)$C*H*OTES), 3.56 (1H, m, C*H*(OTES)$CH(CH_3)CH_2$OPMB), 3.20 (1H, dd, J = 9.0, 9.0 Hz, CH_A*H*$_B$OPMB), 2.37 (1H, d, = 1.8 Hz, C*H*CCHOTBS), 1.96-1.90 (1H, m, C*H*$(CH_3)CH_2$OPMB), 1.91-1.85 (1H, m, CH_2C*H*(CH_3)CHOTBS), 1.76 (1H, ddq, J = 7.2, 6.6, 6.6 Hz, CH(OTES)C*H*(CH_3)CHOTES), 1.46 (1H, m, C(=O)CH(OTBS)CH_AH$_B$), 1.32-1.25 (1H, m, C(=O)CH(OTBS)*C*H$_A$*H*$_B$), 1.01 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2OPMB), 0.97 (3H, d, J = 6.6 Hz, CH_2CH(CH_3)CHOTES), 0.95 (18H, m, 2 x OSi(CH_2CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.89 (3H, d, J = 6.6 Hz, CH(OTES)C*H*(CH_3)CHOTES), 0.62 (2H, q, J = 7.8 Hz, OSi(CH_2CH$_3$)), 0.61 (2H, q, J = 7.8 Hz, OSi(CH_2CH$_3$)), 0.52 (2H, q, J = 7.8 Hz, OSi(CH_2CH$_3$)), 0.15 (3H, s, Si(CH_3)CH_3), 0.11 (3H, s, Si(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 131.2, 129.3, 113.8, 86.5, 78.6, 77.1, 72.8, 72.6, 71.9, 60.5, 55.4, 42.3, 39.6, 36.4, 33.6, 27.1, 25.9, 25.4, 22.8, 18.3, 16.9, 16.3, 12.3, 7.4, 7.2, 7.0, 6.5, 6.1, 5.9, 5.8, 5.7, 5.6, -4.3, -5.1.

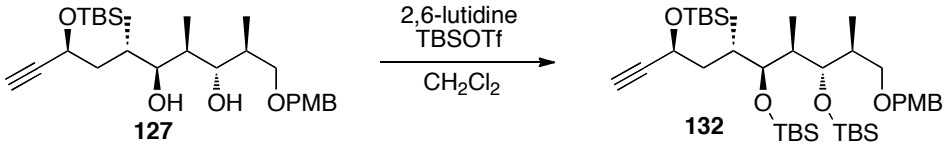


(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130), synthesised according to a procedure modified from Paterson *et al*.[11] To a stirred solution of alkyne **128** (21.5 mg; 41.4 μmol) in THF (0.8 mL) was added sequentially PPTS (15.6 mg; 62.2 μmol), pH 7 buffer (2 μL; 111 μmol) and $Hg(OAc)_2$ (4.0 mg; 12.4 μmol) and the resulting mixture stirred at 45 ^oC for 48 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (2 mL) and the mixture was extracted with Et_2O (3 x 5 mL), the combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 10% EtOAc/X4) gave methyl ketone **130** (13.2 mg; 59%) as a colourless oil. **R*f*** = 0.31 (10% EtOAc/X4); **[α]$^{20}_D$** = -8.1 (c 1.24, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.8 Hz, Ar*H*), 6.87

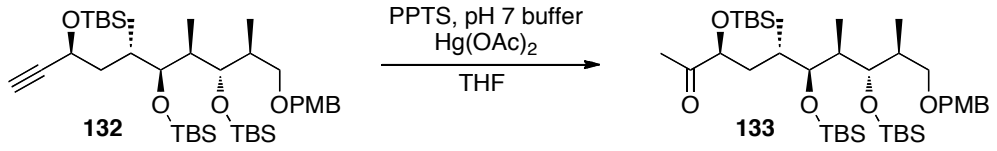
(2H, d, J = 8.8 Hz, Ar*H*), 4.41 (2H, ABq, J = 11.6 Hz, OC*H*$_2$PMP), 4.07 (1H, dd, J = 9.6, 3.6 Hz, C*H*OTBS), 3.80 (3H, s, OC*H*$_3$), 3.54 (1H, dd, J = 9.2, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.31 (1H, dd, J = 9.2, 7.2 Hz, CH$_A$*H*$_B$OPMB), 3.25 (1H, dd, J = 10.8, 4.0 Hz, C*H*(-O-)CH(CH$_3$)CH$_2$OPMB), 3.22 (1H, dd, J = 6.8, 5.6 Hz, CH(OTBS)CH$_2$CH(CH$_3$)C*H*(-O-)), 2.16 (3H, s, C(=O)C*H*$_3$), 2.05 (1H, ddd, J = 13.2, 9.6, 2.8 Hz, C*H*$_A$H$_B$CHOTBS), 1.94-1.85 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.89 (1H, ddd, J = 13.6, 6.8, 3.6 Hz, CH$_A$*H*$_B$CHOTBS), 1.77-1.69 (1H, m, CH(-O-)C*H*(CH$_3$)CH(-O-)), 1.27 (3H, s, C(C*H*$_3$)CH$_3$), 1.23 (3H, s, C(CH$_3$)C*H*$_3$), 0.99 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CH$_2$OPMB), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.83 (3H, d, J = 6.8 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)), 0.80 (3H, d, J = 6.8Hz, CH(OTBS)CH$_2$CH(C*H*$_3$)), 0.05 (3H, s, Si(C*H*$_3$)CH$_3$), 0.04 (3H, s, Si(CH$_3$)C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 212.8, 159.2, 131.0, 129.3, 113.9, 100.5, 77.6, 76.7, 73.5, 72.9, 72.2, 55.4, 38.1, 38.0, 35.3, 28.7, 25.9, 25.3, 25.1, 23.6, 18.3, 15.4, 14.3, 12.5, -4.6, -4.9; **IR** (film, cm^{-1}) 3411, 2957, 2932, 2857, 1715, 1612, 1586, 1513, 1463, 1378, 1362, 1301, 1248, 1181, 1097, 1036, 909, 885, 837, 777, 740, 668; **HRESIMS** calculated for $C_{30}H_{52}O_6SiNa^+$: 559.3425; found: 559.3427.



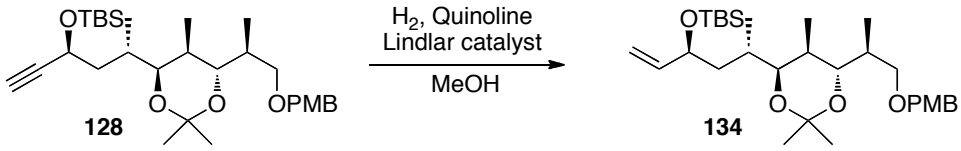
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-6,8-bis(triethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-decan-2-one (131). The previous procedure used for the preparation of methyl ketone **130** was followed with alkyne **129** (55.2 mg; 78.0 μmol), PPTS (29.4 mg; 117 μmol), pH 7 buffer (3 μL; 156 μmol), Hg(OAc)$_2$ (4.0 mg; 12.4 μmol) and THF (1.6 mL). Crude ^{1}H NMR showed that the starting material had decomposed *via* deprotection of the TES ether.



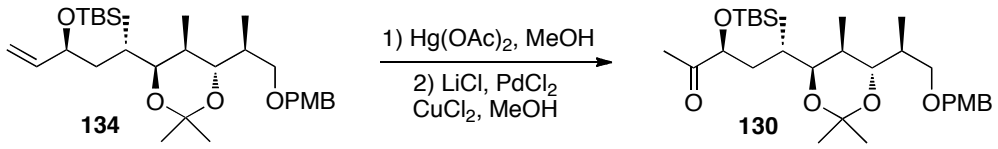
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3,6,8-tris-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-dec-1-yne (132). The previous procedure used for the preparation of TBS ether **72** was followed with 1,3-diol **127** (39.9 mg; 83.3 μmol), 2,6-lutidine (58 μL; 500 mmol), TBSOTf (86 μL; 375 μmol) and CH_2Cl_2 (1 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave *tri*-TBS ether **132** (12.6 mg; 21%) as a clear, colourless oil. **R*f*** = 0.32 (50% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = -28.6 (c 0.63, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 4.40 (2H, ABq, J = 12.0 Hz, OC*H*$_2$PMP), 4.39-4.36 (1H, m, CHCC*H*OTBS), 3.80 (3H, s, OC*H*$_3$), 3.62 (1H, dd, J = 9.6, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.58 (1H, dd, J = 7.2, 3.0 Hz, C*H*(OTBS)CH(CH_3)CH_2OPMB), 3.57 (1H, dd, J = 5.4, 2.4 Hz, CH_2C*H*(OTBS)CHCH_3), 3.21 (1H, dd, J = 9.0, 9.0 Hz, CH$_A$*H*$_B$OPMB), 2.37 (1H, d, J = 1.8 Hz, C*H*CCHOTBS), 2.00-1.95 (1H, m C*H*(CH_3)CH_2OPMB), 1.92-1.86 (1H, m, CHCCH(OTBS)C*H*$_A$H$_B$), 1.87-1.83 (1H, m, CH_2C*H*(CH_3)CHOTBS), 1.78 (1H, ddq, J = 7.2, 6.6, 5.4 Hz, CH(OTBS)C*H*(CH_3)CHOTBS), 1.44 (1H, ddd, J = 13.8, 10.8, 2.4 Hz, CCCCH(OTBS)CH$_A$*H*$_B$), 1.01 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH_2OPMB), 0.89 (3H, d, J = 7.0 Hz, CH_2CH(C*H*$_3$)CHOTBS), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.86 (3H, d, J = 7.2 Hz, CH(OTBS)C*H*(CH_3)CHOTBS), 0.15 (3H, s, Si(C*H*$_3$)CH_3), 0.10 (3H, s, Si(C*H*$_3$)CH_3), 0.09 (3H, s, Si(C*H*$_3$)CH_3), 0.05 (3H, s, Si(CH_3)C*H*$_3$), 0.05 (3H, s, Si(CH_3)C*H*$_3$), 0.04 (3H, s, Si(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.1, 131.1, 129.3, 113.8, 86.5, 77.6, 72.8, 72.5, 72.0, 60.5, 55.4, 42.0, 39.9, 36.6, 34.3, 26.4, 26.2, 25.9, 18.7, 18.5, 18.3, 16.7, 16.1, 12.4, -3.2, -3.32, -3.35, -4.1, -4.3, -5.0.



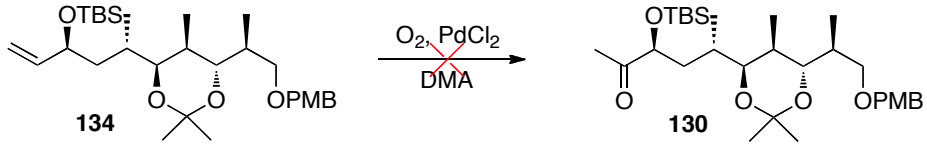
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3,6,8-tri-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-decan-2-one (133). The previous procedure used for the preparation of methyl ketone **130** was followed with alkyne **132** (12.6 mg; 17.8 μmol), PPTS (6.7 mg; 26.7 μmol), pH 7 buffer (1 μL; 35.6 μmol), $Hg(OAc)_2$ (1.7 mg; 5.34 μmol) and THF (0.5 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave methyl ketone **133** (7.4 mg; 57%) as a clear, colourless oil. **R*f*** = 0.32 (50% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = -24.3 (c 0.37, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.0 Hz, Ar*H*), 6.86 (2H, d, J = 8.4 Hz, Ar*H*), 4.40 (2H, ABq, J = 10.8 Hz, OCH_2PMP), 4.00 (1H, dd, J = 11.4, 2.4 Hz, C(=O)C*H*OTBS), 3.80 (3H, s, OCH_3), 3.61 (1H, dd, J = 4.2, 3.6 Hz, CH_2CH(CH_3)C*H*OTBS), 3.59 (1H, dd, J = 4.8, 4.8 Hz, C*H*(OTBS)CH(CH_3)CH_2OPMB), 3.57 (1H, dd, J = 8.4, 4.8 Hz, C$H_A$$H_B$OPMB), 3.22 (1H, dd, J = 9.0, 9.0 Hz, CH$_A$$H_B$OPMB), 2.14 (1H, s, C$H_3$C=O), 1.99 (1H, m C*H*($CH_3$)$CH_2$OPMB), 1.86-1.80 (1H, m, , CH_2C*H*(CH_3)CHOTBS), 1.73-1.70 (1H, ddq, J = 7.2, 6.6, 4.8 Hz, CH(OTBS)C*H*(CH_3)CHOTBS), 1.65 (1H, ddd, J = 13.2, 11.4, 2.4 Hz, C(=O)CH(OTBS)C$H_A$$H_B$), 1.25-1.20 (1H, m, C(=O)CH(OTBS)CH$_A$$H_B$), 1.01 (3H, d, J = 6.6 Hz, CH(CH_3)CH_2OPMB), 0.91 (9H, s, SiC(CH_3)$_3$), 0.91 (3H, d, J = 6.6 Hz, CH_2CH(CH_3)CHOTBS), 0.88 (9H, s, SiC(CH_3)$_3$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.84 (3H, d, J = 7.2 Hz, CH(OTBS)C*H*(CH_3)CHOTBS), 0.08 (3H, s, Si(CH_3)CH_3), 0.07 (3H, s, Si(CH_3)CH_3), 0.04 (3H, s, Si(CH_3)CH_3), 0.04 (3H, s, Si(CH_3)CH_3), 0.03 (3H, s, Si(CH_3)CH_3), 0.03 (3H, s, Si(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.8, 129.3, 113.8, 77.3, 72.8, 72.4, 55.4, 41.5, 37.0, 36.2, 34.1, 29.9, 26.3, 26.2, 26.0, 24.8, 24.7, 18.7, 18.5, 18.2, 16.2, 16.0, 12.4, -3.1, -3.2, -3.4, -4.0, -4.7, -4.9; **IR** (film, cm^{-1}) 2929, 2856, 1716, 1613, 1513, 1471, 1360, 1301, 1250, 1171, 1092, 1039, 905, 835, 774, 669; **HRESIMS** calculated for $C_{39}H_{76}O_6Si_3H^+$: 725.5022; found: 725.5009.



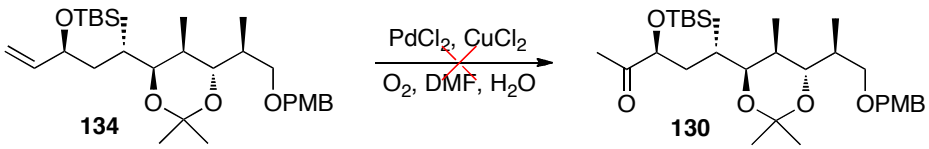
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-dec-2-ene (134). To a stirred solution of alkyne **128** (27.1 mg; 52.2 µmol) in MeOH (0.5 mL) at rt was successively added quinoline (2 µL; 16.9 µmol) and Lindlar catalyst (2.7 mg; 10 % w/w). The reaction mixture was stirred at room temperature under a H_2 atmosphere for 1 h and then filtered through a pad of celite (Et_2O). The solution was concentrated *in vacuo* and the residue diluted with Et_2O (5 mL), washed with 10% HCl, H_2O, sat. aq. $NaHCO_3$ and brine (5 mL each). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave alkene **134** (25.0 mg; 92%) as a colourless oil. **R*f*** = 0.25 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 582 (1H, ddd, J = 17.4, 10.8, 6.6 Hz, $CH_2CHCHOTBS$), 5.13 (1H, m, $CH_AH_BCHCHOTBS$), 5.01 (1H, m, $CH_AH_BCHCHOTBS$), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.24-4.20 (1H, m, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.55 (1H, dd, J = 9.0, 4.8 Hz, CH_AH_BOPMB), 3.32 (1H, dd, J = 9.6, 7.2 Hz, CH_AH_BOPMB), 3.27 (1H, dd, J = 10.8, 4.2 Hz, C*H*(-O-)$CH(CH_3)CH_2OPMB$), 3.22 (1H, dd, J = 7.2, 6.0 Hz, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 1.96 (1H, ddd, J = 9.6, 9.0, 5.4 Hz, $CH(OTBS)CH_AH_BCH(CH_3)CH$(-O-)), 1.94-1.88 (1H, m, $CH(OTBS)CH_AH_BCH(CH_3)CH$(-O-)), 1.90-1.85 (1H, ddq, J = 6.6, 4.2, 2.4 Hz, CH(-O-)$CH(CH_3)CH$(-O-)), 1.76-1.69 (1H, m, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 1.28 (3H, s, $C(CH_3)CH_3$), 1.26 (3H, s, $C(CH_3)CH_3$), 1.00 (3H, d, J = 7.2 Hz, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 0.89 (9H, s, $OSi(CH_3)_3$), 0.83 (3H, d, J = 7.2 Hz, CH(-O-)$CH(CH_3)CH$(-O-)), 0.80 (3H, d, J = 6.6 Hz, CH(-O-)$CH(CH_3)CH_2OPMB$), 0.05 (3H, s, $OSi(CH_3)CH_3$), 0.03 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 142.7, 131.0, 129.3, 129.3, 113.8, 113.6, 100.4, 76.2, 73.9, 72.9, 72.5, 72.2, 55.4, 41.9, 38.1, 35.3, 28.9, 26.0, 23.7, 15.8, 14.4, 12.6, -3.9, -4.7.



(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130). The previous procedure used for the attempted preparation of methyl ketone **53** was followed with alkene **134** (20.3 mg; 39.3 μmol), $Hg(OAc)_2$ (15.0mg; 47.1μmol) and MeOH (0.5 mL), followed by LiCl (33 mg; 39.3 μmol), $PdCl_2$ (7.0 mg; 39.3 μmol), $CuCl_2$ (15.9 mg; 118 μmol) and MeOH (0.5 mL). NMR analysis of the crude residue showed approximately 1/3 conversion to the desired product, accompanied by decomposition products.

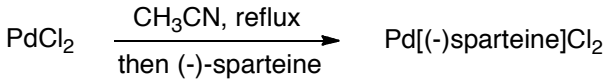


(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130). The previous procedure used for the attempted preparation of methyl ketone **53** was followed with alkene **134** (25.0 mg; 48.4 μmol), $PdCl_2$ (0.1 mg; 484 μmol), DMA (0.5 mL) and H_2O (30 μL). NMR analysis of the crude residue showed that no reaction had occurred and alkene **134** (19.6 mg; 78%) was returned.

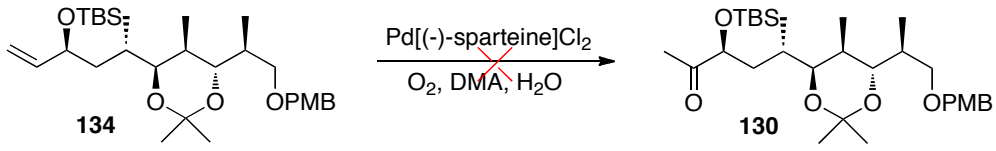


(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130), synthesis attempted according to the procedure of Jenkins *et al*.[30] To a solution of alkene **134** (19.6 mg; 37.9 μmol) in a 1:1 (v/v) mixture of DMF/H_2O (1.3 mL) was added $PdCl_2$

(1.2 mg; 6.77 µmol) and $CuCl_2$ (7.4 mg; 55.0 µmol). The resulting mixture was stirred at rt for 5 h under an O_2 atmosphere. The reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. NMR analysis of the crude residue showed only starting material, alkene **134**.

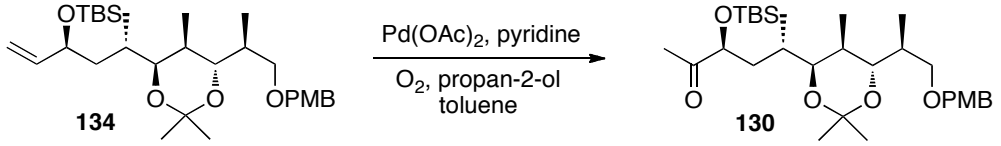


[(-)-Sparteine]palladium chloride, synthesised according to the procedure of Sigman *et al*.[31] $PdCl_2$ (100 mg; 56.4 µmol) was suspended in CH_3CN (2.8 mL) and refluxed until formation of $(CH_3CN)_2PdCl_2$ was complete, as indicated by the change in colour of the suspension from dark purple to yellow-orange. The mixture was cooled to rt and (-)-sparteine (130 µL; 56.4 µmol) was added. The dark orange-red solution was stirred at rt for 1 h, during which time an orange precipitate formed. The solid was isolated by vacuum filtration and triturated from $CHCl_3$ with Et_2O to give Pd[(-)-sparteine]Cl_2 (104 mg; 45%) as an orange powder.



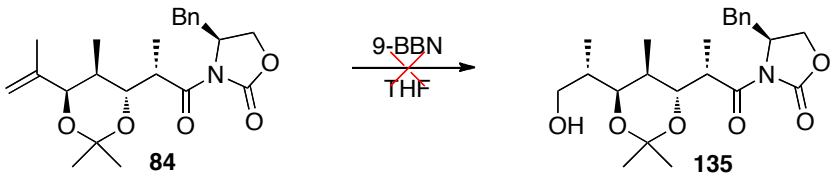
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130), synthesis attempted according to the procedure of Sigman and Cornell.[32] A suspension of Pd[(-)-sparteine]Cl_2 (0.2 mg; 48.6 µmol) in a 4:1 (v/v) solution of DMA/H_2O (0.2 mL) was heated under a N_2 atmosphere to 70 ^oC until the catalyst dissolved (5 min). The mixture was cooled to rt and the flask was evacuated of N_2 and mixture stirred vigorously under an O_2 atmosphere for 10 min. Alkene **134** (18.7 mg; 36.2 µmol) was then added at rt *via* cannula and the mixture subsequently heated to 70 ^oC under O_2 for 18 h. The reaction mixture was cooled to rt and diluted with Et_2O (2

mL), washed with 1M HCl (2 x 4 mL) and the combined aqueous washings were back extracted with Et_2O (4 x 4 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. NMR analysis of the crude residue showed only starting material, alkene **134**.



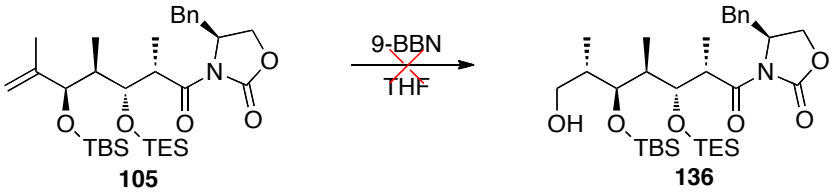
(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3-(*tert*-butyldimethylsilyloxy)-10-(4-methoxyphenyl)oxy-5,7,9-trimethyl-6,8-[(bis-dimethyl-methylene)dioxy]-decan-2-one (130). The previous procedured used for the attempted synthesis of methyl ketone **53** was followed with pyridine (0.5 μL; 6.3 μmol), $Pd(OAc)_2$ (0.4 mg; 1.6 μmol), toluene (160 μL), propan-2-ol (32 μL), alkene **134** (16.3 mg; 31.5 μmol) and further addition of propan-2-ol (130 μL). The reaction mixture was passed through magnesium silicate and concentrated *in vacuo*. NMR analysis of the crude residue showed an approx. 1:1 mixture of alkene **134** and methyl ketone **130** that were unable to be separated by column chromatography.

4.2.5 Aldehyde Fragment Synthesis

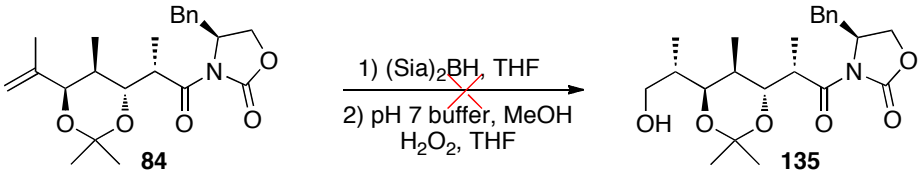


[[3-(2*S*,3*R*,4*S*,5*R*,6*S*)-4*S*]-3-(7-hydroxy-2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-oxo)-4-(phenylmethyl)]-2-oxazolidinone (135). To a stirred solution of alkene **84** (17.7 mg; 44.1 μmol) in THF (1 mL) at 0 ^{o}C was added a solution of 9-BBN (135 μL; 0.5 M in THF; 67.5 μmol). After 15 min the reaction mixture was warmed to rt for 24 h. The mixtured was re-cooled to 0 ^{o}C and

quenched with 55 μL each of 1:1 EtOH/THF, pH 7 buffer and 30% aq. H_2O_2. After 15 min the solution was warmed to rt and stirred for a further 3 h. Sat. aq. $NaHCO_3$ (5.5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracted were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed that no reaction had occurred, returning alkene **84**.

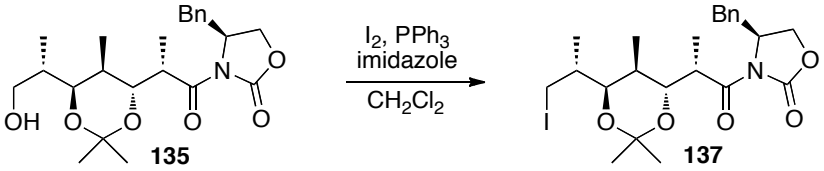


[[3-(2*S*,3*R*,4*S*,5*R*,6*S*)-4*S*]-3-(3,5-di-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6-trimethyl-1-oxo)-4-(phenylmethyl)]-2-oxazolidinone (136). The previous procedure used for the attempted preparation of alcohol **135** was followed with alkene **105** (22.5 mg; 38.1 μmol), 9-BBN (114 μL; 0.5 M in THF; 57.2 μmol) and THF (0.6 mL). Crude ^{1}H NMR indicated that no reaction had occurred.



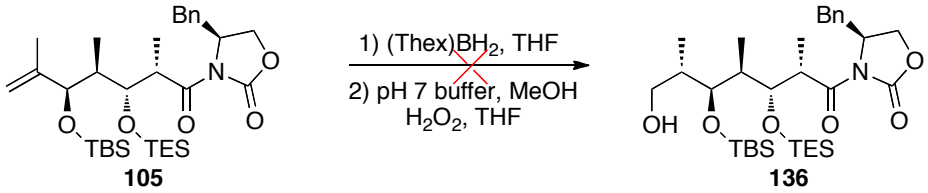
[[3-(2*S*,3*R*,4*S*,5*R*,6*S*)-4*S*]-3-(7-hydroxy-2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-oxo)-4-(phenylmethyl)]-2-oxazolidinone (135). To a stirred solution of BH_3.THF (640 μL; 1M in THF; 640 μmol) in THF (0.2 mL) at 0 ^{o}C was added 2-methyl-2-butene (136 μL; 1.28 mmol) dropwise and the resulting solution was stirred at 0 ^{o}C for 3 h. The resultant disiamyl borane solution was then added dropwise to a cooled (0 ^{o}C) solution of alkene **84** (20.7 mg; 51.6 μmol) in THF (1.3 mL) and the mixture was stirred at 0 ^{o}C for 3 h before warming to room temperature for an additional 12 h. The reaction was quenched at 0 ^{o}C by successive addition of pH 7 buffer (1 mL), MeOH (1 mL), 30% H_2O_2 (1 mL) and THF (1 mL), followed by stirring at room temperature for 1 h. 1.5 M Na_2SO_3 (5 mL) was

added and mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 20% Et_2O/CH_2Cl_2) gave alcohol **135** (15.2 mg; 70%, 93% ds) as a colourless oil. **R*f*** = 0.29 (20% Et_2O/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.23-7.21 (2H, m, Ar*H*), 4.68-4.61 (1H, m, C*H*CH_2Ph), 4.18-4.15 (2H, m, CHC*H*$_2$O), 4.08 (1H, dq, J = 7.2, 5.2Hz, CH(-O-)C*H*(CH_3)C=O), 3.65-2.58 (1H, m, C*H*(-O-)CH(CH_3)C=O), 3.65-2.58 (1H, m, CH_2(OH)CH(CH_3)C*H*(-O-)), 3.65-2.58 (1H, m, C*H*$_A$H$_B$OH), 3.50 (1H, dd, J = 10.8, 6.0 Hz, CH$_A$*H*$_B$OH), 3.30 (1H, dd, J = 13.2, 3.2 Hz, C*H*$_A$H$_B$Ph), 2.76 (1H, dd, J = 13.6, 10.0 Hz, CH$_A$*H*$_B$Ph), 2.03-1.94 (1H, m, CH(-O-)C*H*(CH_3)CH(-O-)), 1.80-1.74 (1H, m, CH_2(OH)C*H*(CH_3)CH(-O-)), 1.61 (1H, br s, O*H*), 1.32 (3H, s, C(C*H*$_3$)CH$_3$), 1.31 (3H, s, C(CH$_3$)C*H*$_3$), 1.27 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)C=O), 1.04 (3H, d, J = 6.8 Hz, CH_2(OH)CH(C*H*$_3$)CH(-O-)), 0.99 (3H, d, J = 6.8 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.1, 153.4, 135.5, 129.6, 129.1, 129.1, 127.5, 100.7, 76.3, 70.9, 66.3, 64.8, 55.9, 41.2, 38.0, 35.7, 35.1, 25.2, 24.3, 14.1, 13.0, 12.2.

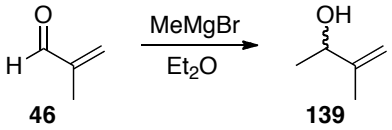


[[3-(2*S*,3*R*,4*S*,5*R*,6*S*)-4*S*]-3-(7-iodo-2,4,6-trimethyl-3,5-[(bis-dimethyl-methylene)dioxy]-1-oxo)-4-(phenylmethyl)]-2-oxazolidinone (137), synthesis attempted according to the procedure of Hu *et al*.[33] To a stirred solution of imidazole (7.4 mg; 109 μmol) and triphenylphosphine (10.4 mg; 39.8 μmol) in CH_2Cl_2 (0.5 mL) at 0 ^oC was added I_2 (10.1 mg; 39.8 μmol). After 10 min, a solution of alcohol **135** (15.2 mg; 36.2 μmol) in CH_2Cl_2 (1 mL) was added *via* cannula. The resulting solution was stirred at 0 ^oC for 15 min before warming to room temperature for an additional 12 h. The reaction mixture was diluted with sat. aq. $Na_2S_2O_3$ (1 mL), followed by H_2O (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography

(buffered silica, 20% Et_2O/CH_2Cl_2) gave a mixture of iodide **137**, alcohol **135** and free auxiliary **(*S*)-74**.

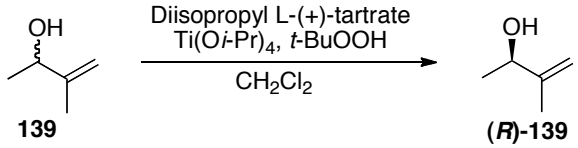


[[3-(2*S*,3*R*,4*S*,5*R*,6*S*)-4*S*]-3-(3,5-di-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6-trimethyl-1-oxo)-4-(phenylmethyl)]-2-oxazolidinone (136). To a stirred solution of 2,3-dimethyl-2-butene (40 μL; 332 μmol) in THF (0.5 mL) at 0 °C was added BH_3.THF (303 μL; 1M in THF; 303 μmol) and the resulting solution stirred at 0 °C for 2 h, warmed to rt for 1 h, then recooled to 0 °C. The resulting mixture was added *via* cannula to a cooled (0 °C) solution of alkene **105** (24.5 mg; 41.5 μmol) in THF (0.5 mL) and the mixture was stirredat 0 °C for 2 h before warming to rt for 18 h. The reaction was cooled to 0 °C and 0.5 mL each of pH 7 buffer, MeOH, 30% aq. H_2O_2 and THF were added successively and the mixtured warmed to rt for 1 h. Na_2SO_3 (1.5 M; 5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR showed that no reaction had occurred, returning only alkene **105**.



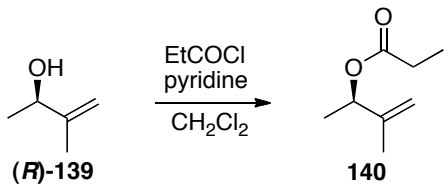
2-Methyl-but-1-en-3-ol (139), synthesised according to the procedure of Paterson and Perkins.[34] To a stirred solution of methacrolein (**46**) (10.0 mL; 121 mmol) in Et_2O (48 mL) at -78 °C was added MeMgBr (40.3 mL; 3 M in Et_2O; 121 mmol) dropwise over 30 min, after which time the reaction was quenched with sat. aq. NH_4Cl (100 mL). The mixture was extracted with Et_2O (3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Distillation under reduced pressure gave racemic alcohol **139** as a colourless oil (7.54 g; 72%). **bp.** 38-39 °C at 10 mmHg; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 4.93 (1H, m, C$H_A$$H_B$C($CH_3$)CHOH), 4.76 (1H, m, $CH_A$$H_B$C($CH_3$)CHOH), 4.22 (1H, q, J = 6.4 Hz, C*H*OH), 1.95 (1H, br s, O*H*), 1.72 (3H, m, CH_2C(CH_3)CHOH), 1.25 (3H, d, J = 6.4 Hz, CH_3CHOH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.1, 109.6, 71.7, 21.9, 17.9.



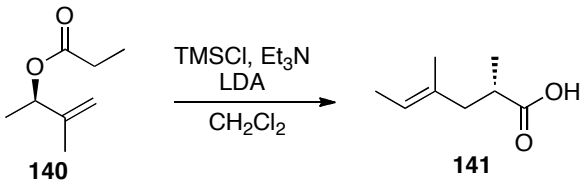
139 **(*R*)-139**

(3*R*)-2-methyl-but-1-en-3-ol [(*R*)-139], To a stirred solution of racemic alcohol **139** (5.04 g; 58.5 mmol) in CH_2Cl_2 (235 mL) at rt was added diisopropyl (*L*)-(+)-tartrate (1.85 mL; 8.78 mmol), followed by 4 Å molecular sieves (4 g). The reaction mixture was then cooled to -20 ^oC and Ti(O*i*-Pr)$_4$ (1.73 mL; 5.85 mmol) was added. After 30 min, *t*-BuOOH (5.66 mL; 6 M in decane; 33.9 mmol) was added and stirring was continued at -20 ^oC for 3 h. The reaction mixture was then stored in the freezer (-20 ^oC) for 48 h. The reaction was quenched by addition of a precooled (0 ^oC) solution of $FeSO_4$/citric acid (33 g $FeSO_4$ and 11 g citric acid in 100 mL H_2O) with vigorous stirring for 40 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were concentrated *in vacuo* to approx. 50 mL and stirred vigorously with 5% NaOH in brine (50 mL) at 0 ^oC for 1 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **(*R*)-139** (2.16 g; 86%, >86% ee) as a colourless oil. **R*f*** = 0.30 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = +1.57 (c 2.55, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.95 (1H, m, C$H_A$$H_B$C($CH_3$)CHOH), 4.769 (1H, m, $CH_A$$H_B$C($CH_3$)CHOH), 4.24 (1H, m, C*H*OH), 1.74 (3H, m, CH_2C(CH_3)CHOH), 1.57 (1H, br s, O*H*), 1.27 (3H, d, J = 6.6 Hz, CH_3CHOH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.1, 109.7, 71.7, 21.9, 18.0.



(*R*)-139 140

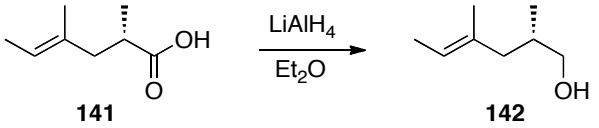
[(3*S*)-2-methyl-but-1-enyl] propionate (140), synthesised according to the procedure of Paterson and Perkins.[34] To a stirred solution of alcohol **(*R*)-139** (2.09 g; 24.3 mmol) in CH_2Cl_2 (87 mL) at rt was added dry pyridine (2.74 mL; 34.0 mmol), followed by propionyl chloride (2.97 mL; 34.0 mmol). After stirring at rt for 4 h, the reaction was diluted with CH_2Cl_2 (100 mL), washed with 1 M HCl (2 x 100 mL) and sat. aq. $NaHCO_3$ (100 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave ester **140** (3.43 g; 99 %) as a colourless oil. **R*f*** = 0.65 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = +14.2 (c 1.55, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.29 (1H, d, J = 6.6 Hz, CH_3CH(-O-)$C(CH_3)CH_2$), 4.95 (1H, s, $CH_AH_BC(CH_3)CH$(-O-)CH_3), 4.84 (1H, m, $CH_AH_BC(CH_3)CH$(-O-)CH_3), 2.33 (2H, q, J = 7.2 Hz, CH_2CH_3), 1.74 (3H, s, $CH_2C(CH_3)CH$(-O-)CH_3), 1.31 (3H, d, J = 6.6 Hz, CH_3CH(-O-)$C(CH_3)CH_2$), 1.14 (3H, t, J = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 144.9, 111.5, 73.2, 28.0, 19.2, 18.4, 9.2.



140 141

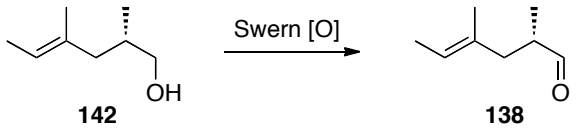
(2*R*,4*E*)-2,4-dimethyl-hex-4-enoic acid (141), synthesised according to the procedure of Paterson and Perkins.[34] To a stirred solution of ester **140** (1.00 g; 7.03 mmol) in THF (70 mL) at -78 ^oC was added a solution of TMSCl/Et_3N solution (9.11 mL; prepared by addition of triethylamine (5.5 mL) to TMSCl (5.5 mL)), followed by centrifuging to separate off the gelatinous whipe precipitate of amine hydrochloride), followed by a solution of LDA (6.53 mL; 1.4 M in THF; 9.14 mmol). The reaction was stirred at -78 ^oC for 1 h, allowed to warm slowly to room temperature, stirred for 1 h, then heated to reflux for 4 h. The reaction mixture was quenched by addition of 1 M HCl (40 mL) and stirred for a further 40 min. The

mixture was then basified by addition of 10% NaOH, washed with Et_2O (3 x 100 mL), acidified with 3M H_2SO_4 and extracted in Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give crude acid **141** (715 mg; 72%) as a colourless liquid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.00 (1H, br s, COO*H*), 5.27 (1H, m, $CH_3CHC(CH_3)CH_2$), 2.62 (1H, ddq, J = 8.0, 7.2, 6.8 Hz, C*H*(CH_3)COOH), 2.41 (1H, dd, J = 13.6, 6.4 Hz, $CH_AH_BCH(CH_3)COOH$), 2.05 (1H, dd, J = 13.6, 8.0 Hz, $CH_AH_BCH(CH_3)COOH$), 1.59 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.57 (3H, d, J = 6.8 Hz, $CH_3CHC(CH_3)CH_2$), 1.12 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)COOH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 182.8, 132.6, 121.5, 43.7, 37.8, 16.46, 16.45, 13.6.



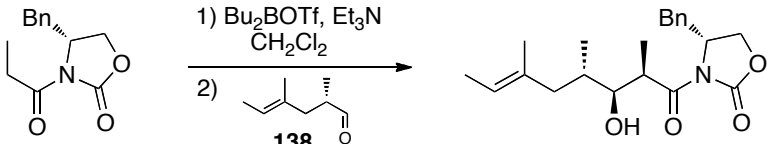
141 **142**

(2*R*,4*E*)-2,4-dimethyl-hex-4-en-1-ol (142). To a stirred solution of $LiAlH_4$ (840 mg; 22.1 mmol) in Et_2O (63 mL) at -78 ^oC was added acid **141** (715 mg; 5.03 mmol) in Et_2O (7 mL) *via* cannula. The resulting mixture was allowed to warm slowly to 0 ^oC and stirred at 0 ^oC for 30 min. The reaction was quenched by addition of 1 M H_2SO_4 (50 mL). The mixture was then extracted with Et_2O (3 x 50 mL), the combined organic layers were washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **142** (541 mg; 84%) as a colourless oil. **R*f*** = 0.34 (5% Et_2O/CH_2Cl_2)**; [α]$^{20}_D$** = -3.60 (c 1.67, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.22 (1H, m, $CH_3CHC(CH_3)CH_2$), 3.47 (1H, dd, J = 10.8, 6.0 Hz, CH_AH_BOH), 3.39 (1H, dd, J = 10.8, 6.0 Hz, CH_AH_BOH), 2.09 (1H, m, C*H*$(CH_3)CH_2OH$), 1.91 (1H, br s, O*H*), 1.86-1.76 (2H, m, $CH_2CH(CH_3)CH_2OH$), 1.59 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.57 (3H, d, J = 6.8 Hz, $CH_3CHC(CH_3)CH_2$), 0.85 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CH_2OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.7, 120.4, 68.7, 44.5, 33.9, 16.9, 15.8, 13.5.



142 **138**

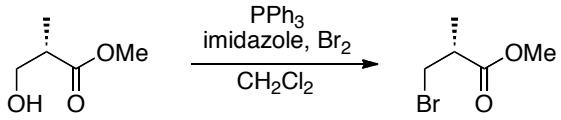
(2*R*,4*E*)-2,4-dimethyl-hex-4-enal (138). The previous procedure used for the preparation of aldehyde **88** was followed with alcohol **142** (250 mg; 1.95 mmol), DMSO (5.85 mmol; 415 μL), $(COCl)_2$ (1.46 mL; 2.93 mmol), Et_3N (1.63 mL; 11.7 mmol) and CH_2Cl_2 (20 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **138** (246 mg; 100%) as a colourless oil. **R*f*** = 0.53 (100% CH_2Cl_2)**; [α]$^{20}_D$** = +6.79 (c 2.80, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (1H, d, J = 2.4 Hz, C*H*O), 5.24 (1H, m, $CH_3CHC(CH_3)CH_2$), 2.53-2.43 (1H, m, C*H*(CH_3)CHO), 2.40 (1H, dd, J = 13.6, 9.6 Hz, $CH_AH_BCH(CH_3)CHO$), 1.97 (1H, dd, J = 13.6, 7.6 Hz, $CH_AH_BCH(CH_3)CHO$), 1.58 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.56 (3H, m, $CH_3CHC(CH_3)CH_2$), 1.01 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.4, 132.4, 121.7, 44.6, 41.1, 15.7, 13.6, 13.4; **IR** (film, cm^{-1}) 2972, 2920, 2862, 2714, 2256, 1727, 1671, 1652, 1455, 1382, 1115, 1069, 964, 913, 850, 805, 734, 648.



(***R***)-77 **138** **143**

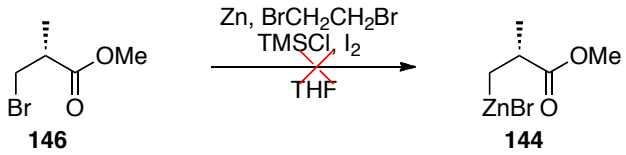
[[3-(2*R*,3*S*,4*S*,6*E*)-4*R*]-3-(3-hydroxy-2,4,6-trimethyl-1-oxo-oct-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (143). The previous procedure used for the preparation of aldol adduct **78** was followed with oxazolidinone **(*R*)-77** (327 mg; 1.40 mmol), Bu_2BOTf (1.68 mL; 1M in CH_2Cl_2; 1.68 mmol), Et_3N (254 μL; 1.82 mmol), aldehyde **138** (177 mg; 1.40 mmol) and CH_2Cl_2 (3 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **143** (287 mg; 57%, >88% ds) as a white solid. **R*f*** = 0.42 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = -47.3 (c 0.93, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35-7.32 (2H, m, Ar*H*), 7.29-7.26 (1H, m, Ar*H*), 7.22-7.20 (2H, m, Ar*H*), 5.24 (1H, q, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 4.69 (1H, m, C*H*CH_2Ph), 4.23 (1H, dd, J = 9.0, 7.2 Hz, $CHCH_AH_BO$), 4.19 (1H, dd, J = 9.0, 2.4 Hz, $CHCH_AH_BO$), 3.97 (1H, dq, J = 6.6, 2.4 Hz, CH(OH)CH(CH_3)C=O), 3.62 (1H, ddd, J = 8.4,

2.4, 2.4 Hz, C*H*OH), 3.27 (1H, dd, J = 13.8, 3.6 Hz, CH_AH_BPh), 2.95 (1H, d, J = 3.0 Hz, O*H*), 2.79 (1H, dd, J = 13.2, 9.6Hz, CH_AH_BPh), 2.52 (1H, d, J = 12.6 Hz, CH_AH_BCH(CH_3)CHOH), 1.78-1.72 (1H, m, CH_2CH(CH_3)CHOH), 1.70 (1h, dd, J = 13.2, 9.6 Hz, CH_AH_BCH(CH_3)CHOH), 1.60 (3H, s, CH_3CHC(CH_3)CH_2), 1.58 (3H, d, J = 6.6 Hz, CH(OH)CH(CH_3)C=O), 1.25 (3H, d, J = 7.2 Hz, CH_2CH(CH_3)CHOH), 0.80 (3H, d, J = 6.6 Hz, CH_3CHC(CH_3)CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.7, 153.1, 135.2, 135.0, 129.6, 129.1, 127.6, 120.7, 76.2, 66.3, 55.4, 44.2, 40.0, 37.9, 34.0, 15.7, 15.4, 13.5, 9.7; **IR** (film, cm^{-1}) 3523, 2968, 2919, 1781, 1696, 1454, 1385, 1290, 1210, 1107, 1013, 983, 762, 702; **HRESIMS** calculated for $C_{21}H_{29}NO_4H^+$: 360.2169; found: 360.2170.

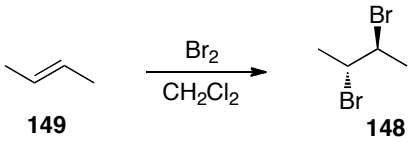


(***S***)-32 **146**

(2*S*)-Methyl-3-bromo-2-methyl-propionate (146), synthesised according to the procedure of Spilling *et al*.[35] To a stirred solution of PPh_3 (4.76 g; 18.1 mmol) and imidazole (1.23 g; 18.1 mmol) in CH_2Cl_2 (130 mL) at 0 ^oC was added a solution of bromine (0.98 mL; 19.2 mmol) in CH_2Cl_2) and the resulting solution stirred at 0 ^oC for 10 min. (*S*)-Roche ester (**(*S*)-32**) (2.00 mL; 18.1 mmol) was then added and the solution warmed to rt overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography (buffered silica, 50% EtOAc/X4) to give bromide **146** (2.85 g; 87%) as a clear, colourless oil. **R*f*** = 0.59 (50% EtOAc/X4)**; ^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (3H, s, OCH_3), 3.54 (1H, dd, J = 10.4, 6.8 Hz, CH_AH_BBr), 3.43 (1H, dd, J = 10.0, 6.0 Hz, CH_AH_BBr), 2.86 (1H, ddq, J = 7.2, 6.8, 6.0 Hz, C*H*CH_3), 1.25 (3H, d, J = 7.2 Hz, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8, 52.1, 42.1, 34.1, 16.3.

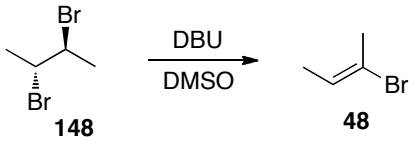


(2*R*)-3-Methoxy-2-methyl-3-oxopropylzinc bromide (144), synthesis attempted according to a procedure modified from Wang *et al*.[36] Zinc powder (219 mg; 3.35 mmol) was washed successively with 2 M HCl (5 mL), H_2O (5 mL), EtOH (5 mL) and Et_2O (5 mL) and dried under high vacuum. The zinc powder was suspended in THF (1.9 mL) and 1,2-dibromoethane (12 μL; 134 μmol) added with stirring at rt for 10 min. A few drops of TMSCl were added and the mixture was stirred for a further 10 min before bromide **146** (505 mg; 2.79 mmol) was added, along with a few crystals of I_2. The reaction mixture stirred at rt overnight, then added dropwise to a stirred solution of (*E*)-2-bromo-2-butene (189 μL; 1.86 mmol) in THF (37 mL). $Pd(PPh_3)_2Cl_2$ (73.4 mg; 186 mmol) was added one portion and the mixture stirred at rt for 24 h. The reaction was quenched by addition of sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Crude NMR showed that no reaction had occurred and that only bromide **146** remained, indicating that zinc insertion had not occurred.



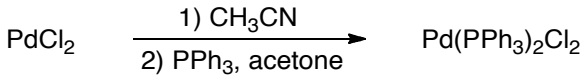
Meso-2,3-dibromobutane (148), synthesised according to a procedure modified from Cochran *et al.*[37] Trans-2-butene (**149**) (10-20 mL) was condensed using a cold finger (-78 ^oC) into CH_2Cl_2 (100 mL) at -15 ^oC. The reaction mixture was maintained at -15 ^oC and a 1 M solution of Br_2 was added dropwise until the first persistent colour change from colourless to red was apparent. The product was immediately washed with 1 M $Na_2S_2O_3$ (100 mL), sat. aq. $NaHCO_3$ (100 mL) and H_2O (100 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Distillation under reduced pressure gave meso-2,3-dibromobutane (**148**) (23.5 g) as a colourless liquid. **bp.** 83-84 ^oC at 70

mmHg; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.19 (2H, dq, J = 4.8, 2.4 Hz, C*H*Br), 1.86 (6H, d, J = 6.0 Hz, CHCH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 54.3, 25.5.

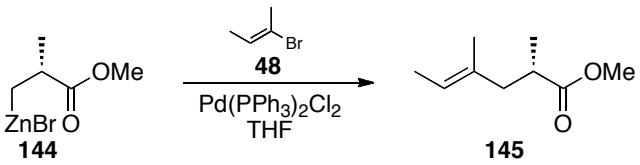


148 **48**

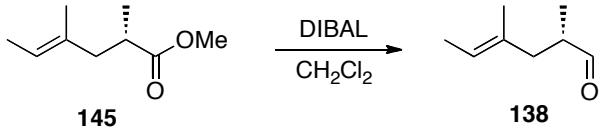
(*E*)-2-Bromo-2-butene (48), synthesised according to the procedure of Cochran *et al.*[37] To a stirred solution of meso-2,3-dibromobutane (**148**) (5.00 mL; 4.9 mmol) in DMSO (27 mL) was added DBU (6.12 mL: 40.9 mmol) and the resulting was solution was stirred in the dark at rt for 45 min. The mixture was then subjected to high vacuum (0.4 mmHg) and the product was collected in a liquid N_2 trap to yield (*E*)-2-bromo-2-butene (**48**) (4.42 g; 80%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (1H, m, $CH_2CHC(Br)CH_3$), 2.20 (3H, m $CH_2CHC(Br)CH_3$), 1.61 (3H, m, $CH_2CHC(Br)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 126.7, 119.6, 22.9, 15.1.



Bis(triphenylphosphine)palladium chloride, synthesised according to a procedure modified from Michelin *et al*.[38] $PdCl_2$ (300 mg; 169 mmol) was suspended in CH_3CN (8.5 mL) and refluxed under N_2 until formation of $Pd(CH_3CN)_2Cl_2$ was complete, as indicated by a colour change from dark brown to yellow. The mixture was cooled to rt and the excess solvent removed *in vacuo*. The resultant solid was suspended in acetone (8.5 mL) at rt under N_2 and a solution of PPh_3 (888 mg; 3.38 mmol) in acetone (8.5 mL) was added dropwise over 20 min. The solution obtained was reduced in volume to approx. ¼ and treated with Et_2O to give a yellow precipitate, which was isolated by vacuum filtration to give $Pd(PPh_3)_2Cl_2$ (1.05 g; 88%) as a yellow solid.

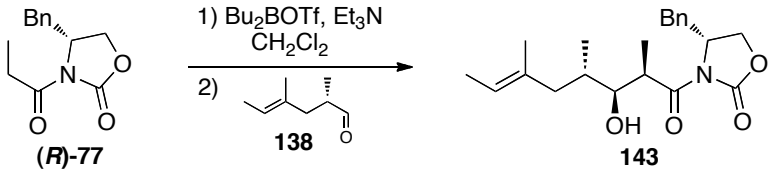


(2*R*,4*E*)-Methyl-2,4-dimethyl-hexanoate (145), synthesised according to the procedure of Correa and Pilli.[39] To a stirred solution of (*E*)-2-bromo-2-butene (**48**) (500 μL; 4.93 mmol) in THF (100 mL) at 0 °C was added dropwise over 1 min a solution of (*R*)-3-methoxy-2-methyl-3-oxopropylzinc bromide (**144**) (11.8 mL; 0.5M in THF; 5.90 mmol). $Pd(PPh_3)_2Cl_2$ (97 mg; 246 μmol) was then added in one portion and the mixture stirred at 0 °C for 10 min, followed by rt for 24 h. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL) and product extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave ester **145** (526 mg; 68 %) as a colourless oil. **R*f*** = 0.30 (50% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = +3.92 (c 1.02, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.20 (1H, q, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 3.62 (3H, s, OCH_3), 2.59 (1H, dq, J = 7.2, 6.6 Hz, $CH(CH_3)COOCH_3$), 2.34 (1H, dd, J = 13.2, 7.2 Hz, $CH_AH_BCH(CH_3)COOCH_3$), 2.00 (1H, dd, J = 13.8, 7.8 Hz, $CH_AH_BCH(CH_3)COOCH_3$), 1.55 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.54 (3H, d, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 1.06 (3H, d, J = 6.6 Hz, $CH(CH_3)COOCH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.2, 132.9, 121.1, 44.0, 38.0, 16.6, 15.4, 13.5.



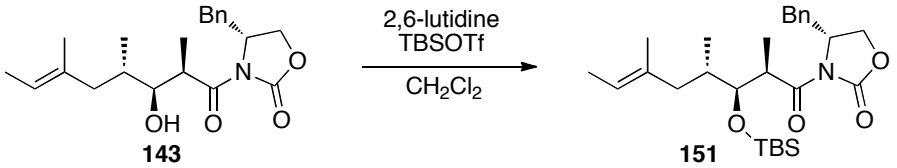
(2*R*,4*E*)-2,4-dimethyl-hexanal (138). To a stirred solution of ester **145** (449 mg; 2.87 mmol) in CH_2Cl_2 (14 mL) at -78 °C was added dropwise a solution of DIBAL (3.01 mL; 1M in hexanes; 3.01 mmol). The resulting solution was stirred at -78 °C for 1 h, quenched with sat. aq. NH_4Cl (20 mL) and warmed to rt. A mixture of sat. aq. potassium sodium tartrate (20 mL) and Et_2O (20 mL) was then added with vigorous stirring for 10 min. Layers were separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL),

dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **138** (256 mg; 71%) as a colourless oil. **R*f*** = 0.39 (100% X4/CH_2Cl_2); **[α]$^{20}_{D}$** = +6.79 (c 2.80, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.60 (1H, d, J = 2.0 Hz, C*H*O), 5.25 (1H, m, $CH_3CHC(CH_3)CH_2$), 2.49 (1H, dddq, J = 13.6, 8.0, 6.8, 2.0 Hz, C*H*(CH_3)CHO), 2.40 (1H, m, $CH_AH_BCH(CH_3)CHO$), 1.97 (1H, m, $CH_AH_BCH(CH_3)CHO$), 1.59 (3H, m, $CH_3CHC(CH_3)CH_2$), 1.57 (3H, m, $CH_3CHC(CH_3)CH_2$), 1.02 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.4, 132.3, 121.6, 44.6, 41.0, 15.7, 13.5, 13.3.

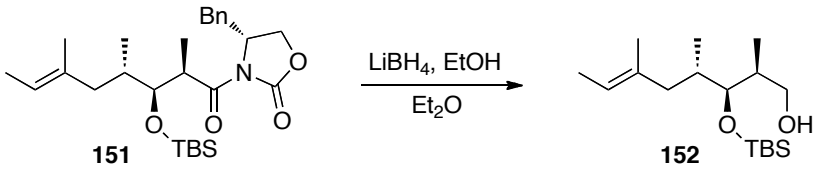


[[3-(2*R*,3*S*,4*S*,6*E*)-4*R*]-3-(3-hydroxy-2,4,6-trimethyl-1-oxo-oct-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (143). The previous procedure used for the preparation of aldol adduct **78** was followed with oxazolidinone **(*R*)-77** (1.57 g; 6.74 mmol), Bu_2BOTf (8.09 mL; 1M in CH_2Cl_2; 8.09 mmol), Et_3N (1.22 mL; 8.76 mmol), aldehyde **138** (850 mg; 6.74 mmol) and CH_2Cl_2 (14 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **143** (1.32 g; 55%, >98% ds) as a white solid. **R*f*** = 0.42 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_{D}$** = -45.9 (c 0.68, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35-7.32 (2H, m, Ar*H*), 7.29-7.26 (1H, m, Ar*H*), 7.22-7.20 (2H, m, Ar*H*), 5.24 (1H, q, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 4.69 (1H, m, C*H*CH_2Ph), 4.23 (1H, dd, J = 9.0, 7.2 Hz, $CHCH_AH_BO$), 4.19 (1H, dd, J = 9.0, 2.4 Hz, $CHCH_AH_BO$), 3.97 (1H, dq, J = 6.6, 2.4 Hz, CH(OH)C*H*(CH_3)C=O), 3.62 (1H, ddd, J = 8.4, 2.4, 2.4 Hz, C*H*OH), 3.27 (1H, dd, J = 13.8, 3.6 Hz, CH_AH_BPh), 2.95 (1H, d, J = 3.0 Hz, O*H*), 2.79 (1H, dd, J = 13.2, 9.6 Hz, CH_AH_BPh), 2.52 (1H, d, J = 12.6 Hz, $CH_AH_BCH(CH_3)CHOH$), 1.78-1.72 (1H, m, $CH_2CH(CH_3)CHOH$), 1.70 (1h, dd, J = 13.2, 9.6 Hz, $CH_AH_BCH(CH_3)CHOH$), 1.60 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.58 (3H, d, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 1.25 (3H, d, J = 7.2 Hz, $CH_2CH(CH_3)CHOH$), 0.80 (3H, d, J = 6.6 Hz, CH(OH)CH(C*H*$_3$)C=O); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.7, 153.1, 135.2, 135.0, 129.6, 129.1, 127.6, 120.7, 76.2, 66.3, 55.4, 44.2, 40.0, 37.9, 34.0, 15.7, 15.4, 13.5, 9.7; **IR**

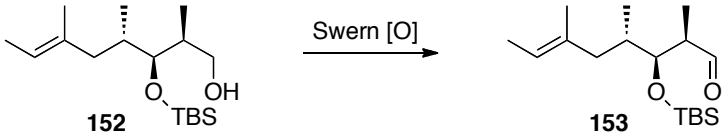
(film, cm^{-1}) 3523, 2968, 2919, 1781, 1696, 1454, 1385, 1290, 1210, 1107, 1013, 983, 762, 702; **HRESIMS** calculated for $C_{21}H_{29}NO_4H^+$: 360.2169; found: 360.2170.



[[3-(2*R*,3*S*,4*S*,6*E*)-4*R*]-3-(3-[*tert*-butyldimethylsilyloxy]-2,4,6-trimethyl-1-oxo-oct-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (151). The previous procedure used for the preparation of TBS ether **72** was followed with alcohol **143** (1.32 mg; 3.68 mmol), 2,6-lutidine (857 μL; 7.36 mmol), TBSOTf (1.27 mL; 5.52 mmol) and CH_2Cl_2 (37 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave TBS ether **151** (1.74 g; 99%) as white solid. **R*f*** = 0.39 (50% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = +20.7 (c 1.02, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.31 (2H, m, Ar*H*), 7.30-7.25 (1H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 5.14 (1H, q, J = 6.0 Hz, $CH_3CHC(CH_3)CH_2$), 4.63 (1H, m, $CHCH_2Ph$), 4.19-4.13 (2H, m, $CHCH_2O$), 3.97 (1H, dq, J = 6.4, 6.4 Hz, $CH(OH)CH(CH_3)C{=}O$), 3.95 (1H, dd, J = 6.4, 3.6 Hz, CHOTBS), 3.27 (1H, dd, J = 13.2, 3.2 Hz, CH_AH_BPh), 2.77 (1H, dd, J = 13.6, 9.6 Hz, CH_AH_BPh), 2.19 (1H, d, J = 13.2 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.76-1.69 1H, m, $CH_2CH(CH_3)CHOTBS$), 1.60 (1h, dd, J = 13.2, 10.8 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.55 (3H, d, J = 6.8 Hz, $CH_3CHC(CH_3)CH_2$), 1.51 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.24 (3H, d, J = 6.8 Hz, $CH(OH)CH(CH_3)C{=}O$), 0.93 (9H, s, $OSi(CH_3)_3$), 0.85 (3H, d, J = 6.4 Hz, $CH_2CH(CH_3)CHOTBS$), 0.08 (3H, s, $OSi(CH_3)CH_3$), 0.05 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.3, 153.0, 135.5, 134.3, 129.6, 129.1, 120.3, 76.9, 66.1, 55.8, 42.6, 41.3, 37.8, 36.8, 27.1, 26.3, 15.9, 15.5, 14.2, 14.1, 13.5, -3.6, -3.9; **IR** (film, cm^{-1}) 3531, 3062, 3028, 2928, 2856, 1783, 1681, 1497, 1471, 1455, 1385, 1291, 1240, 1209, 1110, 1064, 1019, 984, 967, 944, 835, 813, 772, 738, 701, 677, 655; **HRESIMS** calculated for $C_{27}H_{43}O_4NSiNa^+$: 496.2854; found: 496.2880.

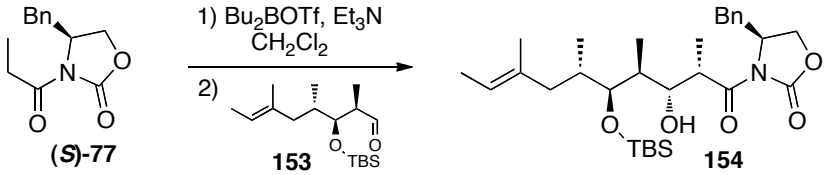


(2*S*,3*S*,4*S*,6*E*)-3-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-octan-1-ol (152). The previous procedure used for the preparation of alcohol **102** was followed with oxazolidinone **151** (254 mg; 536 μmol), EtOH (75 μL; 1.29 mmol), $LiBH_4$ (643 μL; 2 M in THF; 1.29 mmol) and Et_2O (5.4 mL). Purification by column chromatography (buffered silica, 50% CH_2Cl_2/X4) gave alcohol **152** (126 mg; 78%) as a colourless oil. **R*f*** = 0.40 (50% CH_2Cl_2/X4); **$[\alpha]^{20}_D$** = +7.88 (c 1.02, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.20-5.16 (1H, m, $CH_3CHC(CH_3)CH_2$), 3.58 (1H, dd, J = 5.4, 2.4 Hz, C*H*OTBS), 3.57 (1H, dd, J = 10.8, 7.8 Hz, CH_AH_BOH), 2.46 (1H, dd, J = 10.8, 6.6 Hz, CH_AH_BOH), 2.44 (1H, dd, J = 13.2, 3.6 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.93-1.87 (1H, m, $CH(CH_3)CH_2OH$), 1.85-1.77 (1H, m, $CH_2CH(CH_3)CHOTBS$), 1.73 (1H, br s, O*H*), 1.66 (1H, dd, J = 13.2, 10.2 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.57 (3H, d, J = 9.0 Hz, $CH_3CHC(CH_3)CH_2$), 1.57 (3H, s, $CH_3CHC(CH_3)CH_2$), 0.90 (9H, s, $OSi(CH_3)_3$) 0.88 (3H, d, J = 7.2 Hz, $CH(OTBS)CH(CH_3)CH_2OH$), 0.80 (3H, d, J = 6.6 Hz, $CH_2CH(CH_3)CHOTBS$), 0.06 (3H, s, $OSi(CH_3)CH_3$), 0.06 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.6, 120.4, 76.8, 66.8, 43.9, 38.7, 35.3, 26.2, 18.5, 16.2, 15.5, 12.0, -3.8, -4.1; **IR** (film, cm^{-1}) 3332, 2957, 2929, 2857, 1472, 1462, 1406, 1380, 1360, 1252, 1094, 1028, 1005, 966, 939, 858, 837, 813, 772, 673; **HRESIMS** calculated for $C_{17}H_{36}O_2SiH^+$: 301.2557; found: 301.2562.



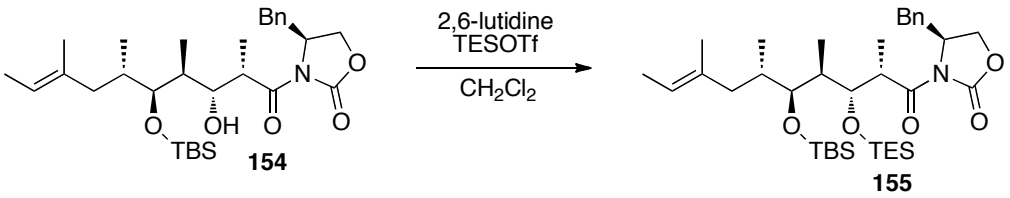
(2*R*,3*S*,4*S*,6*E*)-3-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-octanal (153). The previous procedure used for the preparation of aldehyde **88** was followed with alcohol **152** (111 mg; 369 μmol), DMSO (79 μL; 1.11 mmol), $(COCl)_2$ (277 μL; 2 M in CH_2Cl_2; 554 μmol), Et_3N (309 μL; 2.21 mmol) and CH_2Cl_2 (4 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **153** (110 mg;

100%) as a colourless oil. **R*f*** = 0.70 (100% CH_2Cl_2); **[α]$^{20}_D$** = -24.5 (c 1.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (1H, d, J = 1.2 Hz, C*H*O), 5.17-5.14 (1H, m, $CH_3CHC(CH_3)CH_2$), 3.97 (1H, dd, J = 5.2, 3.2 Hz, C*H*OTBS), 2.49 (1H, ddq, J = 6.8, 3.6, 0.8 Hz, CH(OTBS)C*H*(CH_3)CHO), 2.18-2.14 (1H, m, $CH_AH_BCH(CH_3)CHOTBS$), 1.88-1.76 (1H, m, $CH_2CH(CH_3)CHOTBS$), 1.67 (1H, dd, J = 13.2, 10.0 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.56 (3H, m, $CH_3CHC(CH_3)CH_2$), 1.54 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.10 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CHO), 0.90 (9H, s, OSi(CH_3)$_3$) 0.81 (3H, d, J = 7.2 Hz, $CH_2CH(CH_3)CHOTBS$), 0.06 (3H, s, OSi(CH_3)CH_3), -0.02 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.4, 134.0, 120.7, 75.0, 50.1, 43.3, 35.8, 26.0, 18.4, 15.7, 15.4, 13.5, 8.6, -4.0, -4.1; **IR** (film, cm^{-1}) 3435, 2929, 2857, 2708, 1727, 1691, 1472, 1462, 1381, 1361, 1253, 1093, 1030, 1005, 939, 910, 837, 813, 775, 673.



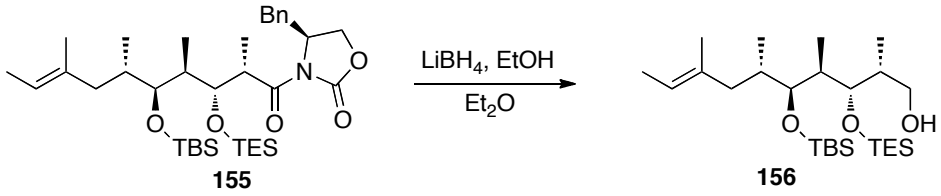
[[3-(2*S*,3*R*,4*S*,5*S*,6S,8E)-4*S*]-3-(5-[*tert*-butyldimethylsilyloxy]-3-hydroxyl-2,4,6,8-tetramethyl-1-oxo-dec-8-enyl)-4-(phenylmethyl)]-2-oxazolidinone (154). The previous procedure used for the preparation of aldol adduct **78** was followed with oxazolidinone **(*S*)-77** (112 mg; 481 μmol), Bu_2BOTf (577 μL; 1 M in CH_2Cl_2; 577 μmol), Et_3N (87 μL; 625 μmol), aldehyde **153** (144 mg; 481 μmol) and CH_2Cl_2 (1 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldol adduct **154** (182 mg; 71 %) as a white solid. **R*f*** = 0.56 (100% CH_2Cl_2); **[α]$^{20}_D$** = +20.7 (c 1.02, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34-7.31 (2H, m, Ar*H*), 7.28-7.26 (1H, m, Ar*H*), 7.22-7.20 (2H, m, Ar*H*), 5.18 (1H, q, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 4.71 (1H, m, C*H*CH_2Ph), 4.21 (1H, dd, J = 8.4, 7.8 Hz, $CHCH_AH_BO$), 4.17 (1H, dd, J = 9.0, 3.0 Hz, $CHCH_AH_BO$), 3.93 (1H, d, J = 10.2 Hz, C*H*OTBS), 3.87 (1H, dq, J = 6.6, 1.8 Hz, CH(OH)C*H*(CH_3)C=O), 3.80 (1H, dd, J = 6.0, 1.2 Hz, C*H*OH), 3.61 (1H, br s, O*H*), 3.10 (1H, dd, J = 13.8, 3.6Hz, CH_AH_BPh), 2.77 (1H, dd, J = 13.8, 9.6 Hz, CH_AH_BPh), 2.38 (1H, d, J = 13.2 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.85-1.78 (1H, m, CH(OTBS)C*H*(CH_3)CHOH), 1.57 (1H, m, $CH_AH_BCH(CH_3)CHOTBS$), 1.57 (3H, d, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 1.55

(3H, s, $CH_3CHC(CH_3)CH_2$), 1.21 (3H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)C{=}O$), 0.90 (9H, s, $OSi(CH_3)_3$), 0.87 (3H, d, J = 7.2 Hz, $CH(OTBS)CH(CH_3)CHOH$), 0.79 (3H, d, J = 7.2 Hz, $CH_2CH(CH_3)CHOTBS$), 0.09 (3H, s, $OSi(CH_3)CH_3$), 0.08 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.4, 153.1, 135.4, 134.7 ,129.6, 129.1, 127.5, 120.3, 72.3, 66.3, 55.6, 44.2, 40.0, 39.0, 37.9, 34.8, 26.2, 26.0, 18.4, 16.4, 15.5, 13.5, 11.4, 8.7, -3.9, -4.1; **IR** (film, cm^{-1}) 3531, 3062, 3028, 2928, 2856, 1783, 1681, 1497, 1471, 1455, 1385, 1291, 1240, 1209, 1110, 1064, 1019, 984, 967, 944, 835, 813, 772, 738, 701, 677, 655; **HRESIMS** calculated for $C_{30}H_{49}NO_5Si$: 532.3453; found: 532.3454.



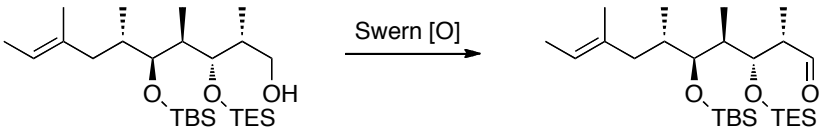
[[3-(2*S*,3*R*,4*R*,5*S*,6S,8E)-4*S*]-3-(5-[*tert*-butyldimethylsilyloxy]-3-triethylsilyloxyl-2,4,6,8-tetramethyl-1-oxo-dec-8-enyl)-4-(phenylmethyl)]-2-oxazolidinone (155). The previous procedure used for the preparation of silyl ether **72** was followed with alcohol **154** (492 mg; 925 μmol), 2,6-lutidine (215 μL; 1.85 mmol), TESOTf (314 μL; 1.39 mmol) and CH_2Cl_2 (9 mL). Purification by column chromatography (buffered silica, 50% CH_2Cl_2/X4) gave TES ether **155** (567 mg; 95%) as a clear, colourless liquid. **R*f*** = 0.49 (50% CH_2Cl_2/X4); **$[\alpha]^{20}_D$** = +20.0 (c 1.15, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.33 (2H, m, Ar*H*), 7.30 -7.26 (1H, m, Ar*H*), 7.23-7.22 (2H, m, Ar*H*), 5.18 (1H, m, $CH_3CHC(CH_3)CH_2$), 4.60 (1H, m, $CHCH_2Ph$), 4.18 (1H, dd, J = 9.6, 2.4 Hz, $CHCH_AH_BO$), 4.13 (1H, dd, J = 9.0, 7.2 Hz, $CHCH_AH_BO$), 4.07 (1H, dd, J = 6.6, 3.6 Hz, C*H*OTBS), 3.95 (1H, dq, J = 6.6, 4.2 Hz, $CH(OTES)CH(CH_3)C{=}O$), 3.57 (1H, dd, J = 3.6, 3.0 Hz, C*H*OTES), 3.27 (1H, dd, J = 13.8, 3.0 Hz, CH_AH_BPh), 2.78 (1H, dd, J = 13.2, 9.6 Hz, CH_AH_BPh), 2.15 (1H, d, J = 10.2 Hz, $CH_AH_BCH(CH_3)CHOTBS$), 1.86-1.80 (1H, m, $CH(OTBS)CH(CH_3)CHOTES$), 1.72 (1H, m, $CH_AH_BCH(CH_3)CHOTBS$), 1.58 (3H, d, J = 6.0 Hz, $CH_3CHC(CH_3)CH_2$), 1.58 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.21 (3H, d, J = 7.2 Hz, $CH(OTES)CH(CH_3)C{=}O$), 0.99 (9H, t, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.93 (3H, d, J = 7.2 Hz, $CH(OTBS)CH(CH_3)CHOTES$), 0.91 (9H, s, $OSi(CH_3)_3$), 0.77 (3H, d, J = 6.6 Hz, $CH_2CH(CH_3)CHOTBS$), 0.64 (6H, q, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.05 (3H, s,

OSi(C*H*$_3$)CH$_3$), 0.05 (3H, s, OSi(CH$_3$)C*H*$_3$); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 175.9, 152.9, 135.4, 134.5, 129.6, 129.1, 127.5, 120.0, 76.3, 74.8, 66.0, 55.9, 42.2, 41.8, 40.8, 37.7, 36.9, 34.8, 26.3, 18.7, 16.3, 15.6, 13.5, 11.8, 7.3, 5.7, -3.2, -3.6; **IR** (film, cm^{-1}) 3027, 2956, 2878, 2857, 1784, 1701, 1497, 1456, 1382, 1348, 1289, 1208, 1103, 1033, 1007, 967, 836, 813, 772, 738, 702, 673; **HRESIMS** calculated for $C_{36}H_{63}NO_5Si_2Na^+$: 668.4137; found: 668.4127.



155 **156**

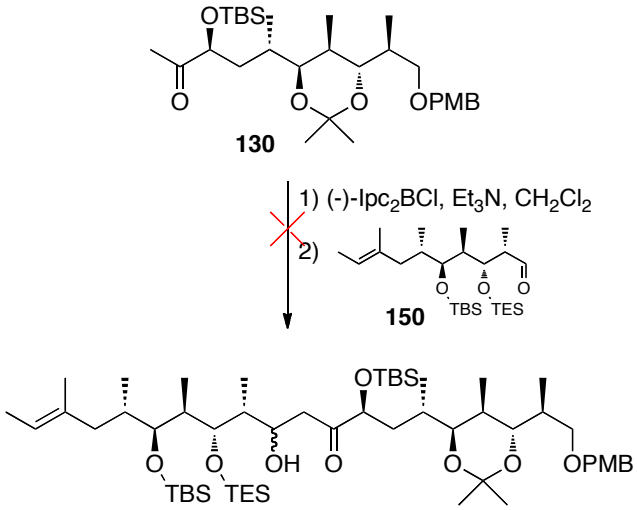
(2*R*,3*S*,4*R*,5*S*,6S,8E)-5-(*tert*-butyldimethylsilyloxy)-3-triethylsilyloxyl-2,4,6,8-tetramethyl-dec-8-en-1-ol (156). The previous procedure used for the preparation of alcohol **102** was followed with oxazolidinone **155** (143 mg; 221 μmol), EtOH (31 μL; 531 μmol), LiBH$_4$ (265 μL; 2 M in THF; 531 μmol) and Et$_2$O (3 mL). Purification by column chromatography (buffered silica, 50% CH$_2$Cl$_2$/X4) gave alcohol **156** (76.9 mg; 74%) as a colourless oil. **R*f*** = 0.40 (50% CH$_2$Cl$_2$/X4); **[α]$^{20}_D$** = -7.44 (c 1.21, CHCl$_3$); **^{1}H NMR** (600 MHz, CDCl$_3$) δ 5.19 (1H, q, J = 6.6 Hz, CH$_3$C*H*C(CH$_3$)CH$_2$), 3.77 (1H, d, J = 7.2 Hz, C*H*OTBS), 3.57 (1H, dd, J = 3.0, 3.0 Hz, C*H*OTES), 3.52 (1H, dd, J = 9.6, 7.8 Hz, C*H*$_A$H$_B$OH), 3.46 (1H, dd, J = 10.2, 6.0 Hz, CH$_A$*H*$_B$OH), 2.11 (1H, d, J = 9.6 Hz, C*H*$_A$H$_B$CH(CH$_3$)CHOTBS), 1.84-1.81 (1H, m, CH(OTBS)C*H*(CH$_3$)CHOTES), 1.84-1.81 (1H, m, CH(OTES)C*H*(CH$_3$)CH$_2$OH), 1.75 (1H, d, J = 10.2 Hz, CH$_A$*H*$_B$CH(CH$_3$)CHOTBS), 1.76-2.74 (1H, m, CH$_2$C*H*(CH$_3$)CHOTBS), 1.57 (3H, d, J = 8.4 Hz, C*H*$_3$CHC(CH$_3$)CH$_2$), 1.57 (3H, s, CH$_3$CHC(C*H*$_3$)CH$_2$), 1.53 (1H, br s, O*H*), 0.97 (9H, t, J = 7.8 Hz, OSi(CH$_2$C*H*$_3$)$_3$), 0.92 (9H, s, OSi(C*H*$_3$)$_3$), 0.88 (3H, d J = 6.6 Hz, CH(OTES)CH(C*H*$_3$)CH$_2$OH) 0.87 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CHOTES), 0.78 (3H, d, J = 6.0 Hz, CH$_2$CH(C*H*$_3$)CHOTBS), 0.63 (6H, q, J = 7.8 Hz, OSi(C*H*$_2$CH$_3$)$_3$), 0.07 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.06 (3H, s, OSi(CH$_3$)C*H*$_3$); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 134.5, 120.1, 77.0, 74.8, 67.2, 42.0, 41.3, 38.0, 37.1, 26.3, 18.7, 15.9, 14.3, 13.5, 11.2, 7.2, 5.7, -3.4, -3.4; **IR** (film, cm^{-1}) 3355, 2957, 2878, 2858, 1461, 1413, 1381, 1360, 1252, 1089, 1038, 972, 939, 835, 772, 741, 674; **HRESIMS** calculated for $C_{26}H_{56}O_3Si_2Na^+$: 495.3660; found: 495.3661.



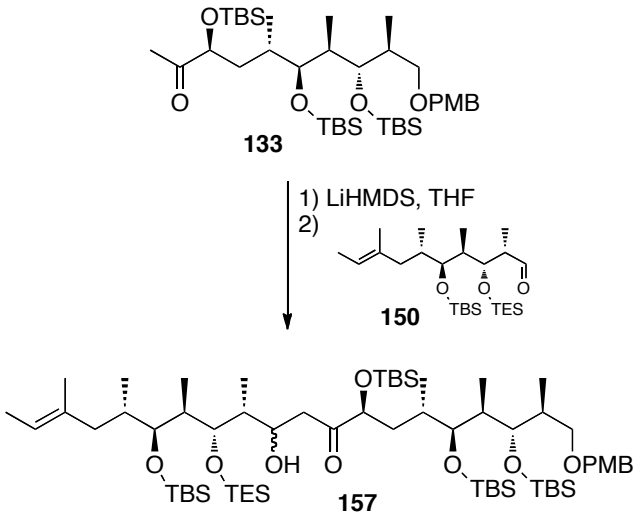
156 **150**

(2*S*,3*R*,4*R*,5*S*,6S,8E)-5-(*tert*-butyldimethylsilyloxy)-3-triethylsilyloxyl-2,4,6,8-tetramethyl-dec-8-enal (150). The previous procedure used for the preparation of aldehyde **88** was followed with alcohol **156** (23.2 mg; 49.1 mmol), DMSO (10 μL; 147 μmol), $(COCl)_2$ (37 μL; 2 M in CH_2Cl_2; 73.7 mmol), Et_3N (41 μL; 295 μmol) and CH_2Cl_2 (0.5 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave aldehyde **150** (23.1 mg; 100%) as a colourless oil. **R*f*** = 0.66 (50% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = +18.2 (c 1.16, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.69 (1H, s, C*H*O), 5.19 (1H, q, J = 6.6 Hz, $CH_3CHC(CH_3)CH_2$), 4.17 (1H, dd, J = 7.2, 1.8 Hz, C*H*OTBS), 3.61 (1H, dd, J = 3.6, 3.0 Hz, C*H*OTES), 2.45 (1H, dq, J = 7.2, 1.8 Hz, CH(OTES)C*H*(CH_3)CHO), 2.10 (1H, d, J = 10.8 Hz, CH_AH_BCH(CH_3)CHOTBS), 1.82 (1H, ddq, J = 7.2, 6.6, 2.4 Hz, CH(OTBS)C*H*(CH_3)CHOTES), 1.78-1-72 (1H, m, CH_2C*H*(CH_3)CHOTBS), 1.71 (1H, d, J = 10.8 Hz, CH_AH_BCH(CH_3)CHOTBS), 1.58 (3H, d, J = 9.0 Hz, C*H*$_3$CHC$(CH_3)CH_2$), 1.57 (3H, s, CH_3CHC(C*H*$_3)CH_2$), 1.12 (3H, d, J = 7.2 Hz, CH(OTES)CH(C*H*$_3$)CHO), 0.93 (9H, t, J = 7.8 Hz, OSi(CH_2C*H*$_3)_3$), 0.90 (9H, s, OSi(C*H*$_3)_3$), 0.86 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CHOTES), 0.78 (3H, d, J = 6.0 Hz, CH_2CH(C*H*$_3$)CHOTBS), 0.57 (6H, q, J = 7.8 Hz, OSi(C*H*$_2$CH$_3)_3$), 0.07 (3H, s, OSi(C*H*$_3$)CH_3), 0.06 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.5, 134.2, 120.2, 76.2, 73.2, 49.7, 42.6, 41.0, 37.6, 26.2, 18.6, 15.6, 15.5, 13.5, 11.9, 7.7, 7.1, 5.6, -3.4, -3.6; **IR** (film, cm^{-1}) 2957, 2878, 2858, 2706, 1728, 1462, 1381, 1252, 1034, 969, 834, 772, 742, 673.

4.2.6 Major Fragment Union and Cyclisation

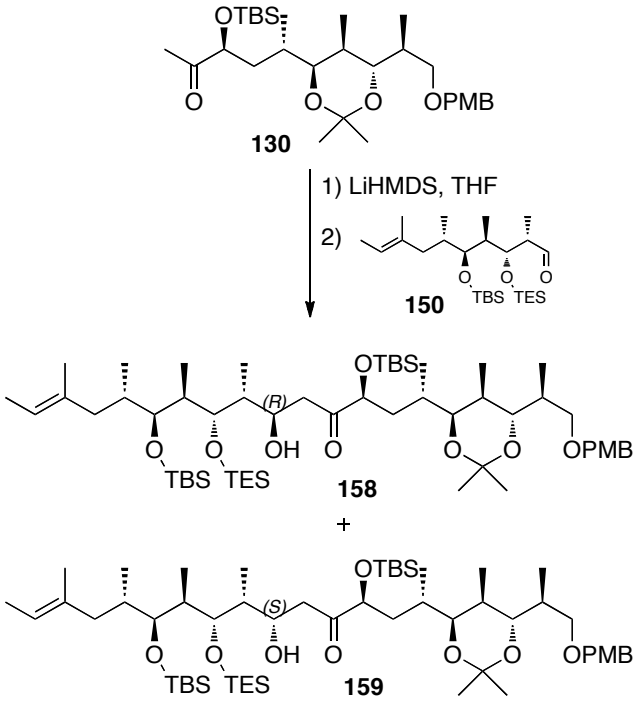


(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-1-(8,15-bis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-hydroxy-4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptamethyl-3,5-[(bis-dimethyl-methylene)dioxy]-icos-18-en-9-one. The previous procedure used for the attempted union of model ketone **53** with model aldehyde **85** was followed with (-)-Ipc_2BCl (22.7 mg; 70.9 μmol), Et_3N (11 μL; 78.0 μmol), ketone **130** (51.7 g; 96.3 μmol), aldehyde **150** (33.4 mg; 70.9 μmol) and Et_2O (1 mL). Crude ^1H NMR showed that no reaction had occurred, returning ketone **130** and aldehyde **150**.



(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-3,5,8,15-tetrakis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-hydroxy-1-(4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptamethyl-icos-18-en-9-one (157). The previous procedure used for the preparation of aldol adduct **108** was used with methyl ketone **133** (7.4 mg; 10.2 μmol), LiHMDS (20 μL; 20.4 μmol), aldehyde **150** (8.4 mg; 17.8 μmol) and THF (0.5 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) aldol adduct **157** as a single isomer (2.0 mg; 16%) and various decomposition products. **R*f*** = 0.43 (50% X4/CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 5.19 (1H, m, CH_3CHCCH_3), 4.41 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.11 (1H, m, C(=O)C*H*OTBS), 4.05 (1H, m, C*H*OH), 3.83 (1H, d. J = 6.0 Hz, C*H*OTES), 3.80 (3H, s, OCH_3), 3.53 (1H, dd, J = 9.6, 5.4 Hz, CH_AH_BOPMB), 3.49 (1H, m, C*H*(OTBS)CH(CH_3)CHOTES), 3.31 (1H, dd, J = 8.4, 7.2 Hz, CH_AH_BOPMB), 3.24 (1H, m, CH_2CH(CH_3)C*H*(OTBS)$CHCH_3$), 3.21 (1H, dd, J = 6.0, 6.0 Hz, C*H*(OTBS)CH(CH_3)CH_2OPMB), 3.03 (1H, br s, O*H*), 2.76-2.71 (1H, m, CH(OH)CH_AH_BC=O), 2.65 (1H, dd, J = 12.0, 7.8 Hz, CH(OH)CH_AH_BC=O), 2.10-2.00 (2H, m, CH_3CHC(CH_3)$CH_AH_B$$CCH_3$ and C(=O)CH(OTBS)$CH_AH_B$$CHCH_3$), 1.95-1.83 (3H, m, C*H*(CH_3)CH_2OPMB, CH(OTBS)C*H*(CH_3)CHOTBS and CH(OTBS)C*H*(CH_3)CHOTES), 1.78-1.60 (3H, m, CH_3CHC(CH_3)CH_2C*H*CH_3, C(=O)CH(OTBS)CH_2C*H*CH_3 and CH(OTES)C*H*(CH_3)CHOH), 1.59 (3H, d, J = 6.6 Hz, C*H*$_3$CHCCH_3), 1.59 (3H, s, CH_3CHCC*H*$_3$), 1.42-1.35 (1H, m, CH_3CHC(CH_3)$CH_AH_B$$CCH_3$), 1.08-1.03 (1H, m, C(=O)CH(OTBS)$CH_AH_B$$CHCH_3$), 0.99 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2OPMB), 0.97 (9H, t, J = 7.8 Hz, OSi(CH_2C*H*$_3$)$_3$), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.90 (9H,

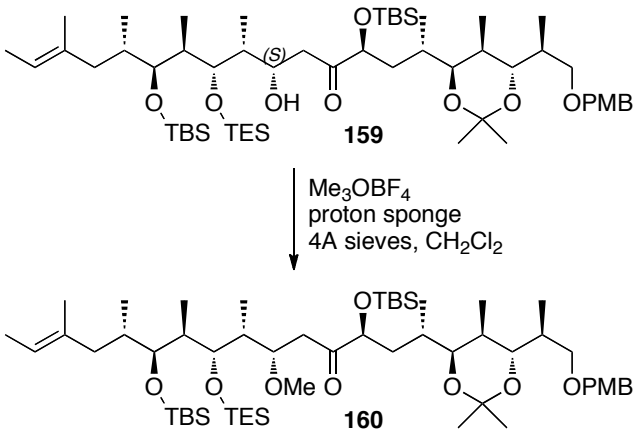
s, OSiC(CH_3)$_3$), 0.90 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CHOTES), 0.82 (3H, d, J= 7.2 Hz, CH(OTBS)C*H*(CH_3)CHOTBS), 0.81 (3H, d, J = 7.2 Hz, CH(OTBS)CH_2C*H*(CH_3)CHOTBS), 0.78 (3H, d, J = 6.0 Hz, CH_3CHC(CH_3)CH_2CHCH_3), 0.63 (6H, q, J = 7.8 Hz, OSi(C$H_2$$CH_3$)$_3$), 0.06 (9H, OSi(C$H_3$)$CH_3$), 0.04 (9H, s, OSi($CH_3$)C$H_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.2, 159.1, 130.9, 129.2, 120.1, 113.8, 76.5, 73.3, 72.9, 72.1, 55.4, 42.0, 41.7, 38.0, 37.9, 36.7, 35.2, 31.1, 28.9, 26.3, 26.2, 25.9, 25.3, 24.8, 23.5, 18.7, 18.2, 16.1, 15.6, 15.2, 14.2, 13.5, 12.5, 7.2, 5.7, -3.4, -4.5, -5.0; **HRESIMS** calculated for $C_{65}H_{130}O_9Si_5Na^+$: 1217.8453; found: 1217.8457.



(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-1-(8,15-bis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-hydroxy-4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptameth3-dimethyl-methylene)dioxy]-icos-18-en-9-one (158) and **(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*S*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-1-(8,15-bis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-hydroxy-4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptamethyl-3,5-[(bis-dimethyl-methylene)dioxy]-icos-18-en-9-one (159).** The previous procedure used for the preparation of aldol adduct **108** was used with methyl ketone **130** (132 mg; 245 μmol), LiHMDS (490 μL; 490 μmol), aldehyde **150** (116 mg; 246 μmol) and THF (0.6 mL). Purification by column

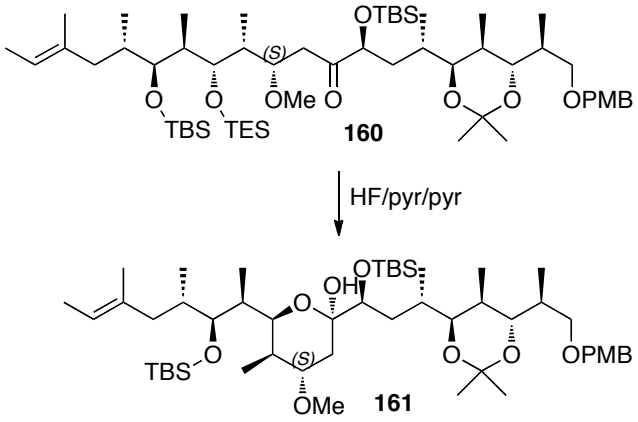
chromatography (buffered silica, 100% CH_2Cl_2) gave aldol isomer **158** (68.4 mg; 28%) and aldol isomer **159** (53.5 mg; 22%). **Major isomer 158: R*f*** = 0.57 (100% CH_2Cl_2); **[α]$^{20}_D$** = -2.20 (c 0.91, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 5.20 (1H, q, J = 6.0 Hz, CH_3CHCCH_3), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.13 (1H, d, J = 7.2 Hz, $CH(CH_3)CH(OTBS)CHCH_3$), 4.11 (1H, dd, J = 9.0, 3.6 Hz, C(=O)C*H*OTBS), 3.80 (3H, s, OCH_3), 3.77 (1H, m, C*H*OH), 3.61 (1H, dd, J = 3.0, 3.0 Hz, C*H*OTES), 3.54 (1H, dd, J = 9.0, 4.8 Hz, CH_AH_BOPMB), 3.32 (1H, s, O*H*), 3.31 (1H, dd, J = 9.0, 7.2 Hz, CH_AH_BOPMB), 3.25 (1H, dd, J = 10.8, 4.2 Hz, $CH(OTBS)CH_2CH(CH_3)CH(-O-)$), 3.22 (1H, dd, J = 7.2, 6.0 Hz, $CH(-O-)CH(CH_3)CH_2OPMB$), 2.96 (1H, dd, J = 18.6, 1.8 Hz, $CH(OH)CH_AH_BC(=O)$), 2.49 (1H, dd, J = 18.6, 9.0 Hz, $CH(OH)CH_AH_BC(=O)$), 2.13 (1H, d, J = 12.0 Hz, $CH_3CHC(CH_3)CH_AH_B$), 2.08 (1H, ddd, J = 13.2, 9.6, 3.0 Hz, $C(=O)CH(OTBS)CH_AH_B$) 1.93-1.88 (1H, m, $CH(CH_3)CH_2OPMB$), 1.91-1.86 (1H, m, $CH(-O-)CH(CH_3)CH(-O-)$), 1.81-1.76 (1H, m, $CH(CH_3)CH(OTBS)CH(CH_3)CHOTES$), 1.79-1.75 (1H, m, $CH(OTBS)CH(CH_3)CHOTES$), 1.74-1.68 (1H, m, $CH(OTBS)CH_2CH(CH_3)CH(-O-)$), 1.73 (1H, dd, J = 12.6, 10.8, $CH_3CHC(CH_3)CH_AH_B$), 1.63 (1H, dd, J = 9.0, 6.6 Hz, $CH(OTES)CH(CH_3)CHOH$), 1.58 (3H, d, J = 7.2 Hz, CH_3CHCCH_3), 1.57 (3H, s, CH_3CHCCH_3), 1.27 (3H, s, $C(CH_3)CH_3$), 1.23 (3H, s, $C(CH_3)CH_3$), 1.08 (1H, ddd, J = 13.2, 9.6, 4.2 Hz, $C(=O)CH(OTBS)CH_AH_B$), 0.99 (3H, J = 6.6 Hz, $CH(CH_3)CH_2OPMB$), 0.97 (9H, t, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.92 (9H, s, $OSiC(CH_3)_3$), 0.90 (9H, s, $OSiC(CH_3)_3$), 0.84 (3H, d, J = 7.2 Hz, $CH(CH_3)CH(OTBS)CH(CH_3)CHOTES$), 0.83 (3H, d, J = 6.6 Hz, $CH(-O-)CH(CH_3)CH(-O-)$), 0.81 (3H, d, J = 6.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH(-O-)$), 0.78 (3H, d, J = 6.6 Hz, $CH(OTBS)CH(CH_3)CHOTES$), 0.77 (3H, d, J = 6.6 Hz, $CH(OTES)CH(CH_3)CHOH$), 0.65 (3H, q, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.64 (3H, q, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.08 (3H, s, $OSi(CH_3)CH_3$), 0.07 (3H, s, $OSi(CH_3)CH_3$), 0.06 (3H, s, $OSi(CH_3)CH_3$), 0.04 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.7, 159.2, 134.6, 130.9, 129.2, 119.9, 113.8, 100.5, 77.6, 76.7, 76.6, 73.4, 72.9, 72.1, 69.2, 55.38, 55.36, 42.0, 41.6, 41.3, 39.9, 38.07, 38.02, 37.4, 35.3, 28.8, 26.3, 25.9, 25.8, 25.4, 23.6, 18.7, 18.20, 18.17, 15.8, 15.6, 15.4, 13.5, 12.4, 12.41, 12.1, 10.6, 7.3, 5.8, -3.4, -3.5, -4.6, -4.9; **IR** (film, cm^{-1}) 3527, 2957, 1706, 1613, 1586, 1513, 1462, 1378, 1301, 1250, 1171, 1099, 1035, 938, 915, 882, 836, 774, 741, 672; **HRESIMS** calculated for $C_{56}H_{106}O_9Si_3Na^+$: 1029.7037; found: 1029.7045. **Minor isomer 159: R*f*** = 0.40 (100% CH_2Cl_2); **[α]$^{20}_D$** = -

16.0 (c 0.38, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 5.20 (1H, q, J = 6.6 Hz, CH_3CHCCH_3), 4.41 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.11 (1H, dd, J = 9.6, 3.6 Hz, C(=O)C*H*OTBS), 4.06 (1H, ddd, J = 8.4, 4.2, 4.2 Hz, C*H*OH), 3.84 (1H, dd, J = 5.4, 1.2 Hz, $CH(CH_3)CH$(OTBS)$CHCH_3$), 3.80 (3H, s, OCH_3), 3.53 (1H, dd, J = 9.0 Hz, 4.8 Hz, CH_AH_BOPMB), 3.49 (1H, dd, J = 4.8, 1.2 Hz, C*H*OTES), 3.31 (1H, dd, J = 9.0, 7.2 Hz, CH_AH_BOPMB), 3.24 (1H, dd, J = 10.2, 3.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 3.22 (1H, dd, J = 6.0, 5.4 Hz, C*H*(-O-)$CH(CH_3)CH_2$OPMB), 3.02 (1H, s, O*H*), 2.73 (1H, dd, J = 18.0, 4.3 Hz, $CH(OH)CH_AH_B$C(=O)), 2.66 (1H, dd, J = 18.0, 8.4 Hz, $CH(OH)CH_AH_B$C(=O)), 2.09 (1H, d, J = 9.6 Hz, $CH_3CHC(CH_3)CH_AH_B$), 2.06 (1H, ddd, J = 13.8, 7.8, 3.0 Hz, $C(=O)CH(OTBS)CH_AH_B$), 1.93-1.89 (1H, m, $CH(CH_3)CH_2$OPMB), 1.91-1.87 (1H, m, CH(-O-)$CH(CH_3)CH$(-O-)), 1.90-1.84 (1H, m, $CH(CH_3)CH(OTBS)CH(CH_3)$CHOTES), 1.80-1.72 (1H, m, CH(OTBS)$CH(CH_3)$CHOTES), 1.79-1.76 (1H, dd, J = 12.6, 10.8, $CH_3CHC(CH_3)CH_AH_B$), 1.76-1.70 (1H, m, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 1.72-1.67 (1H, m, CH(OTES)$CH(CH_3)$CHOH), 1.59 (3H, s, CH_3CHCCH_3), 1.58 (3H, d, J = 7.2 Hz, CH_3CHCCH_3), 1.26 (3H, s, $C(CH_3)CH_3$), 1.22 (3H, s, $C(CH_3)CH_3$), 1.07 (1H, ddd, J = 13.2, 10.2, 3.6 Hz, $C(=O)CH(OTBS)CH_AH_B$), 0.99 (3H, J = 7.2 Hz, $CH(CH_3)CH_2$OPMB), 0.97 (9H, t, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.93 (3H, d, J = 6.6 Hz, CH(OTES)$CH(CH_3)$CHOH), 0.91 (9H, s, $OSiC(CH_3)_3$), 0.90 (9H, s, $OSiC(CH_3)_3$), 0.90 (3H, d, J = 7.2 Hz, $CH(CH_3)CH$(OTBS)$CH(CH_3)$CHOTES), 0.83 (3H, d, J = 6.6 Hz, CH(-O-)$CH(CH_3)CH$(-O-)), 0.82 (3H, d, J = 6.0 Hz, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 0.78 (3H, d, J = 6.0 Hz, $CH(OTBS)CH(CH_3)$CHOTES), 0.64 (6H, q, J = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.06 (6H, s, $OSi(CH_3)CH_3$), 0.05 (3H, s, $OSi(CH_3)CH_3$), 0.04 (3H, s, $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 214.4, 159.2, 148.2, 134.3, 131.0, 129.3, 120.2, 113.86, 113.83, 112.6, 100.4, 77.5, 76.63, 76.56, 73.3, 72.9, 72.2, 71.4, 71.1, 61.7, 55.4, 42.03, 42.00, 41.7, 39.23, 38.99, 38.07, 37.95, 36.6, 36.3, 33.1, 29.9, 28.9, 26.3, 25.91, 25.97, 25.4, 24.1, 23.6, 19.7, 18.7, 18.30, 18.27, 16.4, 16.2, 15.7, 15.3, 14.3, 13.6, 12.5, 12.3, 9.1, 7.2, 6.7, 5.78, 5.76, -3.30, -3.33, -4.4, -4.9; **IR** (film, cm^{-1}) 3504, 2951, 1712, 1613, 1586, 1513, 1462, 1378, 1301, 1249, 1171, 1098, 912, 836, 774, 741, 669; **HRESIMS** calculated for $C_{56}H_{106}O_9Si_3Na^+$: 1029.7037; found: 1029.7040.



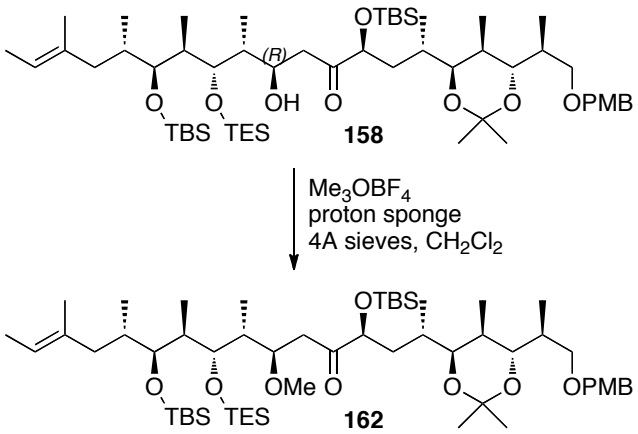
(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*S*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-1-(8,15-bis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-methoxy-4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptamethyl-3,5-[(bis-dimethyl-methylene)dioxy]-icos-18-en-9-one (160). To a stirred solution of aldol isomer **159** (53.5 mg; 53.1 μmol) in CH_2Cl_2 (1.1 mL) at 0 ^oC was added sequentially 4 Å molecular sieves (100 mg), proton sponge (68.3 mg; 319 μmol) and $Me_3O.BF_4$ (47.2 mg; 319 μmol). The reaction was warmed to rt for 1 h, before quenching by addition of sat. aq. $NaHCO_3$ (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave methyl ether **160** (41.4 mg; 76%). **R*f*** = 0.52 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -11.0 (c 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 5.20 (1H, q, J = 6.0 Hz, CH_3CHCCH_3), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.16 (1H, dd, J = 10.2, 3.0 Hz, C(=O)C*H*OTBS), 3.82 (1H, d, J = 5.4 Hz, $CH(CH_3)CH(OTBS)CHCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.62 (1H, ddd, J = 7.8, 4.8, 3.0 Hz, $CHOCH_3$), 3.54 (1H, dd, J = 9.6, 5.4 Hz, CH_AH_BOPMB), 3.47 (1H, d, J = 5.4 Hz, C*H*OTES), 3.32 (1H, dd, J = 9.0, 6.6 Hz, CH_AH_BOPMB), 3.26 (1H, dd, J = 9.6, 3.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH(-O-)$), 3.25 (3H, s, $CHOCH_3$), 3.23 (1H, dd, J = 6.6, 6.0 Hz, $CH(-O-)CH(CH_3)CH_2OPMB$), 2.80 (2H, dd, J = 18.0, 8.4 Hz, $CH(OCH_3)CH_AH_BC(=O)$), 2.55 (1H, dd, J = 18.0, 3.0 Hz, $CH(OCH_3)CH_AH_BC(=O)$), 2.09 (1H, d, J = 10.2 Hz, $CH_3CHC(CH_3)CH_AH_B$), 2.04 (1H, ddd, J = 12.6, 9.6, 1.8 Hz, $C(=O)CH(OTBS)CH_AH_B$), 1.94-1.88 (1H, m, $CH(CH_3)CH_2OPMB$), 1.91-1.85 (1H, m, $CH(OTES)CH(CH_3)CHOCH_3$), 1.90-1.84 (1H, m, $CH(-O-)CH(CH_3)CH(-O-)$), 1.85-1.80 (1H, m, $CH(OTBS)CH(CH_3)CHOTES$), 1.85-1.80 (1H, m,

C*H*(CH_3)CH(OTBS)CH(CH_3)CHOTES), 1.83-1.78 (1H, m, CH_3CHC(CH_3)CH_AH_B), 1.77-1.72 (1H, m, CH(OTBS)CH_2C*H*(CH_3)CH(-O-)), 1.58 (3H, d, J = 6.6 Hz, C*H*$_3$CHCCH_3), 1.57 (3H, s, CH_3CHCC*H*$_3$), 1.26 (3H, s, C(C*H*$_3$)CH_3), 1.22 (3H, s, C(CH_3)C*H*$_3$), 1.12 (1H, ddd, J 12.6, 10.2, 4.8 Hz, C(=O)CH(OTBS)CH_AH_B), 1.00 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH_2OPMB), 0.98 (9H, t, J = 7.8 Hz, OSi(CH_2C*H*$_3$)$_3$), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.89 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CHOTES), 0.87 (3H, d, J = 7.2 Hz, CH(OTES)CH(C*H*$_3$)CHOCH_3), 0.83 (3H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(C*H*$_3$)CH(-O-)), 0.81 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)CH(OTBS)CH(CH_3)CHOTES), 0.79 (3H, d, J = 6.6 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)), 0.65 (6H, q, J = 7.8 Hz, OSi(CH_2C*H*$_3$)$_3$), 0.07 (3H, s, OSi(C*H*$_3$)CH_3), 0.06 (3H, s, OSi(C*H*$_3$)CH_3), 0.05 (3H, s, OSi(CH_3)C*H*$_3$), 0.03 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.5, 159.2, 134.4, 131.0, 129.3, 120.0, 113.8, 100.4, 80.0, 77.5, 77.2, 76.6, 73.4, 72.9, 72.5, 72.2, 58.0, 55.4, 42.9, 41.1, 39.5, 38.1, 37.4, 37.2, 35.8, 35.3, 28.9, 26.3, 25.9, 25.2, 23.5, 18.7, 18.4, 16.6, 15.6, 15.0, 14.3, 13.5, 12.5, 12.2, 11.3, 7.4, 5.9, -3.3, -4.4, -4.96, -5.03; **IR** (film, cm^{-1}) 2957, 2857, 1716, 1700, 1615, 1514, 1457, 1378, 1301, 1249, 1171, 1097, 938, 910, 836, 774, 742, 668.



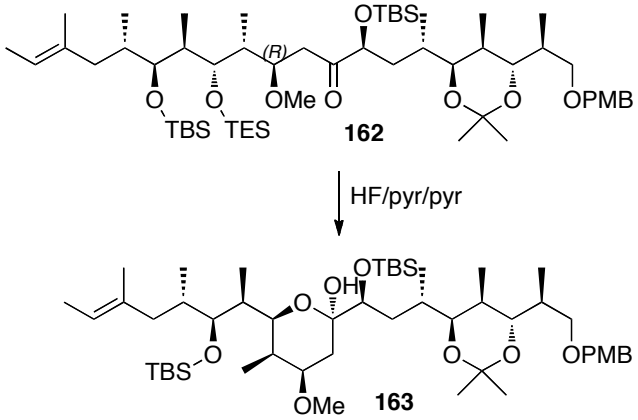
(2*R*,4*S*,5*R*,6*S*)-2-[(1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-1-(*tert*-butyldimethylsilyloxy)-8-(4-methoxyphenyl)oxy-3,5,7-trimethyl-4,6-[(bis-dimethyl-methylene)dioxy]-octanyl]-5-[(1*S*,2*S*,3*S*,5*E*)-2-(*tert*-butyldimethylsilyloxy)-1,3,5-trimethyl-hept-5-enyl]-2-hydroxy-4-methoxyl-5-methyl-tetrahydro-2*H*-pyran (161). The previous procedure used for the preparation of alcohol **82** was followed with TES ether **160** (41.4 mg; 40.5 μmol), HF/pyr/pyr (1 mL) and H_2O (32 μL). Purification by column

chromatography (buffered silica gave hemiacetal **161** (6.1 mg; 17%) as a clear, colourless oil. **R*f*** = 0.54 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +6.57 (c 0.31, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 9.0 Hz, Ar*H*), 5.17 (1H, q, J = 6.6 Hz, CH_3CHCCH_3), 4.92 (1H, s, C(-O-)(O*H*)CHOTBS), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 3.92 (1H, d, J = 5.4 Hz, $CHOCH_3$), 3.90 (1H, d, J = 9.0 Hz, C*H*(-O-)$CH(CH_3)CHOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.54 (1H, dd, J = 9.0, 4.8 Hz, CH_AH_BOPMB), 3.51 (1H, d, J = 3.0 Hz, $CH(CH_3)CH$(OTBS)$CHCH_3$), 3.47 (1H, d, J = 9.0 Hz, C(OH)(-O-)C*H*(OTBS)CH_2), 3.35 (3H, s, $CHOCH_3$), 3.32 (1H, dd, J = 9.0, 7.2 Hz, CH_AH_BOPMB), 3.22 (1H, dd, J = 9.6, 3.0 Hz, CH(OTBS)$CH_2CH(CH_3)$C*H*(-O-)), 3.21 (1H, dd, J = 6.6, 5.4 Hz, C*H*(-O-)$CH(CH_3)CH_2$OPMB), 2.31 (1H, d, J = 12.6 Hz, $CH_3CHC(CH_3)CH_AH_B$CHOTBS), 1.95-1.90 (1H, m, CH(-O-)C*H*$(CH_3)CHOCH_3$), 1.94-1.89 (1H, m, C*H*$(CH_3)CH_2$OPMB), 1.93-1.87 (1H, m, CH(OTBS)$CH_AH_BCHCH_3$), 1.89-1.85 (1H, m, $CH(OCH_3)CH_AH_B$C(-O-)(OH)), 1.88-1.84 (1H, m, CH(-O-)C*H*(CH_3)CH(-O-)), 1.71-1.66 (4H, m, CH(OTBS)CH_2C*H*(CH_3)CH(-O-), $CH_3CHC(CH_3)CH_2$C*H*(CH_3)CHOTBS, $CH(OCH_3)CH_AH_B$C(-O-)(OH) and CH(OTBS)C*H*(CH_3)CH(-O-)), 1.60-1.55 (1H, m, $CH_3CHC(CH_3)CH_AH_B$CHOTBS), 1.57 (3H, d, J = 7.2 Hz, $CH_3CHC(CH_3)CH_2$), 1.55 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.27-1.23 (1H, m, CH(OTBS)$CH_AH_BCHCH_3$), 1.24 (3H, s, $OC(CH_3)CH_3$), 1.24 (3H, s, $OC(CH_3)CH_3$), 0.99 (3H, d, J = 6.6 Hz, $CH(CH_3)CH_2$OPMB), 0.90 (9H, s, $OSiC(CH_3)_2$), 0.89 (9H, s, $OSiC(CH_3)_2$), 0.87 (3H, d, J = 7.2 Hz, CH(-O-)$CH(CH_3)CHOCH_3$), 0.84 (3H, d, J = 6.6 Hz, CH(-O-)$CH(CH_3)$CH(-O-)), 0.79 (3H, d, J = 7.2 Hz, $CH_3CHC(CH_3)CH_2CH(CH_3)$CHOTBS), 0.77 (3H, d, J = 6.6 Hz, CH(OTBS)$CH_2CH(CH_3)$CH(-O-)), 0.75 (3H, d, J = 6.6 Hz, CH(OTBS)$CH(CH_3)$CH(-O-)), 0.12 (3H, s, $OSi(CH_3)CH_3$), 0.08 (3H, s, $OSi(CH_3)CH_3$) 0.08 (6H, s $OSi(CH_3)CH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 131.1, 131.0, 129.3, 129.0, 120.0, 113.8, 100.3, 98.7, 81.6, 77.6, 75.8, 72.9, 72.3, 61.8, 56.5, 55.4, 43.9, 38.2, 37.5, 36.9, 35.4, 29.9, 29.4, 26.5, 26.4, 25.8, 25.3, 23.6, 18.8, 18.6, 15.7, 15.5, 15.0, 14.3, 14.2, 13.5, 12.9, 10.1, 9.9, -3.0, -3.82, -3.88, -4.3; **IR** (film, cm^{-1}) 3488, 2930, 2856, 1731, 1613, 1586, 1513, 1462, 1378, 1249, 1181, 1088, 939, 834, 774, 672.



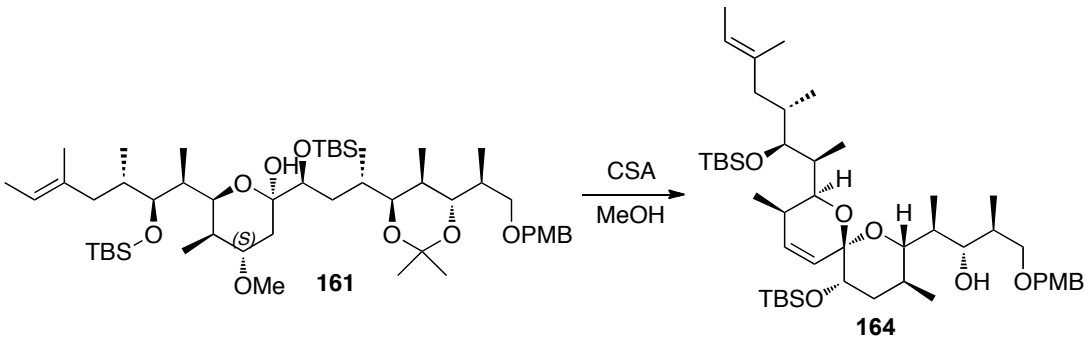
(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*S*,12*R*,13*S*,14*R*,15*S*,16*S*,18*E*)-1-(8,15-bis(*tert*-butyldimethylsilyloxy)-13-triethylsilyloxy-11-methoxy-4-methoxybenzyl)oxy-2,4,6,12,14,16,18-heptamethyl-3,5-[(bis-dimethyl-methylene)dioxy]-icos-18-en-9-one (162). The previous procedure used for the preparation of methyl ether **160** was followed with aldol isomer **158** (68.4 mg; 67.9 μmol) 4 Å molecular sieves (130 mg), proton sponge (87.3 mg; 407 μmol), $Me_3O.BF_4$ (60.2 mg; 407 μmol) and CH_2Cl_2 (1.4 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave methyl ether **162** (53.9 mg; 78%). **R*f*** = 0.43 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 5.20 (1H, q, J = 6.6 Hz, CH_3CHCCH_3), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 4.17 (1H, dd, J = 9.6, 3.0 Hz, C(=O)C*H*OTBS), 3.83 (1H, d, J = 5.4 Hz, $CH(CH_3)CH$(OTBS)$CHCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.64 (1H, ddd, J = 10.2, 7.8, 3.0 Hz, $CHOCH_3$), 3.54 (1H, dd, J = 9.0, 4.8 Hz, CH_AH_BOPMB), 3.53 (1H, m, C*H*OTES), 3.31 (1H, dd, J = 9.0, 6.6 Hz, CH_AH_BOPMB), 3.25 (1H, dd, J = 9.0, 3.6 Hz, $CH(OTBS)CH_2CH(CH_3)CH$(-O-)), 3.22 (3H, s, $CHOCH_3$), 3.22 (1H, m, C*H*(-O-)$CH(CH_3)CH_2$OPMB), 2.80 (2H, dd, J = 17.4, 8.4 Hz, $CH(OCH_3)CH_AH_B$C(=O)), 2.55 (1H, dd, J = 17.4, 3.0 Hz, $CH(OCH_3)CH_AH_B$C(=O)), 2.10 (1H, ddd, J = 13.2, 10.2, 2.4 Hz, C(=O)CH(OTBS)CH_AH_B), 2.08 (1H, d, J = 8.4 Hz, $CH_3CHC(CH_3)CH_AH_B$), 1.93-1.89 (1H, m, $CH(CH_3)CH_2$OPMB), 1.92-1.86 (1H, m, CH(OTES)$CH(CH_3)CHOCH_3$), 1.86-1.81 (3H, m, CH(-O-)$CH(CH_3)$CH(-O-)), 1.84-1.79 (1H, m, CH(OTBS)$CH(CH_3)$CHOTES), 1.82-1.77 (1H, m, $CH(CH_3)$CH(OTBS)$CH(CH_3)$CHOTES), 1.79 (1H, d, J = 7.8 Hz, $CH_3CHC(CH_3)CH_AH_B$), 1.77-1.71 (1H, m, $CH(OTBS)CH_2CH(CH_3)$CH(-O-)), 1.59 (3H, d, J = 5.4 Hz, CH_3CHCCH_3), 1.58 (3H, s, CH_3CHCCH_3), 1.26 (3H, s, $C(CH_3)CH_3$), 1.22 (3H, s, $C(CH_3)CH_3$), 1.10 (1H,

ddd, J 13.8, 10.2, 3.6 Hz, C(=O)CH(OTBS)CH_AH_B), 0.99 (3H, d, J = 6.6 Hz, CH(CH_3)CH_2OPMB), 0.97 (9H, t, J = 7.8 Hz, OSi(CH_2CH_3)$_3$), 0.92 (9H, s, OSiC(CH_3)$_3$), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.89 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CHOTES), 0.83 (3H, d, J = 6.6 Hz, CH(OTES)CH(CH_3)$CHOCH_3$), 0.83 (3H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(CH_3)CH(-O-)), 0.80 (3H, d, J = 6.0 Hz, CH(CH_3)CH(OTBS)$CH(CH_3)$CHOTES), 0.79 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CH(-O-)), 0.63 (6H, q, J = 7.8 Hz, OSi(CH_2CH_3)$_3$), 0.07 (6H, s, OSi(CH_3)CH_3), 0.06 (3H, s, OSi(CH_3)CH_3), 0.04 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.4, 159.2, 134.4, 131.0, 129.3, 120.1, 113.8, 100.4, 79.8, 77.7, 76.6, 73.7, 73.4, 72.9, 72.2, 57.2, 55.4, 42.5, 41.7, 40.2, 38.1, 37.7, 37.5, 36.8, 35.3, 28.9, 26.3, 26.0, 25.2, 23.6, 18.7, 18.3, 16.0, 15.7, 15.1, 14.3, 13.5, 12.5, 11.9, 10.3, 7.3, 5.8, -3.4, -3.6, -4.4, -5.0; **IR** (film, cm^{-1}) 2925, 1717, 1613, 1586, 1513, 1463, 1378, 1301, 1248, 1098, 915, 836, 774, 741, 669; **HRESIMS** calculated for $C_{57}H_{108}O_9Si_3Na^+$: 1043.7193; found: 1043.7197.



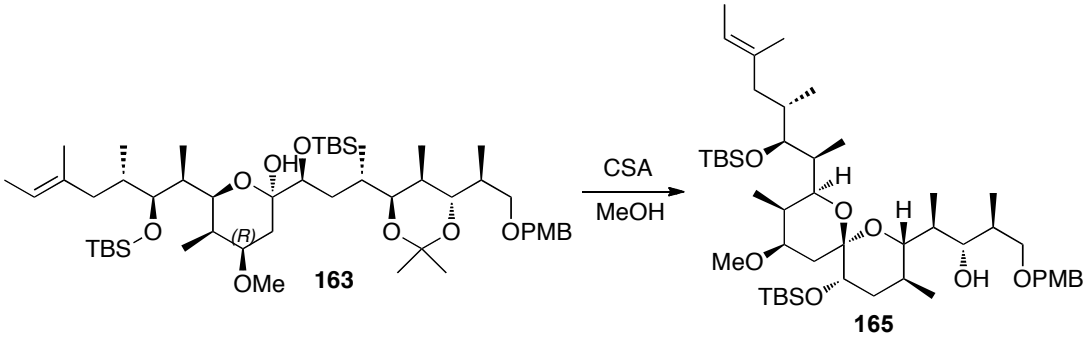
(2*R*,4*R*,5*R*,6*S*)-2-[(1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-1-(*tert*-butyldimethylsilyloxy)-8-(4-methoxyphenyl)oxy-3,5,7-trimethyl-4,6-[(bis-dimethyl-methylene)dioxy]-octanyl]-5-[(1*S*,2*S*,3*S*,5*E*)-2-(*tert*-butyldimethylsilyloxy)-1,3,5-trimethyl-hept-5-enyl]-2-hydroxy-4-methoxyl-5-methyl-tetrahydro-2*H*-pyran (163). The previous procedure used for the preparation of alcohol **82** was followed with TES ether **162** (53.9 mg; 52.8 μmol), HF/pyr/pyr (1 mL) and H_2O (40 μL). Purification by column chromatography (buffered silica, 15% EtOAc/X4) gave hemiacetal **163** (6.5 mg; 14%) as a clear, colourless oil. **R*f*** = 0.43 (15% EtOAc/X4); **$[\alpha]^{20}_D$** = +22.2 (c 0.36, $CHCl_3$); **^{1}H**

NMR (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 9.0 Hz, Ar*H*), 6.87 (2H, d, J = 8.4 Hz, Ar*H*), 5.14 (1H, q, J = 6.6 Hz, CH_3CHCCH_3), 4.41 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 3.82 (1H, d, J = 5.4 Hz, C*H*(-O-)$CH(CH_3)CHOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.69 (1H, ddd, J = 11.4, 4.8, 4.2 Hz, $CHOCH_3$), 3.58 (1H, dd, J = 10.2, 1.2 Hz, $CH(CH_3)CH$(OTBS)$CHCH_3$), 3.53 (1H, dd, J = 9.0, 4.8 Hz, CH_AH_BOPMB), 3.51 (1H, dd, J = 9.0, 1.8 Hz, C(OH)(-O-)C*H*(OTBS)CH_2), 3.35 (3H, s, $CHOCH_3$), 3.31 (1H, dd, J = 9.0, 6.6 Hz, CH_AH_BOPMB), 3.21 (1H, d, J = 10.8 Hz, CH(OTBS)$CH_2CH(CH_3)$C*H*(-O-)), 3.18 (1H, dd, J = 12.6, 1.8 Hz, C*H*(-O-)$CH(CH_3)CH_2$OPMB), 2.18 (1H, d, J = 13.2 Hz, $CH_3CHC(CH_3)CH_AH_B$CHOTBS), 2.08 (1H, m, $CH(OCH_3)CH_AH_B$C(-O-)(OH)), 2.03 (1H, ddd, J = 14.4, 9.0, 3.0 Hz, CH(OTBS)$CH_AH_B CHCH_3$), 1.94-1.88 (1H, m, C*H*$(CH_3)CH_2$OPMB), 1.89-1.84 (1H, m, CH(-O-)C*H*(CH_3)CH(-O-)), 1.73-1.68 (5H, m, CH(-O-)C*H*$(CH_3)CHOCH_3$, CH(OTBS)CH_2C*H*(CH_3)CH(-O-), $CH_3CHC(CH_3)CH_2$C*H*(CH_3)CHOTBS, $CH(OCH_3)CH_AH_B$C(-O-)(OH) and CH(OTBS)C*H*(CH_3)CH(-O-)), 1.55-1.50 (1H, m, $CH_3CHC(CH_3)CH_AH_B$CHOTBS), 1.55 (3H, d, J = 6.6 Hz, C*H*$_3CHC(CH_3)CH_2$), 1.54 (3H, s, $CH_3CHC(CH_3)CH_2$), 1.20 (3H, s, OC(C*H*$_3)CH_3$), 1.18 (3H, s, OC(CH_3)C*H*$_3$), 1.09 (1H, ddd, J = 14.4, 10.2, 1.8 Hz, CH(OTBS)$CH_AH_B CHCH_3$), 0.99 (3H, d, J = 6.6 Hz, CH(C*H*$_3)CH_2$OPMB), 0.92 (9H, s, OSiC(C*H*$_3)_2$), 0.90 (9H, s, OSiC(C*H*$_3)_2$), 0.83 (3H, d, J = 6.6 Hz, CH(-O-)CH(C*H*$_3$)CH(-O-)), 0.79 (3H, d, J = 6.6 Hz, CH(-O-)CH(C*H*$_3$)$CHOCH_3$), 0.76 (3H, d, J = 7.2 Hz, $CH_3CHC(CH_3)CH_2CH(CH_3)$CHOTBS), 0.74 (6H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(C*H*$_3$)CH(-O-)), 0.74 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH(-O-)), 0.09 (6H, s, OSi(C*H*$_3)CH_3$), 0.06 (3H, s, OSi(CH_3)C*H*$_3$) 0.02 (3H, s OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 134.7, 131.0, 129.3, 120.0, 113.8, 100.4, 97.8, 77.4, 76.6, 76.5, 75.1, 73.8, 73.1, 72.9, 72.2, 55.44, 55.41, 44.1, 38.2, 38.1, 36.6, 36.0, 35.3, 31.9, 31.5, 29.5, 26.23, 26.19, 25.9, 25.1, 23.6, 23.3, 18.5, 18.4, 15.7, 15.6, 15.5, 14.7, 14.3, 13.5, 12.8, 10.7, 3.8, -3.68, -3.72, -3.9, -4.3; **IR** (film, cm^{-1}) 3377, 2930, 2857, 1717, 1613, 1513, 1463, 1378, 1301, 1249, 1172, 1097, 1004, 921, 835, 774, 675; **HRESIMS** calculated for $C_{51}H_{94}O_9Si_2Na^+$: 929.6329; found: 929.6323.



(2*S*,3*R*,7*R*,9*S*,11*S*)-2-[(1*S*,2*S*,3*S*,5*E*)-2-(*tert*-butyldimethylsilyloxy)-1,3,5-trimethyl-hept-5-enyl]-8-[(1*S*,2*S*,3*S*)-4-(2-hydroxy-(4-methoxyphenyl)oxy-1,3-dimethyl)-11-(*tert*-butyldimethylsilyloxy)-3,9-dimethyl-1,7-dioxaspiro[6,6]undec-4-ene (164). To a stirred solution of hemiacetal **161** (6.1 mg; 6.72 μmol) in MeOH (0.5 mL) was added a few crystals of CSA and the resulting solution stirred at rt for 16 h before quenching by addition of sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave elimination product **164** (1.1 mg; 20%). **R*f*** = 0.61 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.4 Hz, Ar*H*), 6.84 (2H, d, J = 9.0 Hz, Ar*H*), 5.96 (1H, dd, J = 10.2, 6.6 Hz, CH(CH_3)C*H*CH(-O-)), 5.76 (1H, dd, J = 10.2, 0.6 Hz, CH(CH_3)CHC*H*(-O-)), 5.20 (1H, q, J = 6.6 Hz, CH_3C*H*CCH_3), 3.84 (1H, dd, J = 10.2, 1.2 Hz, CH(CH_3)C*H*(-O-)CH(CH_3)CHCH), 3.79 (1H, dd, J = 6.6, 1.8 Hz, CH(OTBS)CH_2CH(CH_3)C*H*(-O-)), 3.79 (3H, s, OCH_3), 3.56 (1H, dd, J = 8.4, 4.8 Hz, C$H_A$$H_B$OPMB), 3.56-3.53 (1H, m, CH(CH_3)C*H*(OTBS)CHCH_3), 3.54 (1H, dd, J = 9.0, 3.0 Hz, C*H*OH), 3.47 (1H, dd, J = 6.6, 6.0 Hz, $CH_A$$H_B$OPMB), 3.38 (1H, dd, J = 3.6, 1.8 Hz, C(-O-)(-O-)C*H*(OTBS)CH_2), 3.29 (1H, br s, O*H*), 2.19 (1H, d, J = 16.2 Hz, CH_3CHC(CH_3)C$H_A$$H_B$CH($CH_3$)CHOTBS), 2.17-2.10 (1H, m, CH(OTBS)CH_2C*H*(CH_3)CH(-O-)), 2.06-2.00 (2H, m, C*H*(CH_3)CH(OTBS)CHCH_3 and CH(-O-)C*H*(CH_3)CHCH), 1.90-1-86 (3H, m, C*H*(CH_3)CH_2OPMB, CH(-O-)C*H*(CH_3)CHOH and CH(OTBS)C*H*(CH_3)CH(-O-)), 1.76 (1H, ddd, J = 14.4, 13.2, 1.8 Hz, CH(OTBS)C$H_A$$H_BCHCH_3$), 1.71 (1H, dd, J = 13.2, 10.2 Hz, CH_3CHC(CH_3)$CH_A$$H_B$CH($CH_3$)CHOTBS), 1.58 (3H, s, C$H_3CHCCH_3$), 1.58 (3H, s, CH_3CHCCH_3), 1.50 (1H, ddd, J = 13.2, 3.6, 3.0 Hz, CH(OTBS)$CH_A$$H_BCHCH_3$), 1.25 (6H, s, OC(C$H_3$)$_2$), 1.05 (3H, d, J = 6.6 Hz, CH(CH_3)CH_2OPMB), 0.96 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOH), 0.90 (9H, s, OSiC(CH_3)$_3$), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.86 (3H, d, J = 7.2

Hz, CH(-O-)CH(CH_3)CHCH), 0.84 (3H, d, J = 6.6 Hz, CH_3CHC(CH_3)CH_2CH(CH_3)CHOTBS), 0.78 (6H, d, J = 6.6 Hz, CH(OTBS)CH_2CH(CH_3)CH(-O-) and CH(OTBS)CH(CH_3)CH(-O-)), 0.02 (3H, s, OSi(CH_3)CH_3), 0.00 (3H, s, OSi(CH_3)CH_3), 0.00 (3H, s, OSi(CH_3)CH_3), -0.01 (3H, s, OSi(CH_3)CH_3).

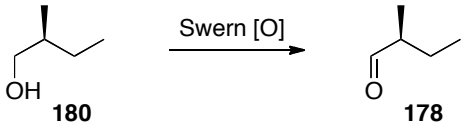


(2*S*,3*R*,7*R*,9*S*,11*S*)-2-[(1*S*,2*S*,3*S*,5*E*)-2-(*tert*-butyldimethylsilyloxy)-1,3,5-trimethyl-hept-5-enyl]-8-[(1*S*,2*S*,3*S*)-2-hydroxy-4-(4-methoxyphenyl)oxy-1,3-dimethyl]-11-(*tert*-butyldimethylsilyloxy)-4-methoxy-3,9-dimethyl-1,7-dioxaspiro[6,6]undecane (165). The previous procedure used for the preparation of spiroacetal **164** was followed with acetonide **163** (6.4 mg; 7.05 μmol), CSA (a few crystals) and MeOH (0.5 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave spiroacetal **165** (1.3 mg; 22%) as a clear, colourless oil. **R*f*** = 0.37 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 9.0 Hz, Ar*H*), 6.85 (2H, d, J = 8.4 Hz, Ar*H*), 5.19 (1H, q, J = 6.6 Hz, CH_3C*H*CCH_3), 4.42 (2H, ABq, J = 11.4 Hz, OCH_2PMP), 3.79 (3H, s, ArOCH_3), 3.78 (2H, d, J = 7.8 Hz, CH(CH_3)C*H*(-O-)CH(CH_3)CHOCH_3), 3.73 (1H, dd, J = 10.8, 1.2 Hz, CH(OTBS)CH_2CH(CH_3)C*H*(-O-)), 3.64 (1H, dd, J = 9.0, 4.8 Hz, C$H_A$$H_B$OPMB), 3.50 (1H, m, C*H*OCH_3), 3.50 (1H, m, CH(CH_3)C*H*(OTBS)CHCH_3), 3.48 (1H, m, $CH_A$$H_B$OPMB), 3.45 (1H, m, C*H*OH), 3.37 (1H, br s, C(-O-)(-O-)C*H*(OTBS)CH_2), 3.31 (3H, s, CHOCH_3), 3.02 (1H, d, J = 7.8 Hz, O*H*), 2.15 (1H, d, J = 12.6 Hz, CH_3CHC(CH_3)C$H_A$$H_B$CHOTBS), 2.14-2.09 (1H, m, CH(OTBS)C*H*(CH_3)CH(-O-)), 2.09-2.04 (1H, m, CH(OTBS)CH_2C*H*(CH_3)CH(-O-)), 2.00 (1H, dd, J = 13.2, 4.8 Hz, CH(OCH_3)C$H_A$$H_B$C(-O-)(-O-)), 1.95-1.90 (1H, m, CH_3CHC(CH_3)CH_2C*H*(CH_3)CHOTBS), 1.93-1.88 (1H, m, C*H*(CH_3)CH_2OPMB), 1.92-1.87 (1H, m, CH(-O-)C*H*(CH_3)CHOCH_3), 1.80 (1H, dq, J = 7.2, 6.6 Hz, CH(-O-)C*H*(CH_3)CHOH), 1.74 (1H, dd, J = 12.6, 1.8 Hz,

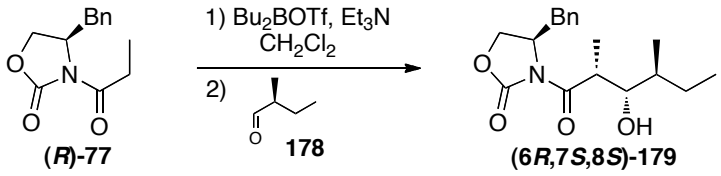
CH(OTBS)C$H_A$$H_BCHCH_3$), 1.71 (1H, dd, J = 13.2, 6.0 Hz, CH_3CHC(CH_3)C$H_A$$H_B$CHOTBS), 1.57 (3H, d, J = 6.6 Hz, CH_3CHCCH$_3$), 1.55 (3H, s, CH$_3$CHCCH_3), 1.49 (1H, ddd, J = 13.2, 3.6, 3.0 Hz, CH(OTBS)C$H_A$$H_B$CHCH$_3$), 1.17 (1H, dd, J = 12.6, 12.6 Hz, CH(OCH$_3$)C$H_A$$H_B$C(-O-)(-O-)), 1.09 (3H, d, J = 7.2 Hz, CH(CH_3)CH$_2$OPMB), 0.91 (3H, d, J = 6.6 Hz, CH(-O-)CH(CH_3)CHOH), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.84 (3H, d, J = 7.2 Hz, CH$_3$CHC(CH$_3$)CH$_2$CH(CH_3)CHOTBS), 0.77 (6H, d, J = 6.6 Hz, CH(-O-)CH(CH_3)CHOCH$_3$) and CH(OTBS)CH$_2$CH(CH_3)CH(-O-)), 0.74 (3H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CH(-O-)), 0.04 (3H, s, OSi(CH_3)CH$_3$), 0.04 (3H, s, OSi(CH_3)CH$_3$), -0.01 (3H, s, OSi(CH$_3$)CH_3), -0.03 (3H, s, OSi(CH$_3$)CH_3); **^{13}C NMR** (600 MHz, CDCl$_3$) δ 130.7, 129.3, 119.5, 113.8, 112.8, 98.5, 76.8, 76.7, 73.3, 72.2, 70.8, 55.4, 55.2, 53.6, 40.2, 38.1, 37.9, 36.8, 36.0, 35.7, 33.3, 32.4, 29.9, 26.3, 25.9, 24.3, 18.7, 18.6, 18.1, 17.8, 16.2, 15.6, 13.6, 12.5, 11.0, 4.2, -3.2, -4.3, -4.2, -4.8; **^{1}H NMR** (600 MHz, C$_6$D$_6$) δ 7.16 (2H, d, J = 9.0 Hz, Ar*H*), 6.81 (2H, d, J = 9.0 Hz, Ar*H*), 5.44 (1H, q, J = 6.6 Hz, CH$_3$C*H*CCH$_3$), 4.27 (1H, d, J = 12.0 Hz, OCH_AH$_B$PMP), 4.26 (1H, s, O*H*), 4.24 (1H, d, J = 5.4 Hz, CH(CH$_3$)C*H*(-O-)CH(CH$_3$)CHOCH$_3$), 4.17 (1H, dd, J = 10.8, 1.8 Hz, CH(OTBS)CH$_2$CH(CH$_3$)C*H*(-O-)), 4.16 (1H, d, J = 11.4 Hz, OCH$_A$$H_B$PMP), 3.97 (1H, dd, J = 10.2, 1.8 Hz, CH(CH$_3$)C*H*(OTBS)CHCH$_3$), 3.86 (1H, ddd, J = 11.4, 4.8, 4.2 Hz, C*H*OCH$_3$), 3.77 (1H, ddd, = 9.0, 9.0, 3.6 Hz, C*H*OH), 3.66 (1H, dd, J = 3.0, 2.4 Hz, C(-O-)(-O-)C*H*(OTBS)CH$_2$), 3.62 (1H, dd, J = 9.0, 3.6 Hz, CH_AH$_B$OPMB), 3.32 (3H, s, ArOCH_3), 3.27 (1H, dd, J = 9.0, 3.0 Hz, CH$_A$$H_B$OPMB), 3.12 (3H, s, CHOC$H_3$), 2.53 (1H, d, 13.8 Hz, CH$_3$CHC(CH$_3$)CH_AH$_B$CHOTBS), 2.46 (1H, dd, J = 13.2, 4.2 Hz, CH(OCH$_3$)CH_AH$_B$C(-O-)(-O-)), 2.37-2.31 (1H, m, CH$_3$CHC(CH$_3$)CH$_2$C*H*(CH$_3$)CHOTBS), 2.31-2.26 (1H, m, CH(OTBS)CH$_2$C*H*(CH$_3$)CH(-O-)), 2.30-2.25 (1H, m, CH(OTBS)C*H*(CH$_3$)CH(-O-)), 2.24-2.18 (1H, m, CH(-O-)C*H*(CH$_3$)CHOCH$_3$), 2.11 (1H, dd, J = 13.8, 10.2 Hz, CH$_3$CHC(CH$_3$)CH$_A$$H_B$CHOTBS), 2.08 (1H, ddd, J = 13.2, 13.2, 1.2 Hz, CH(OTBS)CH_AH$_B$CHCH$_3$), 1.89-1.86 (1H, m, CH(-O-)C*H*(CH$_3$)CHOH), 1.86-1.83 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.70 (3H, s, CH$_3$CHCCH_3), 1.66 (1H, ddd, J = 13.2, 3.6, 2.4 Hz, CH(OTBS)CH$_A$$H_B$CHCH$_3$), 1.59-1.55 (1H, m, CH(OCH$_3$)CH$_A$$H_B$C(-O-)(-O-)), 1.57 (3H, d, J = 6.6 Hz, CH_3CHCCH$_3$), 1.30 (3H, d, J = 7.2 Hz, CH(CH_3)CH$_2$OPMB), 1.26 (3H, d, J = 7.2 Hz, CH$_3$CHC(CH$_3$)CH$_2$CH(CH_3)CHOTBS), 1.13 (9H, s, OSiC(CH_3)$_3$), 1.04 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOCH$_3$), 1.03 (3H, d, J = 7.2 Hz, CH(OTBS)CH$_2$CH(CH_3)CH(-O-)), 1.00 (9H, s, OSiC(CH_3)$_3$), 0.99 (3H, d, J = 7.2 Hz, CH(-O-)CH(CH_3)CHOH), 0.89 (3H, d, J

= 7.8 Hz, CH(OTBS)CH(C*H*$_3$)CH(-O-)), 0.33 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.21 (3H, s, OSi(C*H*$_3$)CH$_3$), 0.01 (6H, s, OSi(CH$_3$)C*H*$_3$); **HRESIMS** calculated for $C_{48}H_{88}O_8Si_2Na^+$: 871.5910; found: 871.5910.

4.3 Experimental Procedures for Chapter Three

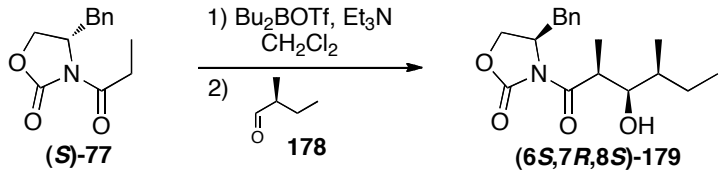


(2*S*)-2-methyl-butan-1-ol (178), synthesised according to the proceure of Swern *et al*.[19] To a stirred solution of DMSO (3.92 mL; 55.2 mmol) in CH_2Cl_2 (150 mL) at -78 ^oC was added oxalyl chloride (13.8 mL; 27.6 mmol) dropwise and the resulting solution stirred at -78 ^oC for 30 min. A solution of alcohol **180** (2.00 mL; 18.4 mmol) in CH_2Cl_2 (30 mL) was added dropwise *via* cannula to the reaction mixture and the resulting solution was stirred at -78 ^oC for 45 min. Et_3N (15.4 mL; 110 mmol) was added dropwise and stirring was continued at -78 ^oC for 30 min before warming slowly to 0 ^oC for a further 30 min. The reaction was quenched by addition of sat. aq. NH_4Cl (300 mL) and the mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracted were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **178** (assumed yield, 80%) as a colourless oil. **R*f*** = 0.56 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = +21.5 (c 1.54, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.62 (1H, d, J = 2.0 Hz, C*H*O), 2.28 (1H, dddq, J = 14.0, 7.2, 6.8, 2.0 Hz, C*H*(CH_3)CHO), 1.75 (1H, ddq, J = 14.0, 7.6, 6.8 Hz, CH(CH_3)CH_AH$_B$$CH_3$), 1.44 (1H, ddq, J = 14.0, 7.6, 7.2 Hz, CH(CH_3)C$H_A$$H_B$$CH_3$), 1.09 (3H, d, 6.8 Hz, CH(CH_3)CH_2CH_3), 0.95 (3H, dd, J = 7.6, 7.2 Hz, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.5, 47.9, 23.6, 12.9, 11.4.



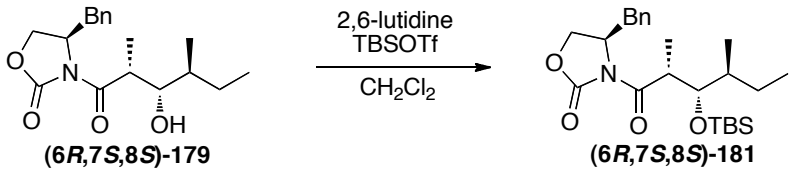
[[3-(2*S*,3*S*,4*S*)-4*R*]-3-(3-hydroxy-2,4-dimethyl-1-oxo-henanyl)-4-(phenylmethyl)]-2-oxazolidinone [(6*R*,7*S*,8*S*)-179]. Synthesised according to the procedure of Evans *et al*.[40] To a stirred solution of oxazolidine **(*R*)-77** (1.63 g; 7.00 mmol) in CH_2Cl_2 (14 mL)

at 0 ^{o}C was added Bu_2BOTf (8.39 mL; 1 M in CH_2Cl_2; 8.39 mmol) dropwise, giving a red solution. After 30 min Et_3N (1.27 mL; 9.09 mmol) was added and the resulting yellow solution was stirred for a further 30 min before cooling to -78 ^{o}C. Aldehyde **178** (1.19 g; 13.8 mmol) in CH_2Cl_2 (7 mL) was added dropwise *via* cannula and the reaction mixture stirred at -78 ^{o}C for 30 min and then at 0 ^{o}C for 4 h, at which time the reaction was quenched by addition of pH 7 buffer (16 mL) and MeOH (24 mL). A solution of 2:1 MeOH/H_2O_2 (24 mL) was then added and the mixture stirred at rt for 1 hour. The volatiles were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **(6*R*,7*S*,8*S*)-179** (960 mg; 66%, >98% ds) as a white solid. **R*f*** = 0.33 (5% Et_2O/CH_2Cl_2); **mp.** 69-70 ^{o}C; **$[\alpha]^{20}_{D}$** = -40.0 (c 1.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.21-7.18 (1H, m, Ar*H*), 4.70 (1H, dddd, J = 9.6, 7.6, 3.6, 3.2, C*H*CH_2Ph), 4.23 (1H, dd, J = 9.2, 7.6 Hz, OC$H_A$$H_BCHCH_2$N), 4.18 (1H, dd, J = 9.2, 3.2 Hz, OC$H_A$$H_B$CHN), 3.95 (1H, dq, J = 7.2, 3.2 Hz, C(=O)C*H*(CH_3)C*H*OH), 3.62 (1H, ddd, J = 9.2, 3.2, 2.4 Hz, C*H*OH), 3.25 (1H, dd, J = 13.6, 3.6 Hz, C$H_A$$H_B$Ph), 2.96 (1H, d, J = 3.6 Hz, O*H*), 2.79 (1H, dd, J = 13.2, 9.2 Hz, C$H_A$$H_B$Ph), 1.79 (1H, ddq, J = 13.6, 7.6, 4.4 Hz, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.52 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.22 (3H, d, J = 6.8 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.18 (1H, ddq, 13.6, 8.4, 7.2, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 0.91 (3H, dd, J = 7.6, 7.2 Hz, CH_2C*H*$_3$), 0.86 (3H, d, J = 6.8 Hz, C(=O)CH(C*H*$_3$)CHOH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 153.0, 135.2, 129.5, 129.1, 127.5, 74.9, 66.3, 55.2, 39.6, 37.9, 37.1, 25.3, 14.8, 11.0, 9.7; **IR** (KBr, cm^{-1}) 3499, 3090, 3064, 3032, 2969, 2940, 2903, 2882, 2854, 1947, 1797, 1686, 1606, 1583, 1488, 1500, 1457, 1384, 1356, 1303, 1244, 1212, 1136, 1121, 1097, 1077, 928, 831, 764, 735, 700, 640, 601, 573, 504, 471.



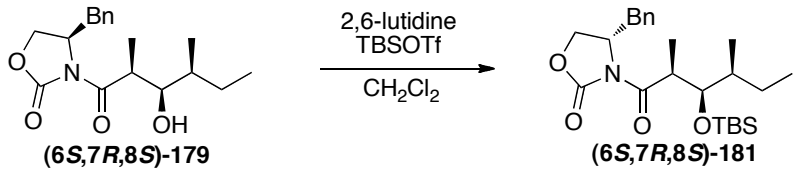
(***S***)-77 (6***S***,7***R***,8***S***)-179

[[3-(2*S*,3*R*,4*S*)-4*S*]-3-(3-hydroxy-2,4-dimethyl-1-oxo-henanyl)-4-(phenylmethyl)]-2-oxazolidinone [(6*S*,7*R*,8*S*)-179]. The previous procedure used for the preparation of **(6*R*,7*S*,8*S*)-179** was followed with oxazolidinone **(*S*)-77** (1.73 mg; 7.42 mmol), Bu_2BOTf (8.90 mL; 1 M in CH_2Cl_2; 8.90 mmol), Et_3N (1.35 mL; 9.65 mmol), aldehyde **178** (1.26 g; 14.6 mmol) and CH_2Cl_2 (15 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **(6*S*,7*R*,8*S*)-179** (2.01 g; 85%, > 98% ds) as a white solid. **R*f*** = 0.29 (5% Et_2O/CH_2Cl_2); **mp.** 91-92 ^{o}C; **$[\alpha]^{20}_{D}$** = +38.4 (c 1.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.21-7.18 (2H, m, Ar*H*), 4.69 (1H, dddd, 9.6, 7.6, 3.6, 3.6, C*H*CH_2Ph), 4.22 (1H, dd, J = 9.2, 7.6 Hz, OC$H_A$$H_B$$CH_2$N), 4.18 (1H, dd, J = 8.8, 2.8 Hz, OC$H_A$$H_B$CHN), 3.98 (1H, dq, J = 6.8, 4.0 Hz, C(=O)C*H*(CH_3)CHOH), 3.69 (1H, ddd, J = 7.2, 4.0, 3.6 Hz, C*H*OH), 3.25 (1H, dd, J = 13.6, 3.6 Hz, C$H_A$$H_B$Ph), 2.78 (1H, dd, J = 13.6, 9.6 Hz, $CH_A$$H_B$Ph), 2.67 (1H, d, J = 4.4 Hz, O*H*), 1.56-1.41 (1H, m, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.56-1.41 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.26 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.20-1.08 (1H, ddq, J = 8.8, 7.2, 5.2, CH(OH)CH(CH_3)$CH_A$$H_B$$CH_3$), 0.97 (3H, d, J = 6.4 Hz, C(=O)CH(C*H*$_3$)CHOH), 0.90 (3H, dd, J = 7.6, 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.7, 153.0, 135.2, 129.5, 129.1, 127.5, 75.1, 66.2, 55.2, 40.0, 37.8, 37.3, 25.7, 14.7, 11.3, 11.3; **IR** (KBr, cm^{-1}) 3525, 3066, 3028, 2964, 2934, 2878, 1779, 1692, 1603, 1490, 1457, 1383, 1353, 1288, 1241, 1201, 1140, 1111, 1076, 1049, 1015, 993, 971, 931, 918, 858, 837, 790, 764, 751, 724, 644, 624, 617, 574, 506.



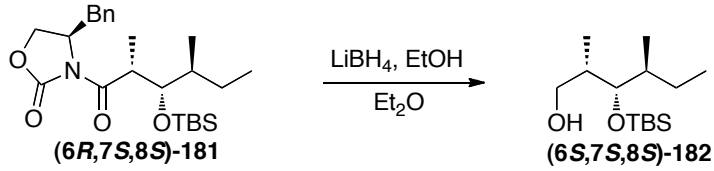
(6*R*,7*S*,8*S*)-179 **(6*R*,7*S*,8*S*)-181**

[[3-(2*R*,3*S*,4*S*)-4*R*]-3-(3-[*tert*-butyldimethylsilyloxy]-2,4-dimethyl-1-oxo-henanyl)-4-(phenylmethyl)]-2-oxazolidinone [(6*R*,7*S*,8*S*)-181]. To a stirred solution of alcohol **(6*R*,7*S*,8*S*)-179** (1.93 g; 6.06 mmol) in CH_2Cl_2 (60 mL) at -78 ^oC was added 2,6-lutidine (1.41 mL; 12.1 mmol) followed by TBSOTf (2.09 mL; 9.09 mmol). The resulting solution was stirred at -78 ^oC for 7 h before warming to 0 ^oC for 10 min. The reaction was quenched by addition of 5% $NaHCO_3$ (60 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave TBS-ether **(6*R*,7*S*,8*S*)-181** (2.54 g; 97%) as a white solid. **R*f*** = 0.34 (50%, X4/CH_2Cl_2); **mp.** 85-86 ^oC; **$[\alpha]^{20}_D$** = -47.1 (c 1.11, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 4.63 (1H, m, C*H*CH_2Ph), 4.17 (2H, d, J = 4.8Hz, OC*H*$_2$CHN), 3.98 (1H, m, C*H*OTBS), 3.96 (1H, dq, J = 6.6, 6.4 Hz, C(=O)C*H*(CH_3)CHOTBS), 3.27 (1H, dd, J = 13.2, 4.8 Hz, CH_AH$_B$Ph), 2.75 (1H, dd, J = 13.2, 9.6 Hz, CH$_A$*H*$_B$Ph), 1.52-1.43 (1H, m, CH(OTBS)CH(CH_3)CH_AH$_B$$CH_3$), 1.52-1,43 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.23 (3H, d, J = 6.4 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 1.04-0.95 (1H, m, CH(OTBS)CH(CH_3)CH$_A$*H*$_B$$CH_3$), 0.93 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CHOTBS), 0.92 (9H, s, OSiC(C*H*$_3$)$_3$), 0.87 (3H, dd, J = 7.2, 6.8 Hz, CH_2C*H*$_3$), 0.07 (3H, s, OSi(C*H*$_3$)CH_3), 0.04 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.3, 153.0, 135.5, 129.6, 129.1, 127.5, 76.3, 66.1, 55.8, 41.2, 40.9, 37.8, 26.2, 25.0, 18.5, 15.4, 14.1, 12.5, -3.8, -4.1; **IR** (KBr, cm^{-1}) 3520, 2963, 2930, 2883, 2858, 1957, 1767, 1700, 1491, 1458, 1393, 1364, 1312, 1294, 1274, 1228, 1253, 1210, 1179, 1154, 1104, 1072, 1055, 1023, 994, 968, 933, 910, 884, 838, 805, 776, 766, 702, 671, 588, 507.



(6*S*,7*R*,8*S*)-179 **(6*S*,7*R*,8*S*)-181**

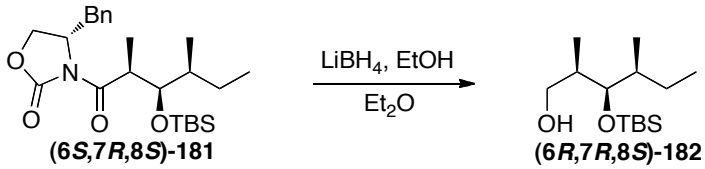
[[3-(2*S*,3*R*,4*S*)-4*R*]-3-(3-[*tert*-butyldimethylsilyloxy]-2,4-dimethyl-1-oxo-henanyl)-4-(phenylmethyl)]-2-oxazolidinone [(6*S*,7*R*,8*S*)-181]. The previous procedure used for the preparation of **(6*R*,7*S*,8*S*)-181** was followed with alcohol **(6*S*,7*R*,8*S*)-179** (1.99 g; 6.23 mmol), 2,6-lutidine (1.45 mL; 12.5 mmol), TBSOTf (2.15 mL; 9.35 mmol) and CH_2Cl_2 (62 mL). Purification by column chromatography (buffered silica, 50% x4/CH_2Cl_2) gave TBS-ether **(6*S*,7*R*,8*S*)-181** (2.46 g; 91%) as a white solid. **R*f*** = 0.38 (50%, X4/CH_2Cl_2); **mp.** 72-73 ^{o}C; **[α]$^{20}_{D}$** = +44.6 (c 1.17, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 4.64 (1H, m, C*H*CH_2Ph), 4.18 (2H, m, OC*H*$_2$CHCH_2N), 4.00 (1H, dd, J = 7.6, 2.8 Hz, C*H*OTBS), 3.98 (1H, dq, J = 7.2, 6.8 Hz, C(=O)C*H*(CH_3)CHOTBS), 3.26 (1H, dd, J = 13.2, 4.8 Hz, C*H*$_A$H$_B$Ph), 2.76 (1H, dd, J = 13.2, 9.6 Hz, CH$_A$*H*$_B$Ph), 1.57-1.48 (1H, m, CH(OTBS)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.41-1.34 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.24 (3H, d, J = 6.8 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 1.22-1.10 (1H, m, CH(OTBS)CH(CH_3)CH$_A$*H*$_B$$CH_3$), 0.92 (9H, s, OSiC(C*H*$_3$)$_3$), 0.89 (3H, dd, J = 7.6, 7.2 Hz, CH_2C*H*$_3$), 0.84 (3H, d, J = 6.8 Hz, C(=O)CH(C*H*$_3$)CHOTBS), 0.08 (3H, s, OSi(C*H*$_3$)CH_3), 0.07 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.4, 153.0, 135.4, 129.6, 129.1, 127.5, 76.1, 66.0, 55.6, 41.8, 40.8, 37.8, 26.6, 26.3, 18.6, 15.1, 14.2, 12.5, -3.6, -3.8; **IR** (KBr, cm^{-1}) 3519, 2963, 2858, 1767, 1700, 1493, 1458, 1394, 1363, 1332, 1290, 1252, 1211, 1179, 1129, 1072, 1024, 993, 970, 934, 881, 836, 812, 772, 702, 690, 673, 588, 545, 495.



(6*R*,7*S*,8*S*)-181 **(6*S*,7*S*,8*S*)-182**

(2*S*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexan-1-ol [(6*S*,7*S*,8*S*)-182], synthesised according to the procedure of Penning *et al*.[24] To a stirred solution of

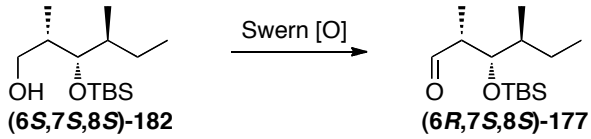
oxazolidinone **(6*R*,7*S*,8*S*)-181** (2.52 g; 5.81 mmol) in Et_2O (116 mL) at -10 °C was added EtOH (814 μL; 13.9 mmol) and $LiBH_4$ (13.9 mL; 1 M in THF; 13.9 mmol). The resulting solution was stirred at -10 °C for 4 h, then quenched with 1 M NaOH (100 mL) and stirring continued at 0 °C for 15 min. The mixture was then poured into brine (60 mL), extracted with Et_2O (4 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **(6*S*,7*S*,8*S*)-182** (1.09 g; 72%) as a colourless oil. **R*f*** = 0.58 (5%, Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = +3.33 (c 1.20, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.62 (1H, dd, J = 5.4, 2.4 Hz, C*H*OTBS), 3.56 (1H, dd, J = 9.6, 9.0 Hz, CH_AH$_B$OH), 3.45 (1H, dd, J = 9.6, 6.0 Hz, CH$_A$$H_B$OH), 1.92 (1H, s, O*H*), 1.87 (1H, m, C*H*(CH$_3$)CH$_2$OH), 1.57-1.50 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$CH$_3$), 1.57-1.50 (1H, m, CH(OTBS)CH(CH$_3$)CH_AH$_B$CH$_3$), 1.11-1.03 (1H, ddq, J = 14.4, 7.2, 3.0 Hz, CH(OTBS)CH(CH$_3$)CH$_A$$H_BCH_3$), 0.89 (9H, s, OSiC(C$H_3$)$_3$), 0.89 (3H, dd, J = 7.6, 7.2, Hz, CH$_2$CH_3), 0.88 (3H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CH$_2$CH$_3$), 0.85 (3H, d, J = 7.2 Hz, CH(CH_3)CH$_2$OH), 0.06 ((3H, s, OSi(CH_3)CH$_3$), 0.05 (3H, s, OSi(CH$_3$)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 76.8, 66.8, 39.4, 38.7, 26.2, 25.9, 18.5, 16.2, 12.2, 12.0, -3.9, -4.2; **IR** (film, cm^{-1}) 3343, 2959, 1472, 1382, 1360, 1252, 1100, 1025, 938, 897, 835, 772, 672.



(6*S*,7*R*,8*S*)-181 **(6*R*,7*R*,8*S*)-182**

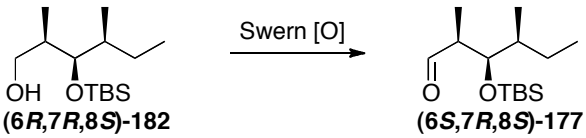
(2*R*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexan-1-ol [(6*R*,7*R*,8*S*)-182]. The previous procedure used for the preparation of **(6*S*,7*S*,8*S*)-182** was followed with oxazolidinone **(6*S*,7*R*,8*S*)-181** (2.43 g; 5.61 mmol), EtOH (786 μL; 13.5 mmol), $LiBH_4$ (13.5 mL; 1 M in THF; 13.5 mmol) and Et_2O (112 mL). Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **(6*R*,7*R*,8*S*)-182** (956 mg; 66%) as a colourless oil. **R*f*** = 0.56 (5%, Et_2O/CH_2Cl_2); **[α]$^{20}_D$** = -3.64 (c 1.10, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.63 (1H, dd, J = 3.6, 3.6 Hz, C*H*OTBS), 3.63 (1H, m, CH_AH$_B$OH), 3.46 (1H, m, CH$_A$$H_B$OH), 2.25 (1H, s, O*H*), 1.93 (1H, dddq, J = 9.0, 8.4, 6.0, 3.0 Hz, CH(OTBS)C*H*(CH$_3$)CH$_2$OH), 1.54-1.48 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$CH$_3$),

1.44 (1H, ddq, J = 13.2, 6.6, 4.2 Hz, CH(OTBS)CH(CH_3)CH_AH$_B$$CH_3$), 1.15 (1H, ddq, J = 13.2, 8.4, 7.2 Hz, CH(OTBS)CH(CH_3)$CH_A$$H_B$$CH_3$), 0.90 (3H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.87 (3H, dd, J = 7.8, 7.2 Hz, CH_2CH_3), 0.84 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CH_2OH), 0.07 (3H, s, OSi(CH_3)CH_3), 0.05 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 77.4, 66.6, 39.7, 38.1, 27.5, 26.2, 18.4, 15.5, 12.7, 12.4, -4.0, -4.1; **IR** (film, cm^{-1}) 3342, 2959, 1472, 1387, 1360, 1252, 1100, 1026, 961, 938, 898, 835, 773, 669.



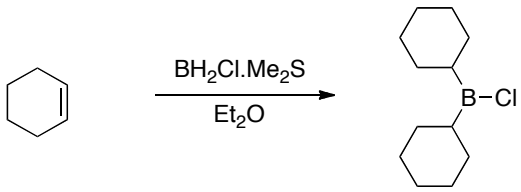
(6*S*,7*S*,8*S*)-182 **(6*R*,7*S*,8*S*)-177**

(2*R*,3*S*,4*S*)-3-[*tert*-butyldimethylsilyloxy]-2,4-dimethylhexanal [(6*R*,7*S*,8*S*)-177]. The previous procedure used for the preparation of aldehyde **178** was followed with alcohol **(6*S*,7*S*,8*S*)-182** (1.07 g; 4.10 mmol), DMSO (872 μL; 12.3 mmol), oxalyl chloride (3.08 mL; 2 M in CH_2Cl_2; 6.15 mmol), Et_3N (3.43 mL; 24.6 mmol) and CH_2Cl_2 (41 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **(6*R*,7*S*,8*S*)-177** (1.05 g; 99%) as a colourless oil. **R*f*** = 0.66 (100%, CH_2Cl_2); **[α]$^{20}_D$** = -37.4 (c 2.03, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (1H, d, J = 0.8 Hz, C*H*O), 4.00 (1H, dd, J = 5.6, 3.2 Hz, C*H*OTBS), 2.46 (1H, ddq, J = 7.2, 3.6, 1.2, CH(OTBS)C*H*(CH_3)CHO), 1.55 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.45 (1H, ddq, J = 13.2, 7.2, 3.6 Hz, CH(OTBS)CH(CH_3)CH_AH$_B$$CH_3$), 1.12-1.02 (1H, m, CH(OTBS)CH(CH_3)$CH_A$$H_B$$CH_3$), 1.09 (3H, d, J = 6.8 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 0.88 (3H, d, J = 6.8 Hz, CH(OTBS)CH(CH_3)CHO), 0.88 (3H, dd, J = 7.6, 7.2 Hz, CH_2CH_3), 0.86 (9H, s, OSiC(CH_3)$_3$), 0.05 (3H, s, OSi(CH_3)CH_3), -0.01 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.5, 75.0, 50.1, 31.0, 26.0, 25.3, 18.4, 15.6, 11.9, 8.8, -4.1, -4.1.

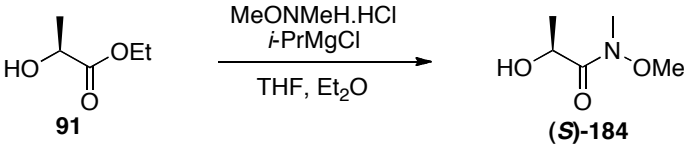


(6*R*,7*R*,8*S*)-182 **(6*S*,7*R*,8*S*)-177**

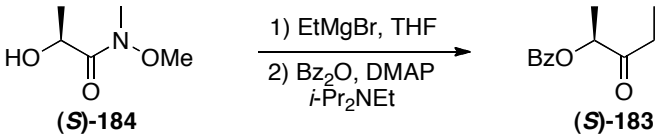
(2*S*,3*R*,4*S*)-3-[*tert*-butyldimethylsilyloxy]-2,4-dimethylhexanal [(6*S*,7*R*,8*S*)-177]. The previous procedure used for the preparation of aldehyde **178** was followed with alcohol **(6*R*,7*R*,8*S*)-182** (519 mg; 1.99 mmol), DMSO (424 μL; 5.98 mmol), oxalyl chloride (1.49 mL; 2M in CH_2Cl_2; 2.99 mmol), Et_3N (1.67 mL; 9.60 mmol) and CH_2Cl_2 (20 mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **(6*S*,7*R*,8*S*)-177** (514 mg; 99%) as a colourless oil. **R*f*** = 0.80 (100%, CH_2Cl_2); **$[\alpha]^{20}_D$** = +49.1 (c 1.63, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.79 (1H, d, J = 0.6 Hz, C*H*O), 3.97 (1H, dd, J = 4.8, 4.2 Hz, C*H*OTBS), 2.49 (1H, ddq, J = 7.2, 4.8, 1.2 Hz, CH(OTBS)C*H*(CH_3)CHO), 1.51-1.44 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.45 (1H, ddq, J = 13.2, 7.2, 4.2 Hz, CH(OTBS)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.13 (1H, ddq, J = 13.2, 9.0, 7.8 Hz, CH(OTBS)CH(CH_3)$CH_A$$H_B$$CH_3$), 1.05 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 0.87 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.82 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CHO), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), 0.01 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.5, 75.3, 50.9, 39.1, 26.6, 26.0, 18.3, 14.5, 12.2, 9.4, -4.0, -4.2.



Dicyclohexylboron chloride, synthesised according to the procedure of Brown *et al.*[41] To a stirred solution of cyclohexene (7.00 mL; 69.1 mmol) in Et_2O (35 mL) at 0 °C was added $BH_2Cl.Me_2S$ (3.30 mL; 31.7 mmol) and the resulting solution was stirred at rt for 2 h. The volatiles were removed *in vacuo* and the product purified by distillation under reduced pressure to give (*c*-Hex)$_2$BCl (5.57 g; 83%) as a clear, colourless oil. **bp.** 68-70 °C at 0.1 mmHg.

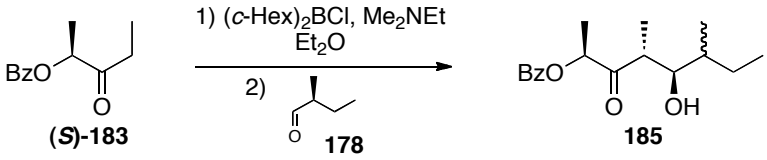


(2*S*)-2-hydroxy-*N*-methoxy-*N*-methylpropionamide [(*S*)-184], synthesised according to the procedure of Paterson *et al.*[42] To a stirred solution of ethyl (*S*)-lactate (**91**) (4.58 mL; 40.0 mmol) and MeONMeH.HCl (9.75 g; 100 mmol) in 1:1 THF:Et_2O (118 mL) at -20 ^oC was added *i*-Pr_2MgCl (100 mL; 2M in THF; 200 mmol) dropwise over 30 min. The resulting solution was stirred at -20 ^oC for a further 30 min before quenching by slow addition of sat. aq. NH_4Cl (150 mL). The product was extract with Et_2O (4 x 50 mL) and CH_2Cl_2 (4 x 50 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was purified by Kugelrohr distillation to give amide **(*S*)-184** (4.94 g; 93%) as a clear, colourless oil. **bp.** 123-124 ^oC @ 0.3 mmHg; **R*f*** = 0.27 (70% EtOAc/X4); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.47 (1H, q, J = 6.6 Hz C*H*(CH_3)), 3.71 (3H, s, NOC*H*$_3$), 3.23 (3H, s, NC*H*$_3$), 3.07 (1H, br, O*H*), 1.35 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)); **^{13}C NMR** (53.3 MHz, $CDCl_3$) δ 175.8, 64.9, 61.3, 32.5, 21.0.



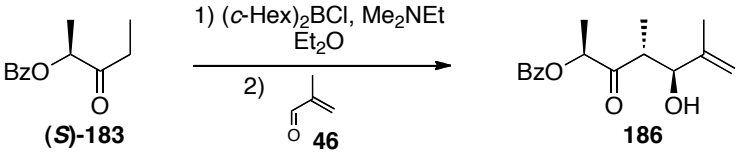
(2*S*)-2-benzoyloxypentan-3-one [(*S*)-183], synthesised according to the procedure of Paterson *et al.*[42] To a stirred solution of amide **(*S*)-184** (4.89 g; 36.7 mmol) in THF (147 mL) at 0 ^oC was added EtMgBr (147 mL; 1 M in THF; 147 mmol) dropwise and the resulting mixture was allowed to warm to rt for 1 h before quenching by slow addition of sat. aq. NH_4Cl (100 mL). The product was extracted with Et_2O (100 mL) and CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to approx. 1/3 the volume. Bz_2O (1.25 g; 55.1 mmol), DMAP (493 mg; 4.04 mmol) and *i*-Pr_2NEt (12.1 mL; 69.7 mmol) were then added and the mixture was stirred overnight at rt before quenching with ethylene diamine (560 μL). The solution was diluted with H_2O (50 mL), extracted with Et_2O (4 x 50 mL) and

the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 20% X4/CH_2Cl_2) gave ketone **(*S*)-183** (4.43 mg; 59%) as a clear, colourless oil. **R*f*** = 0.32 (80% CH_2Cl_2/X4); **$[\alpha]^{20}_D$** = +24.2 (c 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09-8.06 (2H, m Ar*H*), 7.60-7.55 (1H, m, Ar*H*) 7.47-7.43 (2H, m, Ar*H*), 5.35 (1H, q, J = 6.8 Hz, BzOC*H*(CH_3)), 2.64 (2H, ABdq, J = 18.0, 7.2 Hz C(=O)C*H*$_2$CH$_3$), 1.52 (3H, d, J = 6.8 Hz, OCH(C*H*$_3$)), 1.09 (3H, t, J = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.5, 166.0, 133.4, 129.9, 129.6, 128.5, 75.2, 31.5, 16.6, 7.3.

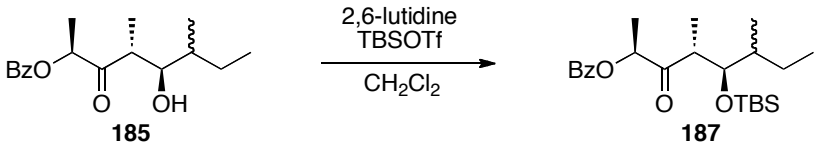


(2*S*,4*R*,5*R*)-2-benzoyloxy-5-hydroxy-4,6-dimethyl-octan-3-one (185), synthesised according to the procedure of Paterson *et al.*[42] To a stirred solution of (*c*-Hex)$_2$BCl (3.66 mL; 12.9 mmol) in Et_2O (86 mL) at -78 ^oC was added Me_2NEt (1.68 mL; 15.5 mmol) dropwise, followed by a solution of ketone **(*S*)-183** (1.78 g; 8.63 mmol) in Et_2O (10 mL) dropwise *via* cannula. The resulting white solution was warmed to 0 ^oC and stirred at 0 ^oC for 2 h before cooling to -78 ^oC. Aldehyde **178** (3.20 g; 37.2 mmol) in Et_2O (10 mL) was added dropwise *via* cannula and the solution stirred at -78 ^oC for a further 2 h, then placed in the freezer (-20 ^oC) overnight. The reaction was quenched at 0 ^oC by addition of MeOH (20 mL), pH 7 buffer (20 mL) and H_2O_2 (30%, 20 mL), before warming to rt for 1 h. The mixture was partitioned onto H_2O (100 mL), extracted wth CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave a 5:1 mixture of aldol adducts **185** (2.38 g; 94%) as a white solid. **R*f*** = 0.19 (100% CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer:** δ 8.09-8.07 (2H, m, Ar*H*), 7.59-7.57 (1H, m, Ar*H*), 7.47-7.44 (2H, m, Ar*H*), 5.46 (1H, q, J = 7.2 Hz, BzOC*H*), 3.81 (1H, d, J = 9.0 Hz, C*H*OH), 3.02 (1H, dq, J = 9.0, 7.2 Hz, C(=O)C*H*(CH_3)CHOH), 2.06 (1H, s, O*H*), 1.57 (3H, d, J = 7.2 Hz, BzOCHC*H*$_3$), 1.52-1.45 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.41 (1H, ddq, J = 13.8, 7.2, 6.0 Hz, C*H*$_A$H$_B$CH$_3$), 1.30

(1H, ddq, J = 13.8, 7.2, 7.2 Hz, $CH_AH_BCH_3$), 1.18 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)CHOH), 0.92 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.86 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2CH_3); **minor isomer:** δ 8.09-8.07 (2H, m, Ar*H*), 7.59-7.57 (1H, m, Ar*H*), 7.47-7.44 (2H, m, Ar*H*), 5.46 (1H, q, J = 7.2 Hz, BzOC*H*), 3.56 (1H, m, C*H*OH), 3.07 (1H, dq, J = 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CHOH), 2.43 (1H, d, J = 6.0 Hz, O*H*), 1.57 (3H, d, J = 7.2 Hz, BzOCHCH_3), 1.52-1.45 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.41 (1H, ddq, J = 13.8, 7.2, 6.0 Hz, $CH_AH_BCH_3$), 1.30 (1H, ddq, J = 13.8, 7.2, 7.2 Hz, $CH_AH_BCH_3$), 1.27 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)CHOH), 0.93 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2CH_3), 0.89 (3H, t, J = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) **major isomer:** δ 211.9, 166.0, 133.5, 129.9, 129.6, 128.6, 75.4, 74.9, 45.9, 36.2, 27.0, 16.0, 14.2, 12.1, 12.0; **minor isomer:** δ 212.6, 166.0, 133.5, 129.9, 129.6, 128.6, 75.4, 74.8, 44.9, 37.1, 27.0, 16.1, 14.2, 12.0, 11.8.

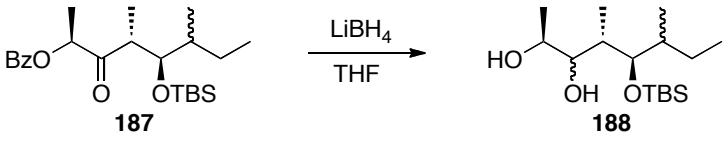


(2*S*,4*R*,5*R*)-2-benzoyloxy-5-hydroxy-4,6-dimethyl-hept-6-en-3-one (186). The previous procedure used for the preparation of aldol adduct **185** was followed with (*c*-Hex)$_2$BCl (103 μL; 363 μmol), Me_2NEt (47 μL; 436 μmol), ketone **(*S*)-183** (50.0 mg; 242 μmol), methacrolein (**46**) (40 μL; 484 mmol) and Et_2O (2.4mL). Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldol adduct **186** (52.2 mg; 78%, >98% ds) as a clear, colourless oil. **R*f*** = 0.19 (100% CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08-8.06 (2H, m, Ar*H*), 7.60-7.55 (1H, m, Ar*H*), 7.47-7.42 (2H, m, Ar*H*), 5.45 (1H, q, J = 7.2 Hz, BzOC*H*(CH_3)C=O), 4.95 (1H, m, CH(OH)CH(CH_3)CH_AH_B), 4.92 (1H, m, CH(OH)CH(CH_3)CH_AH_B), 4.26 (1H, d, J = 8.8 Hz, O*H*), 3.62 (1H, m, C*H*OH), 3.03 (1H, dq, J = 8.8, 6.8 Hz, C(=O)C*H*(CH_3)CHOH), 1.71 (3H, s, CH(OH)C(CH_3)CH_2), 1.56 (3H, d, J = 6.8 Hz, BzOCH(CH_3)C=O), 1.10 (3H, d, J = 6.8 Hz, C(=O)CH(CH_3)CHOH).



185 **187**

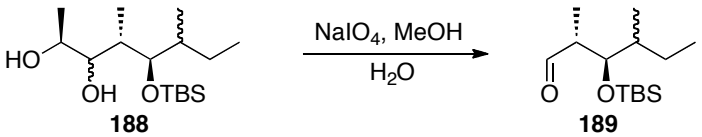
(2*S*,4*R*,5*R*)-2-benzoyloxy-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethyl-octan-3-one (187), The previous procedure used for the preparation of TBS ether **(6*R*,7*S*,8*S*)-179** was followed with alcohol **185** (2.38 g; 8.14 mmol), 2,6-lutidine (1.90 mL; 16.3 mmol), TBSOTf (2.80 mL; 12.2 mmol) and CH_2Cl_2 (81 mL). Purification by column chromatography (buffered silica, 50% X4/CH_2Cl_2) gave TBS ether **187** (2.85 g; 86%) as a clear, colourless oil. **R*f*** = 0.31 (50% X4/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) **major isomer:** δ 8.10-8.07 (2H, m, Ar*H*), 7.60-7.55 (1H, m, Ar*H*), 7.48-7.43 (2H, m, Ar*H*), 5.47 (1H, q, J = 7.2 Hz, BzOC*H*(CH_3)C=O), 3.98 (1H, dd, J = 8.8, 1.6 Hz, C*H*OTBS), 3.10 (1H, dq, J = 8.8, 7.2 Hz, C(=O)C*H*(CH_3)CHOTBS), 1.53 (3H, d, J = 6.8 Hz, BzOCH(C*H*$_3$)C=O), 1.50-1.40 (2H, m, C*H*(CH_3)CH_2CH_3 and C*H*$_A$H$_B$$CH_3$), 1.26-1.17 (1H, m, $CH_AH_BCH_3$), 1.10 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CHOTBS), 0.89 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), -0.07 (3H, s, OSi(CH_3)C*H*$_3$); **minor isomer:** δ 8.10-8.07 (2H, m, Ar*H*), 7.60-7.55 (1H, m, Ar*H*), 7.48-7.43 (2H, m, Ar*H*), 5.47 (1H, q, J = 7.2 Hz, BzOC*H*(CH_3)C=O), 3.95 (1H, dd, J = 8.8, 2.4 Hz, C*H*OTBS), 3.13 (1H, dq, J = 8.4, 6.8 Hz, C(=O)C*H*(CH_3)CHOTBS), 1.52 (3H, d, J = 7.2 Hz, BzOCH(C*H*$_3$)C=O), 1.50-1.40 (2H, m, C*H*(CH_3)CH_2CH_3 and C*H*$_A$H$_B$$CH_3$), 1.26-1.17 (1H, m, $CH_AH_BCH_3$), 1.11 (3H, d, J = 6.8 Hz, C(=O)CH(C*H*$_3$)CHOTBS), 0.89 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), -0.06 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.4, 133.3, 129.9, 128.6, 76.7, 75.2, 46.6, 38.5, 26.5, 25.9, 18.6, 15.7, 14.6, 13.4, 12.5, -3.5, -4.5.



187 **188**

(2*S*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-octan-2,3-diol (188), synthesised according to the procedure of Paterson *et al*.[42] To as stirred solution of benzoate **187** (1.07 mg; 2.63 mmol) in THF (32 mL) at -78 ^{o}C was added $LiBH_4$ (13.0 mL; 2 M in

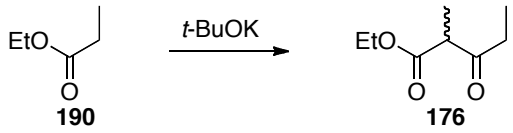
THF; 26.0 mmol). The resulting solution was placed in an ice bath for 10 min before warming to rt overnight. The solution was then cooled to 0 ^{o}C and quenched with H_2O (30 mL). The mixture was partitioned between H_2O (30 mL) and Et_2O (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 40% EtOAc/X4) gave 1,2-diol **188** (801 mg; 99%) as a clear, colourless oil. **R*f*** = 0.37 (20% Et_2O/CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer:** δ 3.77 (1H, dq, J = 6.6, 3.6 Hz, C*H*(OH)(CH_3)CHOH), 3.62 (1H, dd, J = 9.6, 3.6 Hz, C*H*OTBS), 3.54 (1H, dd, J = 5.4, 3.6 Hz, CH(CH_3)C*H*(OH)CHCH_3), 2.92 (1H, br s, O*H*), 2.03 (1H, s, O*H*), 1-.0-1.64 (1H, m, C$H_AH_BCH_3$), 1.54-1.48 (1H, m, C*H*(CH_3)CH_2CH_3), 1.45 (1H, ddq, J = 13.2, 7.8, 4.8 Hz, $CH_AH_BCH_3$), 1.14 (3H, d, J = 6.6 Hz, CH(OH)(CH_3)CHOH), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.88 (3H, d, J = 6.6 Hz, CH(OH)CH(CH_3)CHOTBS), 0.81 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2CH_3), 0.12 (3H, s, OSi(CH_3)CH_3), 0.08 (3H, s, OSi(CH_3)CH_3); **minor isomer:** δ 3.71 (1H, dq, J = 5.4, 3.6 Hz, C*H*(OH)(CH_3)CHOH), 3.63 (1H, dd, J = 9.6, 3.0 Hz, C*H*OTBS), 3.53 (1H, m, CH(CH_3)C*H*(OH)CHCH_3), 2.92 (1H, br s, O*H*), 2.03 (1H, s, O*H*), 1.78-1.70 (1H, m, C$H_AH_BCH_3$), 1.60-1.54 (1H, m, C*H*(CH_3)CH_2CH_3), 1.53-1.47 (1H, m, $CH_AH_BCH_3$), 1.14 (3H, d, J = 6.6 Hz, CH(OH)(CH_3)CHOH), 0.91 (9H, s, OSiC(CH_3)$_3$), 0.82 (3H, d, J = 6.6 Hz, CH(OH)CH(CH_3)CHOTBS), 0.81 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2CH_3), 0.11 (3H, s, OSi(CH_3)CH_3), 0.09 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 83.0, 82.2, 81.2, 76.4, 76.32, 76.28, 69.4, 68.1, 68.0, 60.5, 41.5, 40.6, 39.7, 39.2, 37.7, 35.3, 26.23, 26.22, 26.20, 26.15, 26.10, 25.9, 25.2, 21.2, 18.41, 18.35, 18.28, 18.25, 16.05, 15.97, 15.91, 15.8, 15.3, 15.0, 14.7, 14.3, 12.7.



188 **189**

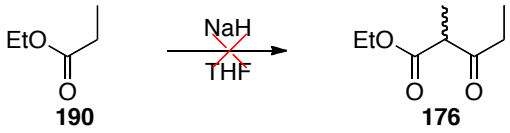
(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-hexanal (189), synthesised according to the procedure of Paterson *et al*.[42] To a stirred solution of 1,2-diol **188** (256 mg; 842 μmol) in MeOH (8 mL) and H_2O (4 mL) at rt was added $NaIO_4$ (1.08 g; 5.05 mmol) and the resulting suspension was stirred at rt for 15 min. The reaction mixture was diluted with H_2O (20 mL), extracted with Et_2O (3 x 20 mL), dried

(Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **189** (286 mg; 100%) as a clear, colourless oil. **R*f*** = 0.26 (20% EtOAc/X4); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer:** δ 9.76 (1H, d, J = 3.0 Hz, C*H*O), 3.75 (1H, dd, J = 4.8, 4.2 Hz, C*H*OTBS), 2.53 (1H, ddq, J = 7.2, 4.8, 3.0 Hz, CH(OTBS)C*H*(CH_3)CHO), 1.55-1.42 (3H, m, C*H*(CH_3)CH_2CH_3, $CH_AH_BCH_3$ and $CH_AH_BCH_3$), 1.06 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CHO), 0.88 (3H, t, J = 7.8 Hz, CH_2CH_3), 0.88 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), 0.04 (3H, s, OSi(CH_3)C*H*$_3$); **minor isomer:** δ 9.77 (1H, d, J = 3.0 Hz, C*H*O), 3.75 (1H, dd, J = 4.8, 4.2 Hz, C*H*OTBS), 2.53-2.49 (1H, m, CH(OTBS)C*H*(CH_3)CHO), 1.60-1.55 (1H, m, $CH_AH_BCH_3$), 1.54-1.42 (2H, m, C*H*(CH_3)CH_2CH_3 and $CH_AH_BCH_3$), 1.09 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CHO), 0.90 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.89 (3H, d, J = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.05 (3H, s, OSi(C*H*$_3$)CH_3), 0.04 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) **major isomer:** δ 205.5, 78.2, 50.0, 40.0, 26.0, 25.7, 18.4, 14.5, 12.5, 12.3, -3.9, -4.2; **minor isomer:** δ 205.5, 78.6, 49.2, 40.6, 26.0, 25.6, 18.4, 14.9, 12.7, 12.1, -4.1, -4.4.

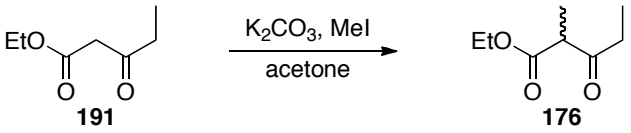


190 **176**

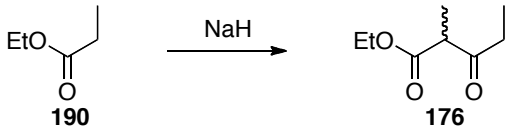
Ethyl 2-methyl-3-oxo-pentanoate (176), synthesised according to the procedure of Yoshizawa *et al.*[43] A mixture of ethyl propionate (**190**) (4.61 mL; 40.0 mmol) and *t*-BuOK (3.14 g; 28.0 mmol) was stirred at 80 °C for 2 h before cooling to rt and neutralising with 1 M HCl. The product was extracted with Et_2O (3 x 25 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo.* Distillation of the residue under reduced pressure gave β-ketoester (**176**) (163 mg; 3%) as a clear, colourless oil. **bp.** 39-40 °C at 0.4 mmHg. **NMR** data as for **176** below.



Ethyl-2-methyl-3-oxo-pentanoate (176), synthesis attempted according to the procedure of Shone *et al.*[44] To a stirred suspension of NaH (1.32 g; 57.4 mmol) in THF (87 mL) was added ethyl propionate (**190**) (6.00 mL; 52.2 mmol) dropwise at such a rate that the temperature did not exceed 35 ^{o}C. The reaction was quenched after 1 h by slow addition of AcOH (4 mL), followed by H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR of the crude residue showed that no reaction had occurred.

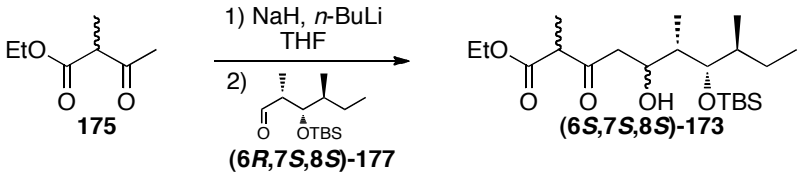


Ethyl-2-methyl-3-oxo-pentanoate (176), synthesis attempted according to the procedure of Kalaitzakis *et al.*[45] To a stirred solution of ethyl 3-oxopentanoate (**191**) (500 μL; 3.51 mmol) in anhydrous acetone (5 mL) was added K_2CO_3 (451 mg; 3.26 mmol). After stirring at rt for 5 min, MeI (269 μL; 4.32 mmol) was added and the mixture was heated to reflux for 6 h. The mixture was cooled to rt and Et_2O (10 mL) added. The mixture was filtered and the solvent removed *in vacuo* to give an inseparable mixture of starting material **191** and product **176**.



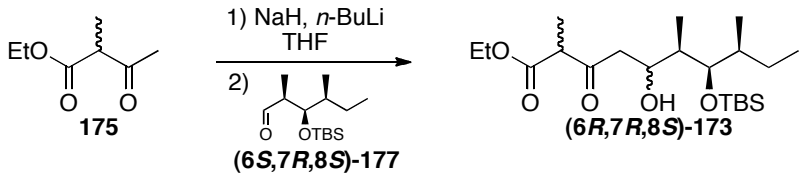
Ethyl-2-methyl-3-oxo-pentanoate (176), synthesised according to the procedure of Hanley *et al.*[46] Sodium hydride (772 mg; 32.2 mmol) was added to ethyl propionate (**190**) (10.0 mL; 86.9 mmol) with stirring and the mixture was slowly heated to 70

^{o}C. When all the hydride had dissolved the mixture was heated at 70 ^{o}C for a further 18 h, before cooling to 0 ^{o}C. A few drops of EtOH were added to quench any remaining hydride and the reaction mixture was then poured into 1 M HCl (30 mL), extracted with Et_2O (3 x 50 mL) and washed with brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude β-ketoester as a yellow oil. Distillation under reduced pressure gave β-ketoester **176** (4.08 g; 30%) as a colourless oil. **bp.** 85-86 ^{o}C at 0.3 mmHg; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.17 (1H, q, J = 7.2 Hz, $CH_3CH_AH_BO$), 4.16 (1H, q, J = 7.2 Hz, $CH_3CH_AH_BO$), 3.51 (1H, q, J = 7.2 Hz, C(=O)C*H*(CH$_3$)C=O), 2.60 (1H, dq, J = 18.0, 7.2, C(=O)C$H_AH_BCH_3$), 2.51 (1H, dq, J = 18.0, 7.2, C(=O)C$H_AH_BCH_3$), 1.32 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)C=O), 1.25 (3H, t, J = 7.2 Hz, CH_3CH$_2$O), 1.06 (3H, t, J = 7.2 Hz, C(=O)CH$_2$CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.7, 170.8, 61.4, 34.8, 14.2, 13.0, 7.8.



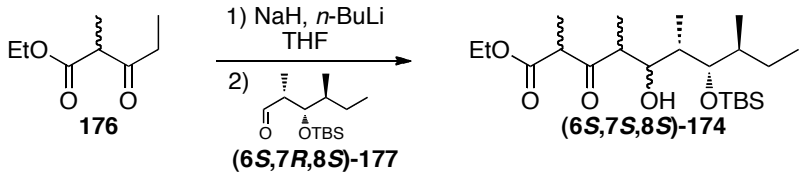
(6*S*,7*S*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethyl-3-oxodecanoate [(6*S*,7*S*,8*S*)-173], synthesised according to a procedure modified from Huckin and Weiler.[47,48] To a stirred suspension of NaH (170 mg; 7.07 mmol) in THF (20 mL) at 0 ^{o}C was added ethyl-2-methylacetoacetate (**175**) (572 μL; 4.04 mmol) and the resulting mixture was stirred at 0 ^{o}C for 10 min, before cooling to -10 ^{o}C. *n*-BuLi (2.53 mL; 1.6 M in hexanes; 4.04 mmol) was then added, with stirring at -10 ^{o}C for a further 10 minutes. The reaction mixture was cooled to -78 ^{o}C and a solution of aldehyde **(6*R*,7*S*,8*S*)-177** (522.8 mg; 2.02 mmol) in THF (5 mL) was added dropwise *via* cannula and the reaction mixture was stirred at -78 ^{o}C for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL) and allowed to warm to rt. The mixture was extracted with brine (4 x 20 mL) and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Residual ethyl-2-methylacetoacetate was removed under high vacuum and the residue was filtered through a plug of buffered silica (100% CH_2Cl_2) to give a

complex mixture of isomers of alcohol **(6*S*,7*S*,8*S*)-173** (785 mg; 96%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.18-4.14 (2H, m, CH_3CH_2O), 4.08-4.04 (0.5H, m, C*H*OTBS), 3.91-3.85 (0.5H, m, C*H*OTBS), 3.84 (0.5H, ddd, J = 6.0, 3.6, 1.8 Hz, C*H*OH), 3.68 (0.5H, m, C*H*OH), 3.55, 3.54, 3.51, 3.51 (4 x 0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 2.81 (0.25H, dd, J = 16.8, 2.4 Hz, $C(=O)CH_AH_BCHOH$), 2.77 (0.25H, dd, J = 17.4, 2.4 Hz, $C(=O)CH_AH_BCHOH$), 2.72 (0.25H, dd, J = 17.4, 5.4 Hz, $C(=O)CH_AH_BCHOH$), 2.72 (0.25H, dd, J = 16.8, 2.4 Hz, $C(=O)CH_AH_BCHOH$), 2.65 (0.25H, dd, J = 16.8, 8.4 Hz, $C(=O)CH_AH_BCHOH$), 2.64 (0.25H, dd, J = 17.4, 3.6 Hz, $C(=O)CH_AH_BCHOH$), 2.59 (0.25H, dd, J = 15.6, 9.0 Hz, $C(=O)CH_AH_BCHOH$), 2.53 (0.25H, dd, J = 17.4, 9.0 Hz, $C(=O)CH_AH_BCHOH$), 1.68-1.50 (1H, m, $C(OH)CH(CH_3)CHOTBS$), 1.58-1.49 (1H, m, $CH(CH_3)CH_2CH_3$), 1.50-1.35 (1H, m, $CH(CH_3)CH_AH_BCH_3$), 1.32 (0.75H, d, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.31 (1.5H, d, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$) , 1.30 (0.75H, d, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.24 (3H, t, J = 7.2 Hz, CH_3CH_2O), 1.11-0.99 (1H, m, $CH(CH_3)CH_AH_BCH_3$), 0.89 (1.5H, d, J = 7.2 Hz, $CH(OTBS)CH(CH_3)CH_2CH_3$), 0.88-0.85 (13.5H, m, $OSiC(CH_3)_3$ and $CH(OTBS)CH(CH_3)CH_2CH_3$), 0.83 (1.5H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.76 (1.5H, d, J = 6.6 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.06 (1H, s, $OSi(CH_3)_2$), 0.06 (1H, s, $OSi(CH_3)_2$), 0.04 (2H, s, $OSi(CH_3)_2$) 0.04 (2H, s, $OSi(CH_3)_2$), (OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.4, 207.2, 206.64, 206.56, 170.41, 170.35, 170.32, 77.6, 77.5, 75.5, 70.8, 70.5, 69.8, 69.7, 61.54, 61.51, 53.7, 53.52, 53.48, 53.45, 46.6, 46.5, 46.3, 46.1, 43.9, 40.9, 40.8, 40.7, 40.6, 39.67, 39.66, 39.64, 39.58, 38.8, 26.2, 26.1, 25.9, 25.71, 25.66, 23.34, 23.33, 23.32, 22.8, 22.3, 18.45, 18.42, 18.41, 15.89, 15.87, 15.38, 15.36, 14.2, 12.8, 12.68, 12.63, 12.60, 12.4, 12.1, 11.4, 9.9, 9.8, -3.5, -3.99, -4.02, -4.11, -4.13, -4.22, -4.24.



(6*S*,7*S*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethyl-3-oxodecanoate [(6*S*,7*S*,8*S*)-173], The previous procedure for the preparation of alcohol **(6*S*,7*S*,8*S*)-173** was used with β-ketoester **175** (242 μL; 1.71 mmol), NaH

(72.0 mg; 3.00 mmol), *n*-BuLi (1.07 mL; 1.6 M in hexanes; 1.71 mmol), aldehyde **(6*S*,7*R*,8*S*)-177** (222 mg; 857 μmol) and THF (8.6 mL). The crude product was filtered through a plug of buffered silica (100% CH_2Cl_2) to give a complex mixture of isomers of alcohol **(6*R*,7*R*,8*S*)-173** (341 mg; 99%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.17-4.12 (2H, m, CH_3CH_2O), 4.10-4.06 (0.5H, m, C*H*OTBS), 3.97-3.94 (0.5H, m, C*H*OTBS), 3.79 (0.5H, ddd, J = 4.2, 4.2, 3.0 Hz, C*H*OH), 3.62 (0.5H, dd, J = 4.8, 3.6 Hz, C*H*OH), 3.57, 3.55, 3.51, 3.50 (4 x 0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 2.75-2.70 (1H, m, $C(=O)CH_AH_BCHOH$), 2.65-2.58 (0.5H, m, $C(=O)CH_AH_BCHOH$), 2.57 (0.25H, dd, J = 16.8, 8.4 Hz, $C(=O)CH_AH_BCHOH$), 2.53 (0.25H, dd, J = 16.8, 9.0 Hz, $C(=O)CH_AH_BCHOH$), 1.73-1.66 (0.5H, m, $CH(OH)CH(CH_3)CHOTBS$), 1.62-1.57 (0.5H, m, $CH(OH)CH(CH_3)CHOTBS$), 1.55-1.37 (2H, m, $CH(CH_3)CH_2CH_3$ and $CH(CH_3)CH_AH_BCH_3$), 1.31 (1.5H, d, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.29 (1.5H, d, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.23 (1H, t, J = 7.2 Hz, CH_3CH_2O), 1.23 (2H, t, J = 7.2 Hz, CH_3CH_2O), 1.11-1.04 (1H, m, $CH(CH_3)CH_AH_BCH_3$), 0.89 (0.75H, d, J = 6.6 Hz, $C(=O)CH(CH_3)CHOTBS$), 0.88 (1.5H, d, J = 7.2 Hz, $C(=O)CH(CH_3)CHOTBS$), 0.87-0.82 (12.75H, m, $C(=O)CH(CH_3)CHOTBS$, $OSiC(CH_3)_3$ and $CH(CH_3)CH_2CH_3$), 0.80 (1.5H, d, J = 6.6 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.75 (0.75H, d, J = 6.6 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.75 (0.75H, d, J = 6.6 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.06 (1H, s, $OSi(CH_3)_2$), 0.05 (1H, s, $OSi(CH_3)_2$), 0.03 (2H, s, $OSi(CH_3)_2$), -0.02 (2H, s, $OSi(CH_3)_2$), (OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.93, 206.85, 206.81, 206.7, 170.5, 170.44, 170.37, 170.28, 77.5, 77.4, 76.6, 70.2, 70.0, 69.6, 69.3, 61.53, 61.51, 61.47, 61.43, 53.8, 53.47, 53.44, 51.7, 46.9, 46.8, 46.50, 46.47, 42.0, 41.8, 40.8, 40.7, 39.62, 39.57, 38.40, 38.36, 37.7, 34.6, 31.6, 31.0, 29.8, 27.2, 27.1, 26.3, 26.22, 26.18, 26.14, 26.12, 26.10, 23.33, 23.30, 22.3, 18.5, 18.4, 15.65, 15.64, 14.56, 14.51, 14.1, 12.7, 12.60, 12.59, 12.5, 12.12, 12.07, 12.04, 10.3, 10.2, -3.5, -3.99, -4.02, -4.09, -4.13.



(6*S*,7*S*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyl-3-oxodecanoate [(6*S*,7*S*,8*S*)-174], The previous procedure for the preparation of alcohol **(6*S*,7*S*,8*S*)-173** was used with β-ketoester **176** (690 mg; 4.36 mmol), NaH (183 mg; 7.63 mmol), *n*-BuLi (2.73 mL; 1.6 M in hexanes; 4.36 mmol), aldehyde **(6*S*,7*R*,8*S*)-177** (563 mg; 2.18 mmol) and THF (22 mL). The crude product was filtered through a plug of buffered silica (100% CH_2Cl_2) to give a complex mixture of isomers of alcohol **(6*S*,7*S*,8*S*)-174** (907 mg; 100%) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.19-4.12 (2H, m, CH_3CH_2O), 3.97-3.77 (1.5H, m, C*H*OTBS and C*H*OH), 3.75 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 3.73 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 3.68 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 3.65 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 3.63 (0.5H, dd, J = 7.2, 3.0 Hz, C*H*OH) 2.95 (0.5H, dq, J = 7.2, 6.6 Hz, $C(=O)CH(CH_3)CHOH$), 2.86 (2 x 0.25H, dq, J = 7.2, 6.6 Hz, $C(=O)CH(CH_3)CHOH$), 1.75-1.35 (3H, m, $C(OH)CH(CH_3)CHOTBS$, $CH(CH_3)CH_2CH_3$ and $CH(CH_3)CH_AH_BCH_3$), 1.32-1.29 (3H, m, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.26-1.22 (3.75H, m, CH_3CH_2O and $C(=O)CH(CH_3)CHOH$), 1.18 (0.75H, d, J = 7.2 Hz, $C(=O)CH(CH_3)CHOH$), 1.08 (0.75H, d, J=7.2 Hz, $C(=O)CH(CH_3)CHOH$), 1.07 (0.75H, d, J=7.2 Hz, $C(=O)CH(CH_3)CHOH$), 1.07-0.95 (1H, m, $CH(CH_3)CH_AH_BCH_3$), 0.92-0.83 (16.5H, m, $CH(OTBS)CH(CH_3)CH_2CH_3$, $OSiC(CH_3)_3$ and $CH(CH_3)CH_2CH_3$), 0.78 (0.75H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.74 (0.75H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)CHOTBS$), 0.08-0.04 (6H, m, $OSi(CH_3)_2$) (OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 211.9, 211.8, 210.9, 210.0, 209.5, 170.6, 170.4, 170.4, 170.2, 170.1, 167.9, 84.5, 80.4, 80.0, 79.5, 79.1, 78.3, 77.0, 76.0, 75.7, 75.5, 75.3, 71.8, 71.2, 61.60, 61.53, 61.49, 61.47, 61.3, 54.4, 53.8, 52.7, 52.0, 51.8, 50.92, 50.87, 50.0, 49.9, 49.0, 48.8, 48.6, 47.5, 47.4, 47.0, 40.89, 40.87, 40.76, 40.6, 39.9, 39.7, 39.4, 39.0, 38.7, 38.3, 37.9, 37.1, 36.8, 35.5, 34.5, 33.8, 32.0, 30.4, 29.8, 29.5, 23.4, 22.8, 22.3, 18.53, 18.49, 18.45, 18.40, 18.38, 18.35, 16.5, 16.2, 15.8, 15.7, 15.6, 15.4, 15.24, 15.18, 15.0, 14.19, 14.17, 14.14, 14.0, 13.3, 13.2, 13.11, 13.05, 13.00, 12.9, 12.7, 12.55, 12.50, 12.41, 12.37, 12.35, 12.29, 12.23, 12.16, 12.0,

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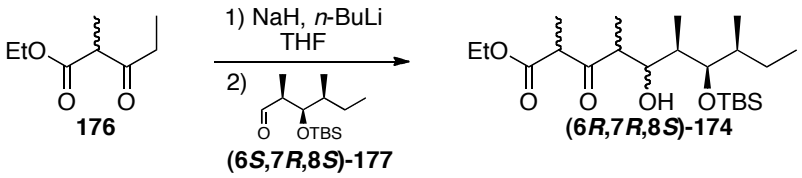
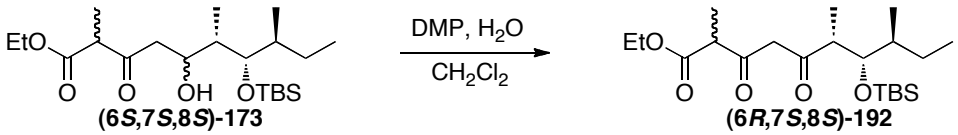


(6*R*,7*R*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyl-3-oxodecanoate [(6*R*,7*R*,8*S*)-174], The previous procedure for the preparation of alcohol **(6*S*,7*S*,8*S*)-173** was used with β-ketoester **176** (358 mg; 2.26 mmol), NaH (94.9 mg; 3.96 mmol), *n*-BuLi (1.41 mL; 1.6 M in hexanes; 2.26 mmol), aldehyde **(6*S*,7*R*,8*S*)-177** (293 mg; 1.13 mmol) and THF (11 mL). The crude product was filtered through a plug of buffered silica (100% CH_2Cl_2) to give a complex mixture of isomers of alcohol **(6*R*,7*R*,8*S*)-174** (463 mg; 98%) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.16-4.10 (2H, m, CH_3CH_2O), 4.04 (0.25H, m, C*H*OTBS), 3.91-3.85 (0.75H, m, C*H*OTBS), 3.80-3.77 (0.25H, C*H*OH), 3.78, 3.73, 3.67, 3.63, (4 x 0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 3.59 (0.25H, dd, J = 4.2, 3.6 Hz, C*H*OH), 3.56 (0.25H, dd, J = 4.2, 3.6 Hz, C*H*OH), 3.54 (0.25H, dd, J = 4.2, 3.6 Hz, C*H*OH), 2.97, 2.95, 2.81, 2.79 (4 x 0.25H, dq, J = 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CHOH), 1.71-1.65 (0.25H, m, C(OH)C*H*(CH_3)CHOTBS), 1.60-1.37 (2.75H, m, C(OH)C*H*(CH_3)CHOTBS, C*H*(CH_3)CH_2CH_3 and CH(CH_3)$CH_AH_BCH_3$), 1.30-1.27 (3H, m, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 1.24-1.20 (3H, m, CH_3CH_2O), 1.16 (1H, d, J = 6.6 Hz, C(=O)CH(*CH*$_3$)CHOH), 1.08-0.99 (3.25H, m, C(=O)CH(*CH*$_3$)CHOH and CH(CH_3)$CH_AH_BCH_3$), 0.94 (0.75H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 0.91-0.78 (15.5H, CH(OTBS)CH(CH_3)CH_2CH_3, OSiC(CH_3)$_3$, CH(OH)CH(CH_3)CHOTBS) and CH(CH_3)CH_2CH_3), 0.76 (0.75H, d, J = 7.2 Hz, CH(OH)CH(CH_3)CHOTBS), 0.73 (0.75H, d, J = 7.2 Hz, CH(OH)CH(CH_3)CHOTBS), 0.07-0.02 (6H, m, OSi(CH_3)$_2$), (OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 211.5, 211.3, 211.2, 210.0, 209.5, 206.6, 205.5, 170.9, 170.8, 170.5, 170.4, 170.20, 170.17, 104.7, 85.4, 83.3, 79.20, 79.18, 78.9, 78.4, 78.0, 77.0, 75.54, 75.47, 75.3, 74.9, 74.6, 72.4, 71.6, 61.5, 61.50, 61.46, 61.40, 61.36, 61.35, 54.1, 53.6, 53.5, 52.7, 51.8, 51.7, 50.9, 50.7, 50.4, 50.0, 49.8, 49.7, 49.2, 49.1, 48.98, 48.96, 48.0, 47.9, 47.5, 47.4,

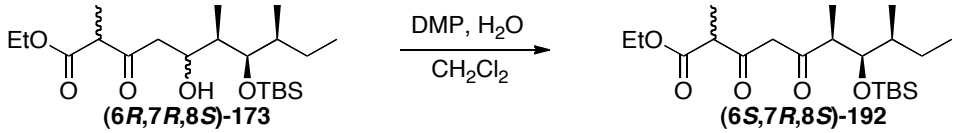
44.1, 44.0, 40.3, 40.2, 40.1, 39.9, 39.8, 39.6, 39.3, 38.9, 38.60, 38.58, 38.52, 38.2, 37.9, 37.8, 37.5, 37.4, 37.1, 36.5, 34.7, 34.4, 33.7, 32.0, 30.4, 29.8, 27.3, 26.23, 26.19, 26.16, 26.14, 26.10, 26.0, 25.93, 25.90, 25.83, 25.80, 25.76, 25.72, 25.50, 25.45, 25.3, 23.3, 22.31, 22.30, 18.51, 18.49, 18.43, 18.40, 18.37, 18.31, 18.29, 15.9, 15.82, 15.81, 15.76, 15.0, 14.9, 14.71, 14.65, 14.14, 14.13, 13.9, 13.6, 13.23, 13.20, 13.19, 13.04, 13.01, 12.94, 12.89, 12.69, 12.68, 12.66, 12.61, 12.58, 12.3, 12.23, 12.15, 12.09, 12.07, 12.00, 11.7, 11.6, 11.2, 9.6, 9.5, 9.3, 8.00, 7.96, 7.75, 7.71, 7.5, 7.4, -3.4, -3.7, -3.9, -4.0, -4.13, -4.15, -4.17, -4.19, -4.20, -4.29, -4.33.



(6*S*,7*S*,8*S*)-173 **(6*R*,7*S*,8*S*)-192**

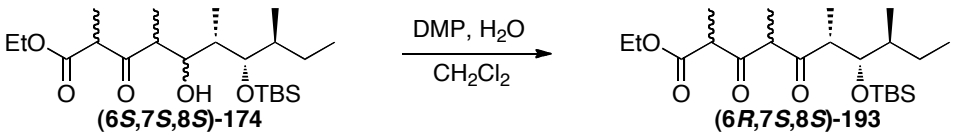
(6*R*,7*S*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethyl-3,5-dioxo-decanoate [(6*R*,7*S*,8*S*)-192], synthesised according to the procedure of Meyer and Schreiber.[9] To a stirred solution of alcohol **(6*S*,7*S*,8*S*)-173** (762 mg; 1.89 mmol) in CH_2Cl_2 (19 mL) at rt in the dark was added Dess-Martin Periodinane (1.20 g; 2.84 mmol), followed immediately by addition of a H_2O/CH_2Cl_2 mixture (3.15 mL of sat. aq. CH_2Cl_2) and addition of the moist CH_2Cl_2 continued every 5 min for 1h (ie. 12 x 3.15 mL aliquots). The reaction mixture was stirred at rt for 2 days before diluting with Et_2O (100 mL). Sat. aq. $NaHCO_3$ (60 mL) containing $Na_2S_2O_3.5H_2O$ (7.7 g) was added to quench the reaction with stirring for 5 minutes. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (60 mL) and brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through buffered silica (100% CH_2Cl_2) to afford tricarbonyl **(6*R*,7*S*,8*S*)-192** (720 mg; 95%) as a yellow oil. **(enol tautomer)** ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 5.58 (0.5H, s, $CH(CH_3)C(=O)CH_2CH(=O)CHCH_3$), 5.57 (0.5H, s, $CH(CH_3)C(=O)CH_2CH(=O)CHCH_3$), 4.14 (2H, q, J = 7.2 Hz, CH_3CH_2O), 3.80 (1H, dd, J = 5.4, 4.8 Hz, CHOTBS), 3.34 (2 x 0.5H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 2.48 (1H, dq, J = 7.2, 6.6 Hz, $C(=O)CH(CH_3)CHOTBS$), 1.50-1.36 (1H, m, $CH(OTBS)CH(CH_3)CH_2CH_3$), 1.34 (2 x 1.5H, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C=O$), 1.32-1.16 (1H, m, $CH(OTBS)CH(CH_3)CH_AH_BCH_3$), 1.22 (3H, t, J = 7.2 Hz, CH_3CH_2O), 1.15-1.00 (1H, m,

CH(OTBS)CH(CH_3)$CH_A H_B CH_3$), 1.08 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 0.89-0.80 (15H, m, , CH(CH_3)CH_2CH_3), OSiC(CH_3)$_3$ and C(=O)CH(CH_3)CHOTBS), -0.01 (3H, s, OSi(CH_3)CH_3), -0.07 (3H, s, OSi(CH_3)CH_3), (enol OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.07, 194.96, 193.2, 193.0, 170.8, 169.3, 99.3, 98.1, 77.4, 77.04, 77.01, 75.2, 73.8, 73.2, 72.7, 61.35, 61.34, 53.5, 49.7, 49.6, 44.7, 43.9, 43.7, 41.4, 40.6, 38.8, 34.6, 33.2, 30.9, 29.8, 26.1, 25.03, 25.01, -4.1, -4.23, -4.26.



(6*R*,7*R*,8*S*)-173 **(6*S*,7*R*,8*S*)-192**

(6*S*,7*R*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethyl-3,5-dioxo-decanoate [(6*S*,7*R*,8*S*)-192]. The previous procedure for the preparation of tricarbonyl **(6*R*,7*S*,8*S*)-192** was used with alcohol **(6*R*,7*R*,8*S*)-173** (524 mg; 1.30 mmol), DMP (827 mg; 1.95 mmol), CH_2Cl_2 (13 mL) and CH_2Cl_2 (sat., 12 x 2.17 mL). The crude residue was filtered through buffered silica (100% CH_2Cl_2) to afford tricarbonyl **(6*S*,7*R*,8*S*)-192** (473 mg; 91%) as a yellow oil. **(enol tautomer) ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.58 (0.5H, s, C(OH)=C*H*C=O), 5.57 (0.5H, s, C(=O)=C*H*COH), 4.18-4.12 (2H, m, CH_3CH_2O), 3.79 (1H, dd, J = 6.0, 3.0 Hz, C*H*OTBS), 3.36 (2 x 0.5H, q, J = 7.2 Hz, CH_3CH_2OC(=O)C*H*(CH_3)C=O), 2.49-2.43 (1H, m, C(=O)C*H*(CH_3)CHOTBS), 1.46-1.37 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.36 (2 x 1.5H, d, J = 7.2 Hz, CH_3CH_2OC(=O)CH(CH_3)C=O), 1.27-1.20 (1H, m, CH(CH_3)$CH_A H_B CH_3$), 1.23 (3H, t, J = 7.2 Hz, CH_3CH_2O), 1.16-1.06 (1H, m, CH(CH_3)$CH_A H_B CH_3$), 1.12 (3H, d, J = 7.2 Hz, CH(CH_3)CH_2CH_3), 0.90-0.81 (15H, m, OSiC(CH_3)$_3$, C(=O)CH(CH_3)CHOTBS and CH(CH_3)CH_2CH_3), 0.02 (3H, s, OSi(CH_3)CH_3), -0.02 (3H, s, OSi(CH_3)CH_3), (enol OH not assigned); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.74, 194.65, 193.4, 193.3, 170.9, 98.5, 98.2, 76.83, 76.80, 61.4, 53.5, 49.8, 49.7, 45.8, 39.7, 26.2, 18.5, 14.3, 14.23, 14.18, 14.16, 14.08, 14.03, 13.97, 13.86, 12.2, -3.74, -3.75, -3.94, -4.95.



(6*S*,7*S*,8*S*)-174 (6*R*,7*S*,8*S*)-193

(6*R*,7*S*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyl-3,5-dioxo-decanoate [(6*R*,7*S*,8*S*)-193]. The previous procedure for the preparation of tricarbonyl **(6*R*,7*S*,8*S*)-192** was used with alcohol **(6*S*,7*S*,8*S*)-174** (913 mg; 2.19 mmol), DMP (1.39 g; 3.29 mmol), CH_2Cl_2 (22 mL) and CH_2Cl_2 (sat., 12 x 3.65 mL). The crude residue was filtered through buffered silica (100% CH_2Cl_2) to afford tricarbonyl **(6*R*,7*S*,8*S*)-193** (907 mg; 100%) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.20-4.08 (2.5H, m, CH_3CH_2O) and C(=O)C*H*(CH_3)C(=O)CH(CH_3)CHOTBS), 4.04, 4.03 (2 x 0.25H, q, J = 7.2 Hz, C(=O)C*H*(CH_3)C(=O)CH(CH_3)CHOTBS), 3.95 (0.25H, dd, J = 5.4, 3.6 Hz, C*H*OTBS), 3.88-3.84 (0.5H, m, C*H*OTBS), 3.83 (0.25H, dd, J = 6.0, 3.6 Hz, C*H*OTBS), 3.75-3.70 (0.5H, m, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 3.62 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 3.61 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 2.91-2.86 (0.5H, m, C(=O)C*H*(CH_3)CHOTBS), 2.84 (0.25H, dq, J = 6.6, 6.0 Hz, C(=O)C*H*(CH_3)CHOTBS), 2.78 (0.25H, dq, J = 7.2, 6.0Hz, C(=O)C*H*(CH_3)CHOTBS), 1.55-1.26 (5.5H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$ and C(=O)CH(*C*H_3)C(=O)CH(CH_3)CHOTBS), 1.25-1.16 (5.5H, m, C(=O)CH(*C*H_3)C(=O)CH(CH_3)CHOTBS, CH_3CH_2O and $CH(CH_3)CH_AH_BCH_3$), 1.12-0.79 (1.5H, m, CH(OTBS)CH(CH_3)CH_2CH_3), 1.06-1.03 (1.5H, m, CH(OTBS)CH(CH_3)CH_2CH_3), 1.07-0.99 (1H, m, $CH(CH_3)CH_AH_BCH_3$), 0.88-0.83 (15H, m, $CH(CH_3)CH_2CH_3$, $OSiC(CH_3)_3$, and C(=O)CH(CH_3)CHOTBS), 0.03- -0.03 (6H, s, $OSi(CH_3)_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 210.5, 210.0, 209.1, 208.8, 207.0, 203.40, 203.37, 202.35, 202.29, 195.3, 195.1, 193.2, 192.0, 191.9, 171.0, 170.9, 170.1, 103.6, 103.4, 77.30, 77.27, 77.25, 76.7, 76.0, 75.8, 75.5, 75.4, 75.1, 61.64, 61.62, 61.56, 61.55, 61.29, 61.26, 60.9, 59.2, 58.8, 58.7, 57.5, 53.5, 52.3, 51.6, 50.8, 50.0, 49.8, 49.7, 49.4, 48.8, 48.5, 48.2, 46.1, 45.9, 44.04, 44.00, 42.4, 41.2, 41.10, 41.08, 41.02, 40.9, 40.78, 40.74, 40.71, 40.66, 37.8, 37.4, 37.1, 34.4, 33.7, 32.0, 30.9, 30.4, 29.8, 27.14, 26.12, 26.09, 26.07, 24.72, 24.69, 24.66, 24.59, 24.4, 24.3, 23.3, 18.43, 18.41, 18.39, 18.37, 16.9, 16.24, 16.16, 16.13, 16.09, 16.08, 16.06, 15.99, 15.92, 15.6, 15.5, 14.2, 14.14, 14.11, 14.10, 14.0, 13.9, 13.8, 13.6, 13.5, 13.4, 13.3, 13.18,

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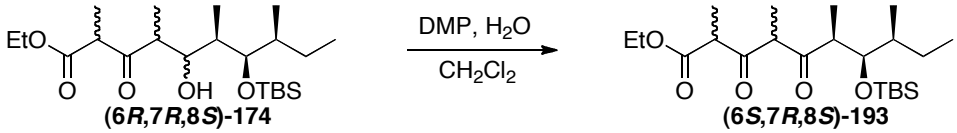
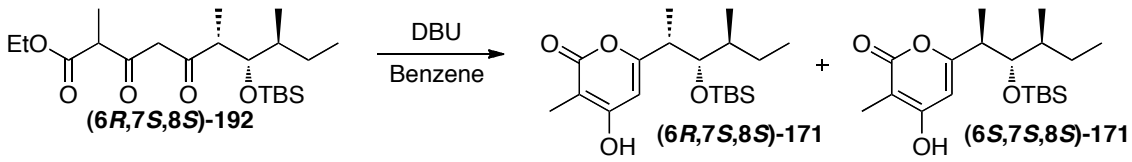


(6*S*,7*R*,8*S*)-174 **(6*S*,7*R*,8*S*)-193**

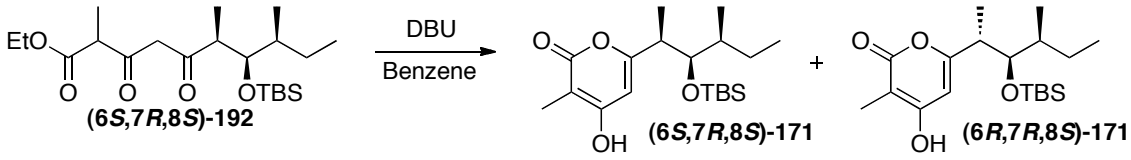
(6*S*,7*R*,8*S*)-ethyl-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyl-3,5-dioxo-decanoate [(6*S*,7*R*,8*S*)-193]. The previous procedure for the preparation of tricarbonyl **(6*R*,7*S*,8*S*)-192** was used with alcohol **(6*R*,7*R*,8*S*)-174** (762 mg; 1.83 mmol), DMP (1.16 g; 2.74 mmol), CH_2Cl_2 (18 mL) and CH_2Cl_2 (sat., 12 x 1.72 mL). The crude residue was filtered through buffered silica (100% CH_2Cl_2) to afford tricarbonyl **(6*S*,7*R*,8*S*)-193** (758 mg; 100%) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.20-4.10 (2.25H, m, CH_3CH_2O and C(=O)C*H*(CH_3)C(=O)CH(CH_3)CHOTBS), 4.09, 4.04, 4.03 (3 x 0.25H, q, J = 7.2 Hz, C(=O)C*H*(CH_3)C(=O)CH(CH_3)CHOTBS), 3.93 (0.25 H, dd, J = 6.0, 2.4 Hz, C*H*OTBS), 3.92 (0.25 H, dd, J = 6.6, 2.4 Hz, C*H*OTBS), 3.86 (0.25 H, dd, J = 7.2, 2.4 Hz, C*H*OTBS), 3.83 (0.25 H, dd, J = 7.2 2.4 Hz, C*H*OTBS), 3.27 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 3.72 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 3.64 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 3.62 (0.25H, q, J = 7.2 Hz, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$), 2.91 (0.5H, dq, J = 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CHOTBS), 2.86 (0.25H, dq, J = 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CHOTBS), 2.82 (0.25H, dq, J = 7.2, 7.2 Hz, C(=O)C*H*(CH_3)CHOTBS), 1.55-1.36 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.34-1.27 (4.5H, $CH_3CH_2OC(=O)CH(CH_3)C(=O)$ and C(=O)CH(*C*H_3)C(=O)CH(CH_3)CHOTBS), 1.26-1.16 (5.5H, C(=O)CH(*C*H_3)C(=O)CH(CH_3)CHOTBS, CH_3CH_2O and CH(CH_3)C$H_AH_BCH_3$), 1.13 (0.75H, d, J = 6.6Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 1.12-1.00 (1H, m, CH(CH_3)$CH_AH_BCH_3$), 1.06 (0.75H, d, J = 6.6Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 1.05 (0.75H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CH_2CH_3) 1.04 (0.75H, d, J = 7.2Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 0.89-0.80 (12.75H, m, CH(CH_3)CH_2CH_3, OSiC(CH_3)$_3$ and C(=O)CH(CH_3)CHOTBS), 0.79 (0.75H, d, J = 7.2 Hz, C(=O)CH(CH_3)CHOTBS), 0.78 (0.75H, d, J = 6.6 Hz, C(=O)CH(CH_3)CHOTBS), 0.75 (0.75H, d, J = 6.6 Hz, C(=O)CH(CH_3)CHOTBS), 0.06- -0.01 (6H, m, OSi(CH_3)$_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ

210.9, 210.6, 209.32, 209.26, 203.40, 203.36, 202.3, 202.2, 194.7, 194.5, 193.3, 192.6, 171.0, 170.7, 170.08, 170.05, 76.6, 76.50, 76.47, 75.8, 75.5, 74.9, 61.68, 61.64, 61.58, 61.33, 61.31, 61.28, 59.8, 59.33, 59.27, 57.9, 52.7, 52.4, 51.6, 51.2, 50.9, 50.4, 49.9, 49.8, 49.5, 49.1, 46.3, 46.1, 44.1, 43.6, 42.1, 41.9, 40.9, 40.4, 40.22, 40.19, 40.11, 40.06, 40.00, 37.9, 37.5, 37.2, 35.9, 34.7, 34.5, 33.8, 32.0, 29.79, 29.75, 29.5, 27.22, 27.19, 27.11, 27.03, 27.01, 26.24, 26.22, 26.19, 26.17, 25.52, 25.46, 25.35, 23.3, 22.8, 22.3, 19.4, 18.59, 18.54, 18.53, 18.51, 18.50, 17.8, 16.0, 16.0, 14.92, 14.88, 14.84, 14.6, 14.21, 14.17, 14.15, 14.12, 14.11, 13.98, 13.95, 13.86, 13.83, 13.80, 13.7, 13.62, 13.57, 13.37, 13.31, 13.13, 13.11, 13.05, 12.9, 12.8, 12.6, 12.34, 12.31, 12.29, 12.28, 7.77, 7.72, 7.5, -3.66, -3.68, -3.70, -3.73, -3.87 -3.89, -3.91.



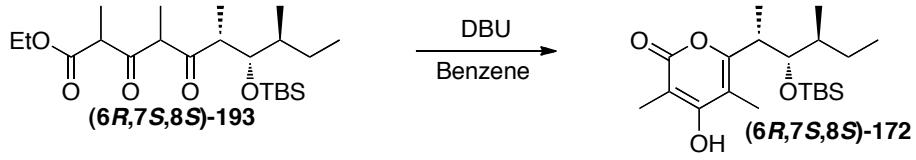
6-[(1*R*,2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*R*,7*S*,8*S*)-171] and **6-[(S*R*,2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*S*,7*S*,8*S*)-171],** synthesised according to the procedure of Hagiwara *et al*.[49] To a stirred solution of tricarbonyl **(6*R*,7*S*,8*S*)-192** (337 mg; 842 μmol) in benzene (8.4 mL) was added DBU (63 μL) dropwise, and the resulting solution heated to 60 ^{o}C for 3 h. The reaction mixture was then cooled to 0 ^{o}C and quenched by addition of 1 M HCl (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was triturated with hexanes to removed any impurities, resulting in a 3:1 mixture of α-pyrones **(6*R*,7*S*,8*S*)-171/(6*S*,7*S*,8*S*)-171** (75.1 mg; 25%) as white needles. **R*f*** = 0.31 (10% Et_2O/CH_2Cl_2); **mp.** 153-155 ^{o}C; **$[\alpha]^{20}_{D}$** = +93.2 (c 0.81, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer (6*R*,7*S*,8*S*)-171:** δ 10.41 (1H, br s, O*H*), 6.22 (1H, s, CH(OH)C*H*=C(-O-)), 3.82 (1H, dd, J = 4.8, 4.2 Hz, C*H*OTBS), 2.72 (1H, dq, J = 6.6, 5.4 Hz, C(-O-

)C*H*(CH_3)CHOTBS), 1.96 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.50-1.42 (1H, m, CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.47-1.39 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.18 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3),1.01-0.94 (1H, m, CH(CH_3)CH_A*H*$_B$$CH_3$), 0.89 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)CHOTBS), 0.86 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$) 0.85 (9H, s, OSiC(C*H*$_3$)$_3$), 0.00 (3H, s, OSi(C*H*$_3$)CH_3), -0.15 (3H, s, OSi(CH_3)C*H*$_3$); **minor isomer (6*S*,7*S*,8*S*)-171:** δ 10.41 (1H, br s, O*H*), 6.24 (1H, s, CH(OH)C*H*=C(-O-), 3.80 (1H, dd, J = 7.2, 3.6 Hz, C*H*OTBS), 2.76-2.71 (1H, m, C(-O-)C*H*(CH_3)CHOTBS), 1.96 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.57-1.51 (1H, m, CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.47-1.39 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.16 (3H, d, J = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 1.00-0.94 (1H, m, CH(CH_3)CH_A*H*$_B$$CH_3$), 0.88 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)CHOTBS), 0.86 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$) 0.81 (9H, s, OSiC(C*H*$_3$)$_3$), 0.01 (3H, s, OSi(C*H*$_3$)CH_3), -0.19 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*R*,7*S*,8*S*)-171:** δ 168.6, 167.4, 166.1, 101.4, 98.8, 77.0, 41.2, 40.5, 26.2, 25.2, 18.3, 15.5, 13.6, 12.4, 8.3, -3.9, -4.4; **minor isomer (6*S*,7*S*,8*S*)-171:** δ 168.7, 167.5, 165.8, 102.0, 98.9, 77.8, 43.1, 38.9, 26.1, 24.0, 18.4, 16.0, 15.6, 12.4, 8.3, -3.9, -4.7; **IR** (KBr, cm^{-1}) 3153, 2962, 2890, 2859, 2704, 1653, 1590, 1456, 1410, 1372, 1293, 1252, 1173, 1150, 1120, 1084, 1054, 966, 937, 864, 835, 774, 754, 675, 645, 534, 483.



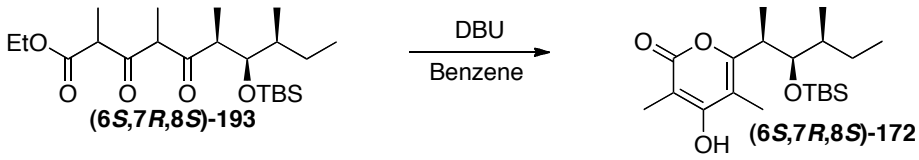
6-[(1*S*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*S*,7*R*,8*S*)-171] and **6-[(S*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*R*,7*R*,8*S*)-171].** The previous procedure for the preparation of α-pyrones **(6*R*,7*S*,8*S*)-171**/**(6*S*,7*S*,8*S*)-171** was used with tricarbonyl **(6*S*,7*R*,8*S*)-192** (381 mg; 952 μmol), DBU (71 μL; 476 μmol) and benzene (9.5 mL). The residue was triturated with hexanes to give a 3:1 mixture of α-pyrones **(6*S*,7*R*,8*S*)-171**/**(6*R*,7*R*,8*S*)-171** (93.1 mg; 28%) as yellow needles. **R*f*** = 0.29 (10% Et_2O/CH_2Cl_2); **mp.** 166-168 ^oC; **[α]$^{20}_D$** = -47.1 (c 0.79, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer (6*S*,7*R*,8*S*)-171:** δ 7.93 (1H, br s, O*H*), 5.99 (1H, s, CH(OH)C*H*=C(-O-)), 3.84 (1H, dd, J = 6.0, 3.6

Hz, C*H*OTBS), 2.68 (1H, dq, J = 7.2, 6.6 Hz, C(-O-)C*H*(CH_3)CHOTBS), 1.96 (3H, s, C(=O)C(CH_3)=COH), 1.50-1.42 (1H, m, CH(CH_3)C$H_A$$H_B$$CH_3$), 1.40-1.34 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.20 (3H, d, J = 6.6 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 1.19-1.10 (1H, m, CH(CH_3)$CH_A$$H_B$$CH_3$), 0.87 (9H, s, OSiC(C$H_3$)$_3$), 0.85 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.81 (3H, d, J = 6.6 Hz, C(-O-)CH(CH_3)CHOTBS), 0.02 (3H, s, OSi(CH_3)CH_3), -0.08 (3H, s, OSi(CH_3)CH_3); **minor isomer (6*R*,7*R*,8*S*)-171:** δ 7.93 (1H, br s, OH), 6.01 (1H, s, CH(OH)CH=C(-O-), 3.87 (1H, dd, J = 7.8, 2.4 Hz, CHOTBS), 2.71-2.66 (1H, m, C(-O-)CH(CH_3)CHOTBS), 1.96 (3H, s, C(=O)C(CH_3)=COH), 1.50-1.42 (1H, m, CH(CH_3)$CH_A$$H_B$$CH_3$), 1.40-1.34 (1H, m, CH(OTBS)CH(CH_3)CH_2CH_3), 1.25 (3H, d, J = 7.2 Hz, CH(OTBS)CH(CH_3)CH_2CH_3), 1.19-1.10 (1H, m, CH(CH_3)$CH_A$$H_B$$CH_3$), 1.14 (3H, d, J = 7.2 Hz, C(-O-)CH(CH_3)CHOTBS), 0.86 (3H, t, J = 7.2 Hz, CH_2CH_3) 0.82 (9H, s, OSiC(CH_3)$_3$), 0.01 (3H, s, OSi(CH_3)CH_3), -0.25 (3H, s, OSi(CH_3)CH_3); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*S*,7*R*,8*S*)-171:** δ 166.1, 165.1, 100.1, 98.8, 76.8, 42.3, 39.7, 31.1, 26.5, 26.2, 18.5, 14.7, 14.3, 12.3, 8.3, -3.6, -4.1; **minor isomer (6*R*,7*R*,8*S*)-171:** δ 167.1, 166.0, 101.8, 99.0, 76.4, 43.9, 38.0, 29.9, 27.2, 26.2, 18.4, 15.6, 13.0, 12.5, 8.3, -3.8, -4.7; **IR** (KBr, cm^{-1}) 3155, 2963, 2931, 2889, 2858, 2702, 1655, 1590, 1457, 1408, 1369, 1294, 1255, 1155, 1124, 1065, 1043, 1021, 969, 937, 884, 861, 835, 774, 753, 675, 642, 536.



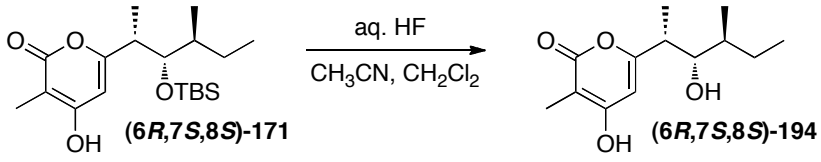
6-[(1*R*,2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*R*,7*S*,8*S*)-172]. The previous procedure for the preparation of α-pyrones **(6*R*,7*S*,8*S*)-171**/**(6*S*,7*S*,8*S*)-171** was used with tricarbonyl **(6*R*,7*S*,8*S*)-193** (486 mg; 1.17 mmol), DBU (88 μL; 586 μmol) and benzene (12 mL). The residue was triturated with hexanes to give α-pyrone **(6*R*,7*S*,8*S*)-172** as a single isomer (193 mg; 45%) as colourless needles. **R*f*** = 0.27 (10% Et_2O/CH_2Cl_2); **mp.** 179-181 °C; **[α]$^{20}_D$** = -50.0° (c 0.80, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.39 (1H, br s, O*H*), 3.84 (1H, dd, J = 9.0, 2.4 Hz, C*H*OTBS), 2.98 (1H, dq, J = 9.0, 6.6Hz, C(-O-

)C*H*(CH_3)CHOTBS), 2.03 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.99 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.36-1.30 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.28-1.21 (1H, m, CH(OTBS)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.18 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 0.91-0.88 (1H, m, CH(OTBS)CH(CH_3)CH_A*H*$_B$$CH_3$), 0.88 (9H, s, OSiC(C*H*$_3$)$_3$), 0.86 (3H, d, J = 7.2 Hz, C(-O-)C*H*(CH_3)CHOTBS), 0.79 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$), 0.02 (3H, s, OSi(C*H*$_3$)CH_3), 0.01 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) δ 167.1, 166.5, 161.1, 107.5, 98.5, 78.2, 40.8, 38.2, 26.2, 24.3, 18.4, 17.1, 16.0, 12.8, 10.0, 9.0, -3.8, -3.9; **IR** (KBr, cm^{-1}) 2961, 2933, 2874, 2859, 1680, 1659, 1573, 1543, 1462, 1379, 1343, 1256, 1177, 1153, 1124, 1080, 1061, 1032, 1006, 936, 854, 836, 777, 758, 695, 670, 619, 514, 472.



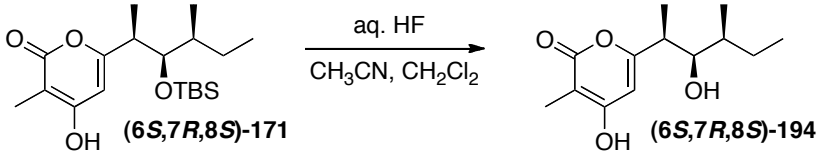
6-[(1*S*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*S*,7*R*,8*S*)-172]. The previous procedure for the preparation of α-pyrones **(6*R*,7*S*,8*S*)-171**/**(6*S*,7*S*,8*S*)-171** was used with tricarbonyl **(6*S*,7*R*,8*S*)-193** (361 mg; 872 μmol), DBU (65 μL; 436 μmol) and benzene (9 mL). The residue was triturated with hexanes to give α-pyrone **(6*S*,7*R*,8*S*)-172** (173 mg; 54%) as white needles. **R*f*** = 0.29 (10% Et_2O/CH_2Cl_2); **mp.** 196-198 °C; **[α]$^{20}_D$** = +140.9 (c 0.66, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65 (1H, br s, O*H*), 3.91 (1H, dd, J = 9.0, 1.2 Hz, C*H*OTBS), 2.96 (1H, dq, J = 9.0, 6.6Hz, C(-O-)C*H*(CH_3)CHOTBS), 1.99 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.99 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.44-1.37 (1H, m, CH(OTBS)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.23-1.17 (1H, m, CH(OTBS)C*H*(CH_3)CH_2CH_3), 1.21 (3H, d, J = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH_2CH_3), 1.13-1.05 (1H, m, CH(OTBS)CH(CH_3)CH_A*H*$_B$$CH_3$), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.81 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$), 0.73 (3H, d, J = 6.6 Hz, CH(OTBS)C*H*(CH_3)CH_2CH_3), 0.07 (3H, s, OSi(C*H*$_3$)CH_3), 0.05 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) δ 166.1, 165.0, 161.3, 106.6, 98.2, 77.3, 39.8, 39.1, 26.9, 26.3, 18.6, 17.2, 13.5, 12.6, 10.0, 8.8, -3.5, -3.5; **IR** (KBr, cm^{-1}) 2960, 2933, 2883, 2859, 1680, 1657, 1574, 1537, 1462, 1405,

1381, 1360, 1344, 1256, 1215, 1177, 1153, 1125, 1064, 1082, 1039, 959, 936, 853, 837, 807, 777, 758, 695, 671, 621, 515, 473.



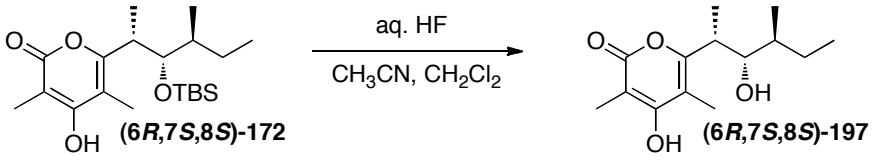
6-[(1*R*,2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*R*,7*S*,8*S*)-194]. To a stirred solution of TBS-ether **(6*R*,7*S*,8*S*)-171** (as a 3:1 mixture with **(6*S*,7*S*,8*S*)-171**) (98.7 mg; 297 μmol) in a 1:1 mixture of CH_3CN/CH_2Cl_2 (15 mL) at rt was added 40% aq. HF (1.30 mL) and the resulting mixture stirred at rt for 3.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (15 mL) and the mixture was extracted with EtOAc (3x30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a white slurry, which was triturated with acetone to afford alcohol **(6*R*,7*S*,8*S*)-194** (as a 3:1 mixture with **(6*S*,7*S*,8*S*)-194**) (66.9 mg; 96%) as a white powder. **R*f*** = 0.46 (100%, EtOAc); **mp.** 212-214 ^oC; **$[\alpha]^{20}_D$** = +51.4 (c 0.92, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) **major isomer (6*R*,7*S*,8*S*)-194:** δ 6.06 (1H, s, C(OH)C*H*=C(-O-)), 3.57 (1H, dd, J = 6.6, 5.4 Hz, C*H*OH), 3.45 (1H, s, CHO*H*), 2.71 (1H, dq, J = 7.2, 6.6 Hz, C(-O-)C*H*(CH_3)CHOH), 1.85 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.68 (1H, ddq, J = 13.2, 7.8, 3.0 Hz, CH(OH)CH(CH_3)C*H*$_A$H$_B$CH$_3$), 1.40-1.35 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.27 (3H, d, J = 6.6 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.17-1.10 (1H, m, CH(OH)CH(CH_3)CH$_A$*H*$_B$CH$_3$), 0.92 (3H, d, J = 6.6 Hz, C(-O-)CH(C*H*$_3$)CHOH), 0.89 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **minor isomer (6*S*,7*S*,8*S*)-194:** δ 6.11 (1H, s, C(OH)C*H*=C(-O-)), 3.51 (1H, dd, J = 7,2, 4.8 Hz, C*H*OH), 3.35 (1H, s, CHO*H*), 2.80-2.75 (1H, m, C(-O-)C*H*(CH_3)CHOH), 1.85 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.57 (1H, ddq, J = 13.2, 7.8, 3.0 Hz, CH(OH)CH(CH_3)C*H*$_A$H$_B$CH$_3$), 1.55-1.49 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.20 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.17-1.10 (1H, m, CH(OH)CH(CH_3)CH$_A$*H*$_B$CH$_3$), 0.98 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)CHOH), 0.92 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*R*,7*S*,8*S*)-194:** δ 169.1, 168.1, 167.0, 101.4, 99.1, 77.4, 42.0, 39.1, 25.1, 16.0, 12.1, 11.7, 8.2; **minor isomer (6*S*,7*S*,8*S*)-194:** δ 169.3, 168.2,

167.4, 102.2, 99.1, 78.4, 43.0, 38.2, 23.5, 16.6, 16.3, 11.9, 8.2; **IR** (KBr, cm^{-1}) 3149, 1973, 2924, 2882, 2729, 1682, 1660, 1593, 1462, 1414, 1391, 1299, 1270, 1233, 1178, 1114, 1076, 1045, 974, 957, 935, 826, 748, 680, 634, 535; **HRESIMS** calculated for $C_{13}H_{20}O_4Na^+$: 263.1259; found: 263.1263.

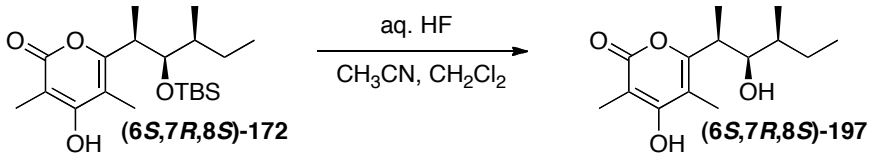


6-[(1*S*,2*R*,3*S*)-2-hydroxy-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*S*,7*R*,8*S*)-194]. The previous procedure for the preparation of **(6*R*,7*S*,8*S*)-194** was used with TBS-ether **(6*S*,7*R*,8*S*)-171** (as a 3:1 mixture with **(6*R*,7*R*,8*S*)-171**) (91.8 mg; 259 μmol), 40% aq. HF (1.10 mL) and 1:1 CH_3CN/CH_2Cl_2 (13 mL). The product was triturated with acetone to give alcohol **(6*S*,7*R*,8*S*)-194** (as a 3:1 mixture with **(6*R*,7*R*,8*S*)-194**) (54.8 mg; 88%) as a white powder. **R*f*** = 0.51 (100%, EtOAc); **mp.** 159-161 °C; **$[\alpha]^{20}_D$** = +7.41 (c 2.30, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) **major isomer (6*S*,7*R*,8*S*)-194:** δ 6.08 (1H, s, C(OH)C*H*=C(-O-)), 3.65 (1H, dd, J = 7.8, 3.6 Hz, C*H*OH), 2.71 (1H, dq, J = 7.8, 7.2 Hz, C(-O-)C*H*(CH_3)CHOH), 1.85 (3H, s, C(=O)C(CH_3)=COH), 1.50-1.40 (1H, m, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.34-1.28 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.28 (1H, s, CHO*H*), 1.27 (3H, d, J = 6.6 Hz, CH(OH)CH(CH_3)CH_2CH_3), 1.26-1.20 (1H, m, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 0.89 (3H, d, J = 6.6 Hz, C(-O-)CH(CH_3)CHOH), 0.88 (3H, dd, J = 7.8, 7.2 Hz, CH_2CH_3); **minor isomer (6*R*,7*R*,8*S*)-194:** δ 6.06 (1H, s, C(OH)C*H*=C(-O-)), 3.70 (1H, dd, J = 9.0, 5.4 Hz, C*H*OH), 2.68 (1H, dq, J = 9.6, 7.2 Hz, C(-O-)C*H*(CH_3)CHOH), 1.85 (3H, s, C(=O)C(CH_3)=COH), 1.55 (1H, ddq, J = 13.8, 6.6, 3.0 Hz, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.34-1.28 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.26-1.20 (1H, m, CH(OH)CH(CH_3)C$H_A$$H_B$$CH_3$), 1.15 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)CH_2CH_3), 0.94 (3H, dd, J = 7.8, 7.2 Hz, CH_2CH_3) 0.87 (3H, d, J = 6.6 Hz, C(-O-)CH(CH_3)CHOH); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*S*,7*R*,8*S*)-194:** δ 168.9, 167.8, 166.9, 101.3, 99.1, 76.2, 43.0, 38.9, 27.7, 14.9, 13.5, 11.9, 8.3; **minor isomer (6*R*,7*R*,8*S*)-194:** δ 169.3, 168.0, 167.1, 102.0, 99.1, 75.6, 43.8, 37.6, 28.0, 15.9, 12.3, 12.2, 8.3; **IR** (KBr, cm^{-1}) 3143, 2969, 2926, 2878, 2710, 1679, 1656,

1591, 1463, 1416, 1380, 1234, 1179, 1144, 1122, 1101, 1077, 1047, 980, 958, 935, 833, 818, 748, 717, 696, 636, 578, 534, 501.

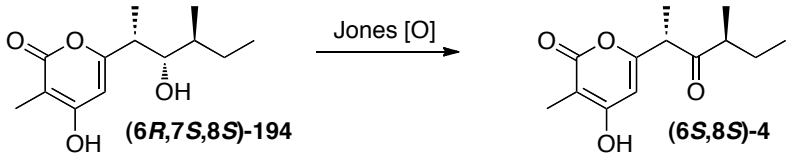


6-[(1*R*,2*S*,3*S*)-2-hydroxy-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*R*,7*S*,8*S*)-197]. The previous procedure for the preparation of **(6*R*,7*S*,8*S*)-194** was used with TBS-ether **(6*R*,7*S*,8*S*)-172** (193 mg; 523 μmol), 40% aq. HF (2.20 mL) and 1:1 CH_3CN/CH_2Cl_2 (26 mL). The product with triturated with acetone to give alcohol **(6*R*,7*S*,8*S*)-197** (126 mg; 95%) as clear needles. **R*f*** = 0.50 (100%, EtOAc); **mp.** 143-145 ^oC; **$[\alpha]^{20}_D$** = -108.6 (c 1.05, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) δ 3.63 (1H, dd, J = 9.0, 3.6 Hz, C*H*OH), 3.08 (1H, dq, J = 9.0, 6.6 Hz, C(-O-)C*H*(CH_3)CHOH), 1.99 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.92 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.46 (1H, ddq, J = 13.2, 7.8, 3.0 Hz, CH(OH)CH(CH_3)C*H*$_A$H$_B$CH$_3$), 1.29 (1H, s, CHO*H*), 1.27 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.20 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.09 (1H, ddq, J = 13.2, 9.6, 7.2 Hz, CH(OH)CH(CH_3)CH$_A$*H*$_B$CH$_3$), 0.94 (3H, d, J = 6.6 Hz, C(-O-)CH(C*H*$_3$)CHOH), 0.84 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, CD_3OD) δ 168.4, 168.1, 162.0, 109.2, 98.9, 78.9, 39.6, 39.3, 23.8, 17.0, 15.4, 12.4, 10.0, 8.8; **IR** (KBr, cm^{-1}) 3188, 2962, 2930, 2878, 1662, 1617, 1566, 1460, 1381, 1273, 1213, 1144, 1100, 1031, 996, 963, 944, 881, 765, 707, 672, 579, 520, 473; **HRESIMS** calculated for $C_{14}H_{22}O_4Na^+$: 277.1416; found 277.1417.



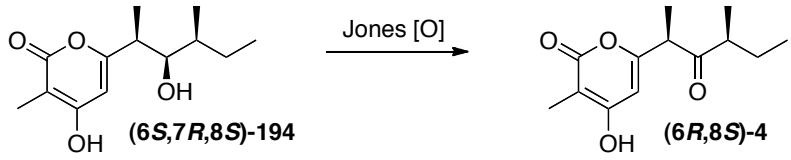
6-[(1*S*,2*R*,3*S*)-2-hydroxy-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*S*,7*R*,8*S*)-197]. The previous procedure for the preparation of **(6*R*,7*S*,8*S*)-194** was used with TBS-ether **(6*S*,7*R*,8*S*)-172** (255 mg; 692 μmol), 40% aq. HF (1.10 mL)

and 1:1 CH_3CN/CH_2Cl_2 (36 mL). The product with triturated with acetone to give alcohol **(6*S*,7*R*,8*S*)-197** (175 mg; 99%) as a white foam. **R*f*** = 0.43 (100%, EtOAc); **$[\alpha]^{20}_D$** = +98.0 (c 1.25, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) δ 3.78 (1H, dd, J = 9.6, 2.4 Hz, C*H*OH), 3.02 (1H, dq, J = 9.6, 7.2 Hz, C(-O-)C*H*(CH_3)CHOH), 2.00 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.91 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.41 (1H, ddq, J = 13.8, 7.2, 6.0 Hz, CH(OH)CH(CH_3)C*H*$_A$H$_B$CH$_3$), 1.29 (3H, d, J = 7.2 Hz, CH(OH)CH(C*H*$_3$)CH_2CH_3), 1.29-1.20 (1H, m, CH(OH)C*H*(CH_3)CH_2CH_3), 1.11 (1H, ddq, J = 13.8, 7.2, 1.8 Hz, CH(OH)CH(CH_3)CH$_A$*H*$_B$CH$_3$), 0.85 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$), 0.80 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)CHOH), **^{13}C NMR** (151 Mz, CD_3OD) δ 168.3, 168.0, 161.7, 109.3, 98.8, 76.1, 39.7, 39.0, 28.3, 16.4, 13.1, 12.3, 10.1, 8.8; **IR** (KBr, cm^{-1}) 3333, 2966, 2932, 2878, 1671, 1568, 1458, 1410, 1380, 1230, 1145, 1086, 1032, 994, 956, 872, 760, 737, 704.



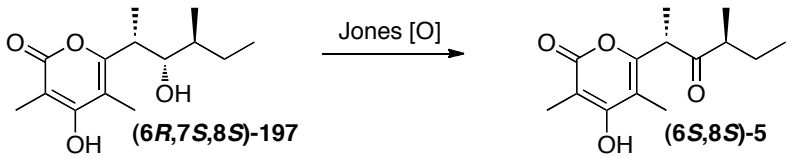
6-[(1*S*,3*S*)-1,3-dimethyl-2-oxo-pentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*S*,8*S*)-4], synthesised according to the procedure of Shone *et al.*[44] To a stirred solution of alcohol **(6*R*,7*S*,8*S*)-194** (as a 3:1 mixture with **(6*S*,7*S*,8*S*)-194**) (56.8 mg; 236 μmol) in acetone (6 mL) at 0 °C was added Jones reagent (410 μL from a stock solution containing CrO_3 (534 mg), H_2SO_4 (460 μL and H_2O (2 mL)) dropwise. The reaction mixture was warmed to rt for 10 min and quenched by addition of isopropanol (300 μL), followed by addition of $NaHCO_3$ (300 mg). The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in Et_2O (10 mL), washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was triturated with hexanes to remove impurities, giving ascosalipyrone **(6*S*,8*S*)-4** (as a 3:1 mixture with **(6*R*,8*S*)-4**) (31.3 mg; 56%) as a yellow powder. **R*f*** = 0.54 (100% EtOAc); **mp.** 115-117 °C; **$[\alpha]^{20}_D$** = +60.7 (c 1.57, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer (6*S*,8*S*)-4:** δ 9.91 (1H, br s, C(=O)C(CH_3)=CO*H*), 6.25 (1H, s, C(OH)C*H*=C(-O-)), 3.80 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.70 (1H,

ddq, J = 13.8, 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CH_2CH_3), 1.94 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.67 (1H, ddq, J = 13.8, 7.8, 6.6 Hz, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.38 (1H, m C(=O)CH($CH_3$)$CH_A$*H*$_B$$CH_3$), 1.36 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3)**,** 1.05 (3H, d, J = 6.6 Hz, C(-O-)CH(CH_3)C=O), 0.85 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **minor isomer (6*R*,8*S*)-4:** δ 9.91 (1H, br s, C(=O)C(CH_3)=CO*H*), 6.25 (1H, s, C(OH)C*H*=C(-O-)), 3.81 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.68 (1H, m, C(=O)C*H*(CH_3)CH_2CH_3), 1.94 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.68 (1H, m, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.35 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3)**,** 1.35 (1H, m, C(=O)CH(CH_3)CH_A*H*$_B$$CH_3$), 1.07 (3H, d, J = 7.2 Hz, C(-O-)CH(CH_3)C=O), 0.80 (3H, t, J = 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*S*,8*S*)-4:** δ 211.6, 167.8, 166.5, 160.8, 101.8, 99.9, 49.4, 47.1, 26.1, 16.0, 14.4, 11.7, 8.3; **minor isomer (6*R*,8*S*)-4:** δ 211.4, 167.8, 166.4, 160.7, 101.8, 99.9, 49.2, 47.0, 25.8, 16.5, 14.6, 11.7, 8.3; **IR** (KBr, cm^{-1}) 2970, 2933, 2879, 2668, 1718, 1665, 1632, 1569, 1459, 1271, 1242, 1181, 1141, 1099, 1028, 994, 949, 936, 859, 757, 617, 565, 531; **HRESIMS** calculated for $C_{13}H_{18}O_4Na^+$: 261.1103; found: 261.1109.



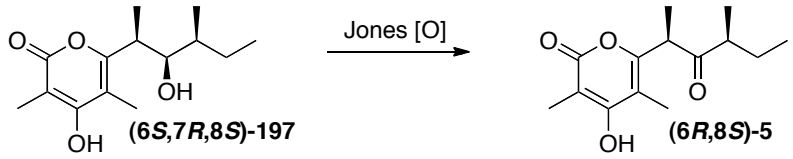
6-[(1*R*,3*S*)-1,3-dimethyl-2-oxo-pentyl]-4-hydroxy-3-methyl-2H-pyran-2-one [(6*R*,8*S*)-4]. The previous procedure for the preparation of **(6*S*,8*S*)-4** was used with alcohol **(6*S*,7R,8*S*)-194** (as a 3:1 mixture with **(6*R*,7*R*,8*S*)-194**) (45.9 mg; 191 μmol), Jones reagent (330 μL) and acetone (5 mL). The crude product was triturated with hexanes to remove impurities, giving ascosalipyrone **(6*R*,8*S*)-4** (as a 3:1 mixture with **(6*S*,8*S*)-4**) (23.3 mg; 51%) as a yellow powder. **R*f*** = 0.57 (100% EtOAc); **mp.** 113-115 ^{o}C; **[α]$^{20}_{D}$** = -48.9 (c 1.17, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) **major isomer (6*R*,8*S*)-4:** δ 9.70 (1H, br s, C(=O)C(CH_3)=CO*H*), 6.22 (1H, s, C(OH)C*H*=C(-O-)), 3.82 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.69 (1H, ddq, J = 13.8, 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CH_2CH_3), 1.95 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.68 (1H, ddq, J = 13.8, 7.2, 7.2 Hz, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.37 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3)**,** 1.35 (1H,

ddq, J = 13.8, 7.2, 6.6 Hz, C(=O)CH(CH_3)CH_A*H*$_B$$CH_3$), 1.08 (3H, d, J = 6.6 Hz, C(-O-)CH(C*H*$_3$)C=O), 0.81 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **minor isomer (6*S*,8*S*)-4:** δ 9.70 (1H, br s, C(=O)C(CH_3)=CO*H*), 6.20 (1H, s, C(OH)C*H*=C(-O-)), 3.78 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.73-2.67 (1H, m, C(=O)C*H*(CH_3)CH_2CH_3), 1.95 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.70-1.59 (1H, m, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.43-1.35 (1H, m, C(=O)CH(CH_3)CH_A*H*$_B$$CH_3$), 1.35 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3)*,* 1.06 (3H, d, J = 6.6 Hz, C(-O-)CH(CH_3)C=O), 0.86 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) **major isomer (6*R*,8*S*)-4:** δ 211.5, 167.8, 166.4, 160.6, 101.8, 99.9, 49.1, 47.0, 25.8, 16.5, 14.6, 11.7, 8.3; **minor isomer (6*S*,8*S*)-4:** δ 211.6, 167.8, 166.4, 160.8, 101.7, 99.9, 49.5, 47.1, 26.2, 16.0, 14.4, 11.7, 8.3; **IR** (KBr, cm^{-1}) 3410, 3106, 2971, 2934, 2879, 2664, 1713, 1665, 1634, 1578, 1561, 1457, 1272, 1242, 1179, 1141, 1097, 1056, 1035, 995, 950, 936, 869, 757, 616, 565, 531; **HRESIMS** calculated for $C_{13}H_{18}O_4Na^+$: 261.1103; found: 261.1114.



6-[(1*S*,3*S*)-1,3-dimethyl-2-oxo-pentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*S*,8*S*)-5]. The previous procedure for the preparation of **(6*S*,8*S*)-4** was used with alcohol **(6*R*,7*S*,8*S*)-197** (105 mg; 439 μmol), Jones reagent (760 μL) and acetone (11 mL). The crude product was triturated with hexanes to remove impurities, giving micropyrone **(6*S*,8*S*)-5** (57.5 mg; 55%) as colourless needles. **R*f*** = 0.46 (100% EtOAc); **mp.** 152-154 ^oC; **[α]$^{20}_D$** = +28.8 (c 1.36, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.84 (1H, br s, O*H*), 3.83 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.58 (1H, ddq, J = 13.2, 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CH_2CH_3), 2.02 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.99 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.59 (1H, ddq, J = 13.8, 7.2, 6.6 Hz, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.39 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3), 1.34 (1H, m, C(=O)CH(CH_3)CH_A*H*$_B$$CH_3$), 0.98 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)C=O), 0.81 (3H, t, J = 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) δ 210.9, 166.4, 165.7, 155.8, 109.6, 99.6, 48.4, 45.5, 27.1, 16.3, 13.5, 11.7, 10.1, 8.9; **IR** (KBr, cm^{-1}) 3209, 2934, 2967, 1722, 1662, 1635, 1576, 1455,

1380, 1212, 1176, 1124, 1079, 1041, 971, 871, 755, 478; **HRESIMS** calculated for $C_{14}H_{20}O_4Na^+$: 275.1259; found: 274.1265.



6-[(1*R*,3*S*)-1,3-dimethyl-2-oxo-pentyl]-4-hydroxy-3,5-dimethyl-2H-pyran-2-one [(6*R*,8*S*)-5]. The previous procedure for the preparation of **(6*S*,8*S*)-4** was used with alcohol **(6*S*,7*R*,8*S*)-197** (168 mg; 659 μmol), Jones reagent (1.15 mL) and acetone (17 mL). The crude product was triturated with hexanes to remove impurities, giving micropyrone **(6*R*,8*S*)-5** (104 mg; 63%) as colourless plates. **R*f*** = 0.52 (100% EtOAc); **mp.** 168-170 ^oC; **$[\alpha]^{20}_D$** = -4.67 (c 1.07, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.74 (1H, br s, O*H*), 3.90 (1H, q, J = 7.2 Hz, C(-O-)C*H*(CH_3)C=O), 2.54 (1H, ddq, J = 13.8, 7.2, 6.6 Hz, C(=O)C*H*(CH_3)CH_2CH_3), 2.02 (3H, s, C(=O)C(C*H*$_3$)=COH), 1.99 (3H, s, C(OH)C(C*H*$_3$)=C(-O-)), 1.65 (1H, ddq, J = 13.8, 7.8, 7.2 Hz, C(=O)CH(CH_3)C*H*$_A$H$_B$$CH_3$), 1.39 (3H, d, J = 7.2 Hz, C(=O)CH(C*H*$_3$)CH_2CH_3), 1.20 (1H, ddq, J = 13.8, 7.2, 6.0 Hz, C(=O)CH(CH_3)CH_A*H*$_B$$CH_3$), 1.02 (3H, d, J = 7.2 Hz, C(-O-)CH(C*H*$_3$)C=O), 0.76 (3H, dd, J = 7.8, 7.2 Hz, CH_2C*H*$_3$); **^{13}C NMR** (151 Mz, $CDCl_3$) δ 210.6, 166.0, 165.2, 155.7, 109.4, 99.4, 47.5, 45.6, 25.9, 17.6, 13.6, 11.9, 10.1, 8.8; **IR** (KBr, cm^{-1}) 3188, 2934, 2964, 2876, 1727, 1680, 1636, 1575, 1455, 1428, 1379, 1340, 1250, 1207, 1174, 1128, 1078, 1041, 1001, 969, 870, 850, 751, 713, 670, 642, 581, 479; **HRESIMS** calculated for $C_{14}H_{20}O_4Na^+$: 275.1259; found: 274.1266.

4.4 References

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Appendices

Appendix A: Additional Spectral Data for Chapter Two

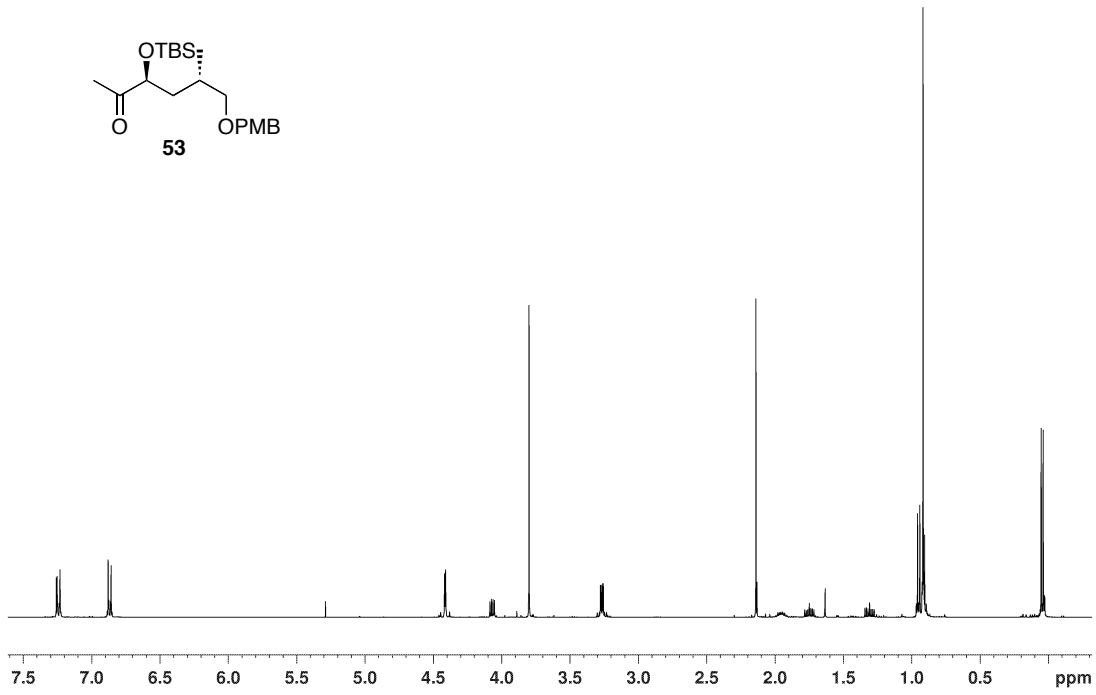

Figure A1: 400 MHz ^{1}H NMR spectrum of model ketone **53** in $CDCl_3$.

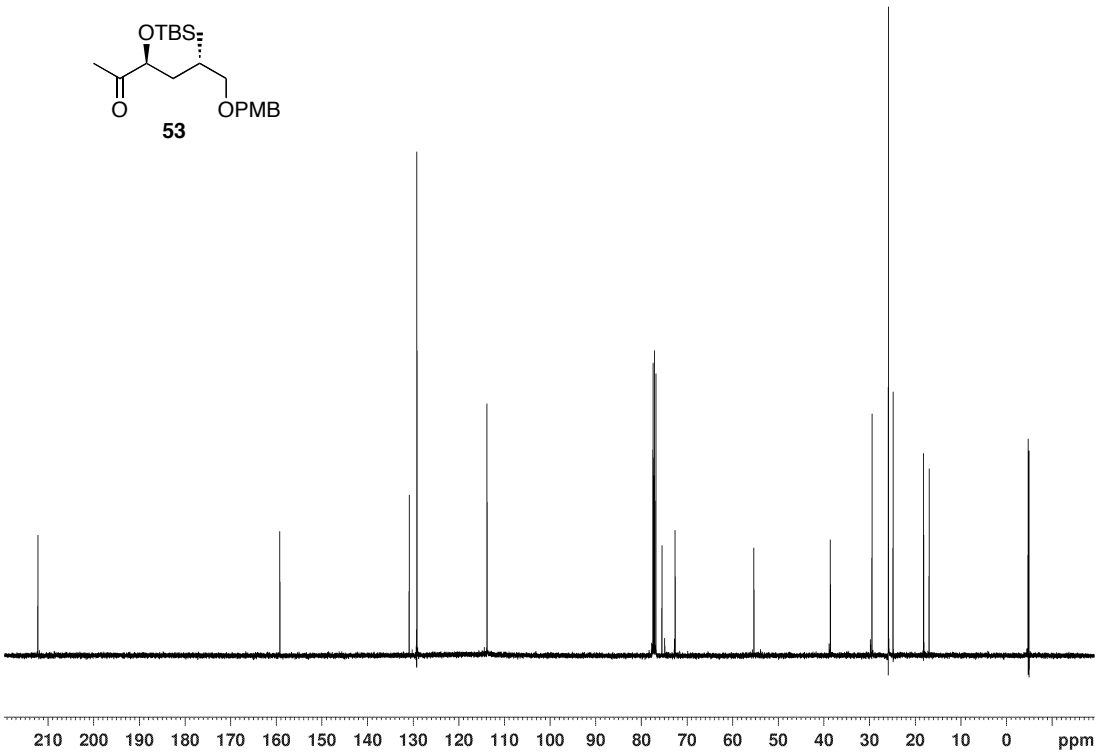

Figure A2: 100 MHz ^{13}C NMR spectrum of model ketone **53** in $CDCl_3$.

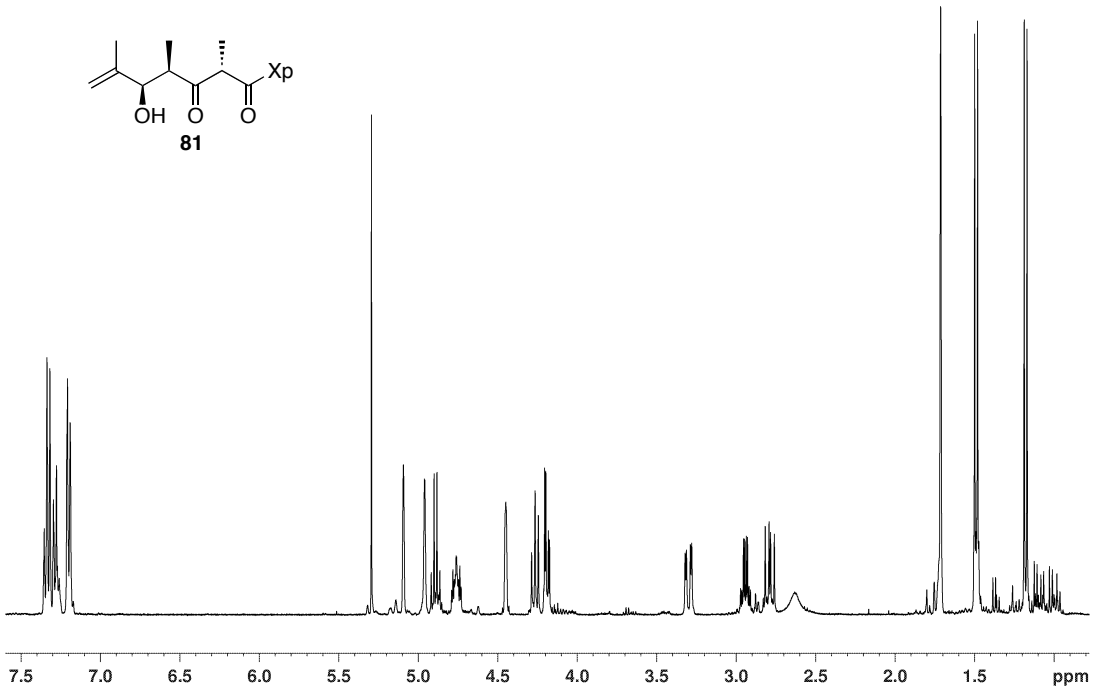

Figure A3: 400 MHz ^{1}H NMR spectrum of aldol adduct **81** in $CDCl_3$.

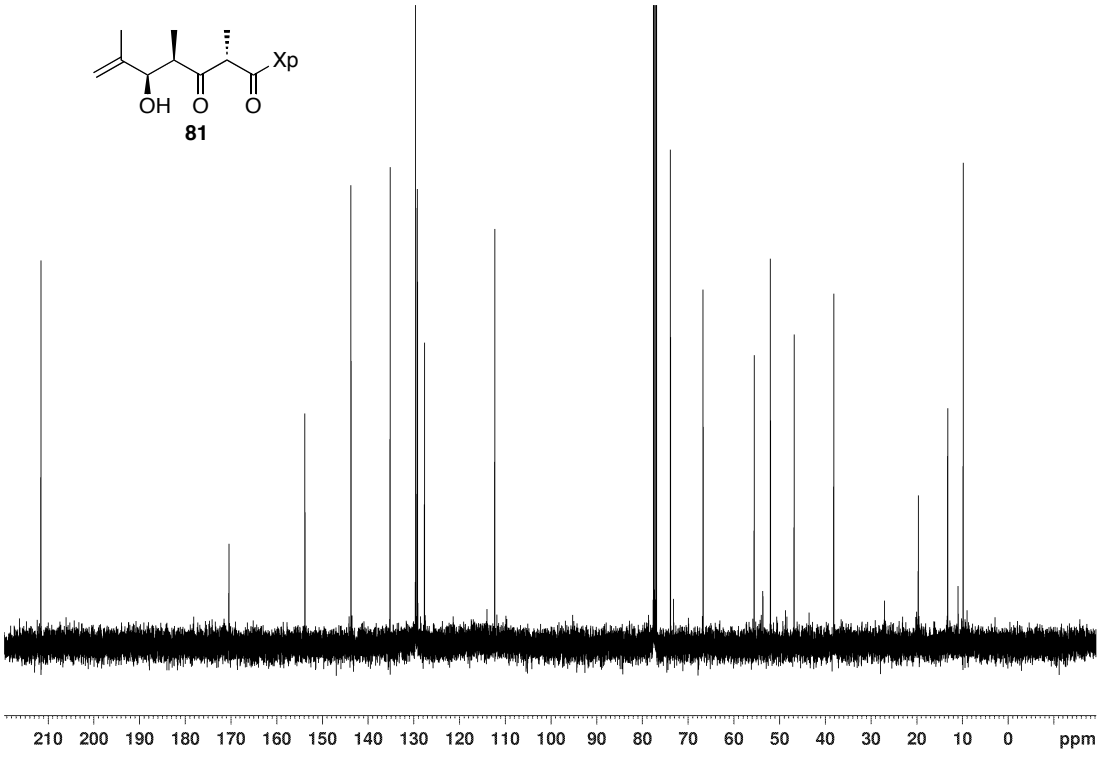

Figure A4: 100 MHz ^{1}H NMR spectrum of aldol adduct **81** in $CDCl_3$.

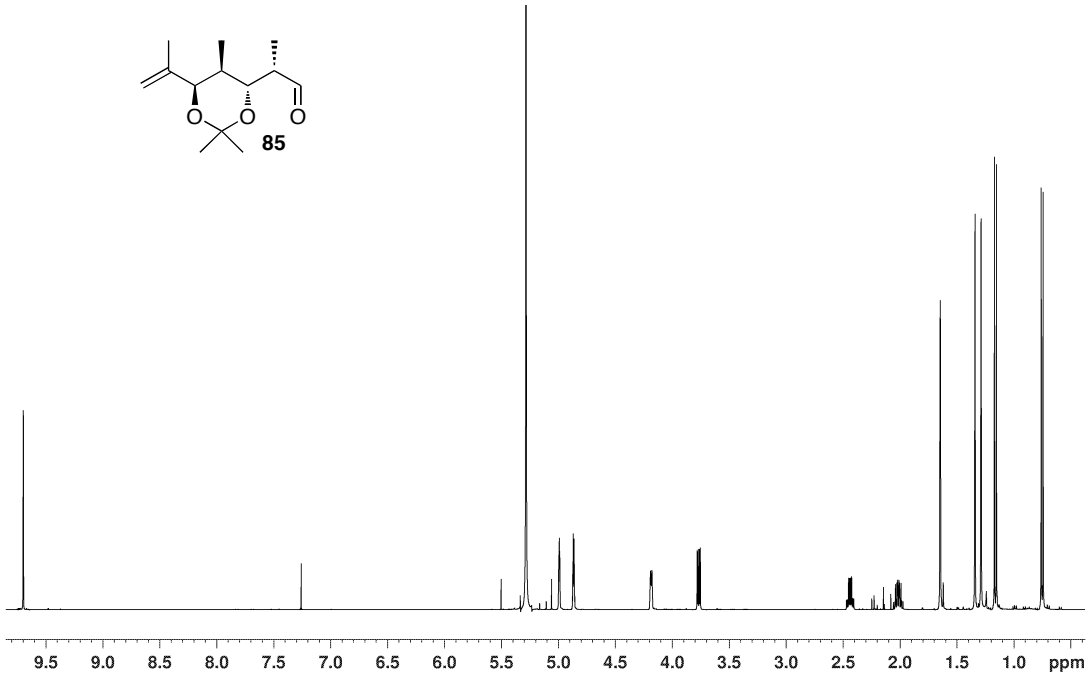

Figure A5: 400 MHz ^{1}H NMR spectrum of model aldehyde **85** in $CDCl_3$.

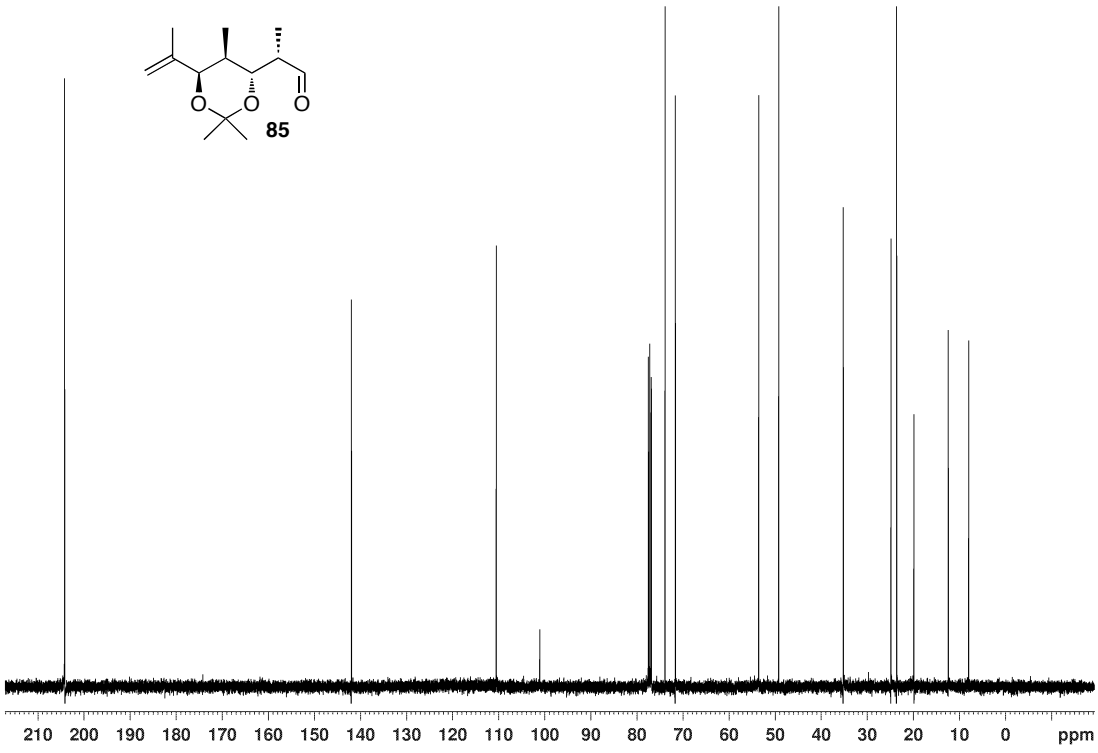

Figure A6: 100 MHz ^{13}C NMR spectrum of model aldehyde **85** in $CDCl_3$.

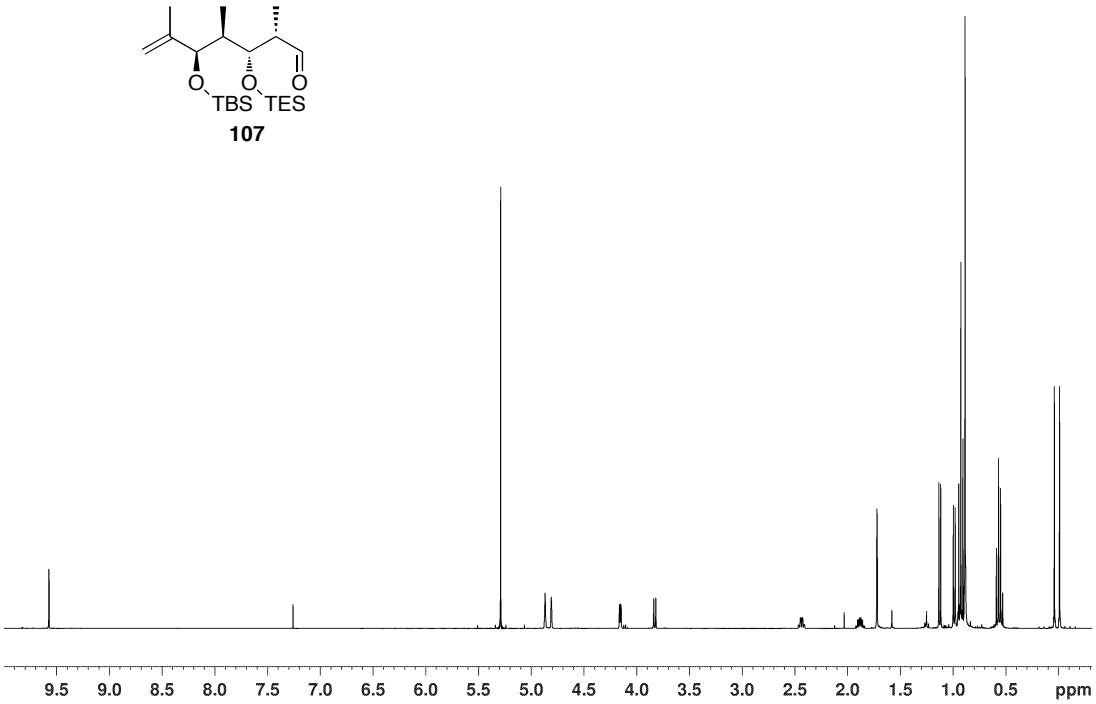

Figure A7: 400 MHz ^{1}H NMR spectrum of model aldehyde **107** in $CDCl_3$.

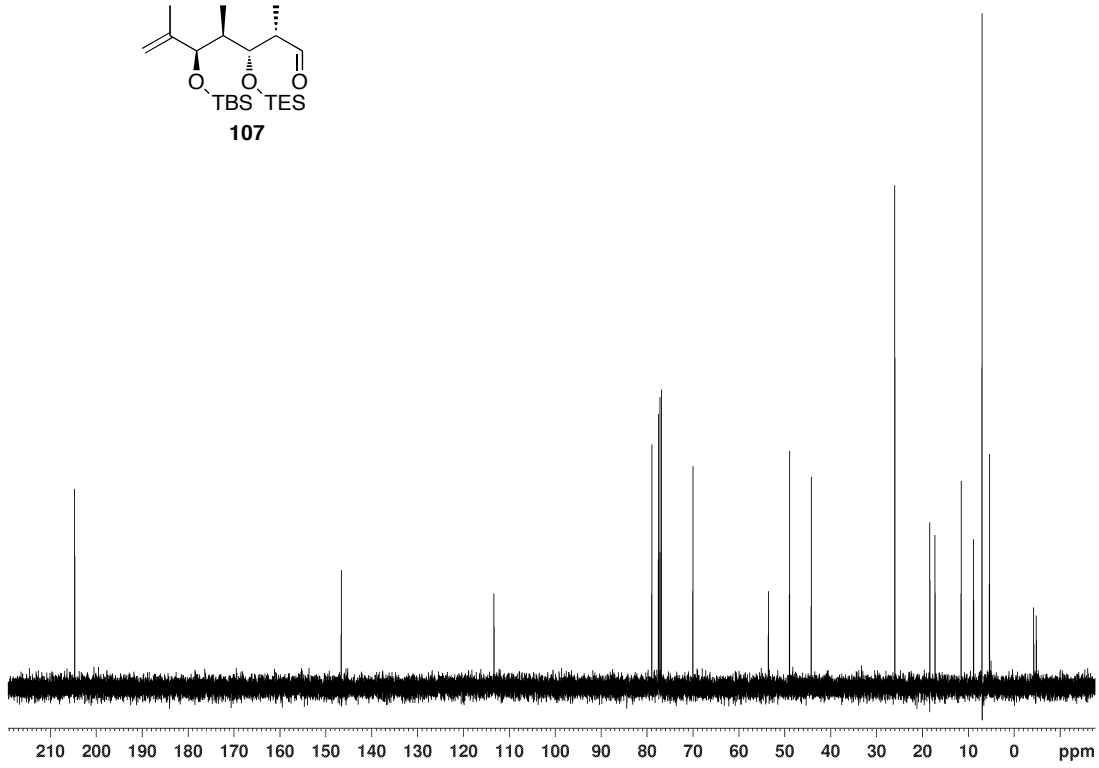

Figure A8: 100 MHz ^{13}C NMR spectrum of model aldehyde **107** in $CDCl_3$.

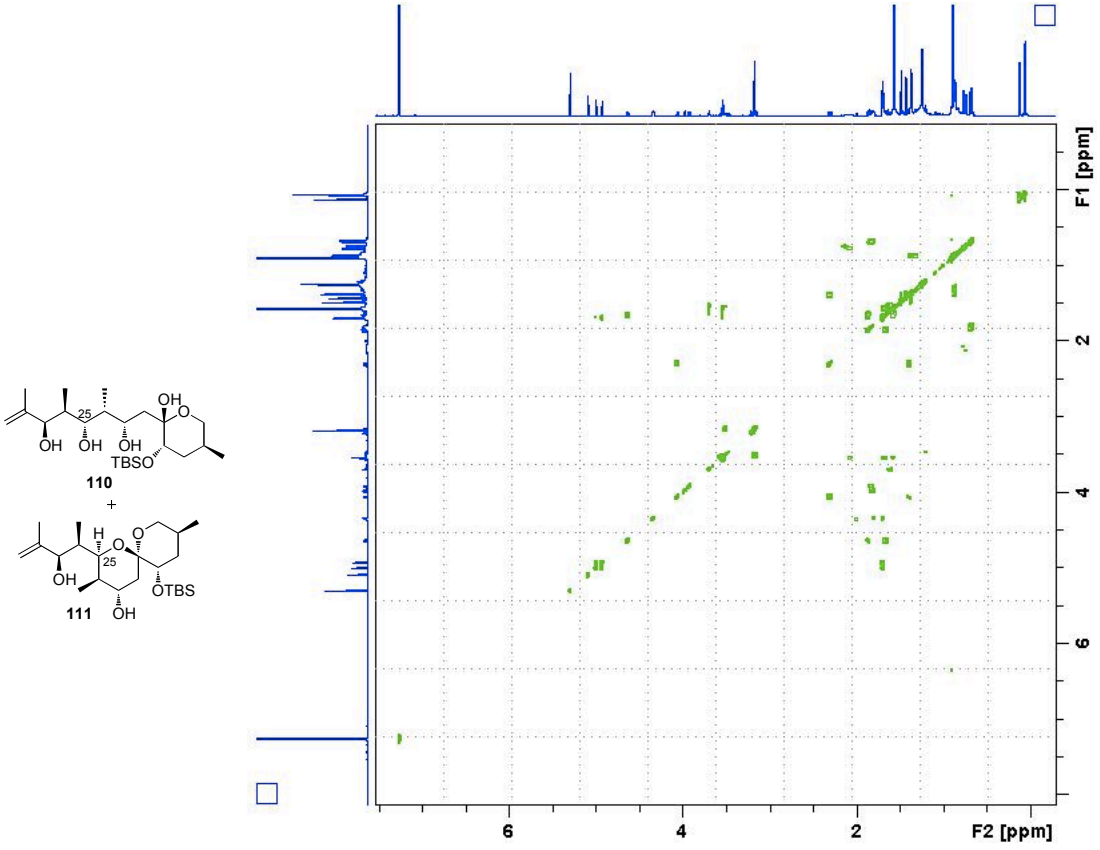

Figure A9: 600 MHz COSY spectrum of mixture of hemiacetal **110** and spiroacetal **111** in $CDCl_3$.

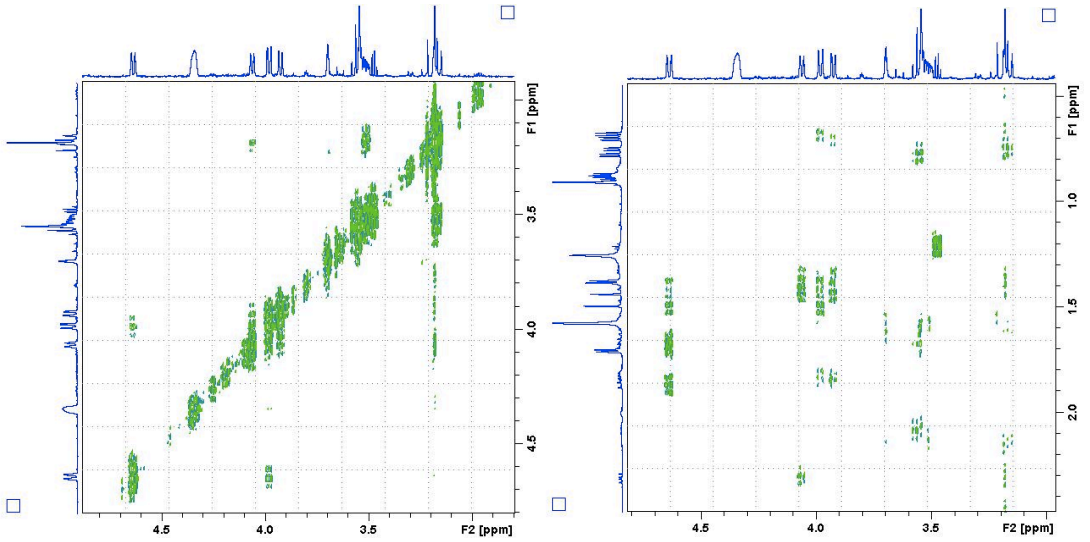

Figure A10: 600 MHz NOESY spectrum of mixture of hemiacetal **110** and spiroacetal **111** in $CDCl_3$.

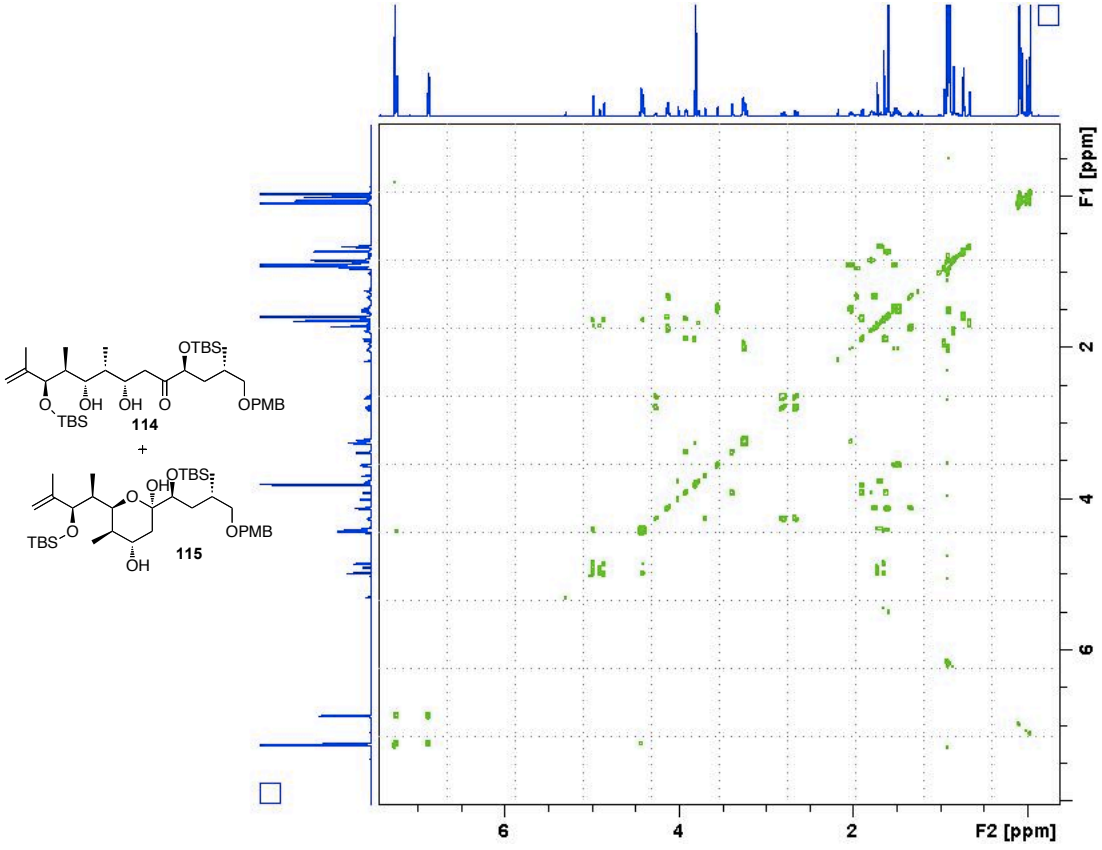

Figure A11: 600 MHz COSY spectrum of mixture of diol **114** and hemiacetal **115** in $CDCl_3$.

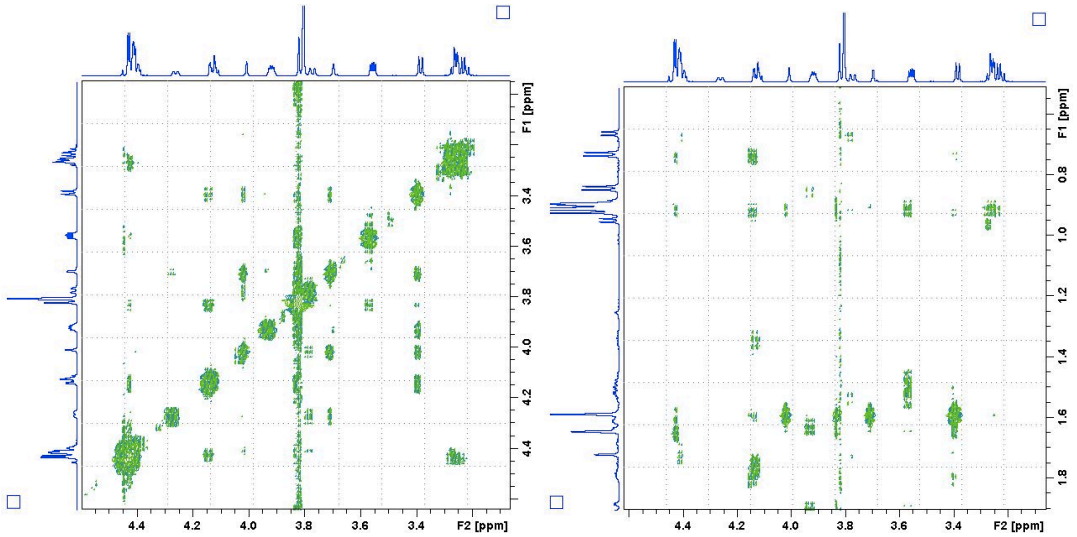

Figure A12: 600 MHz NOESY spectrum of mixture of diol **114** and hemiacetal **115** in $CDCl_3$.

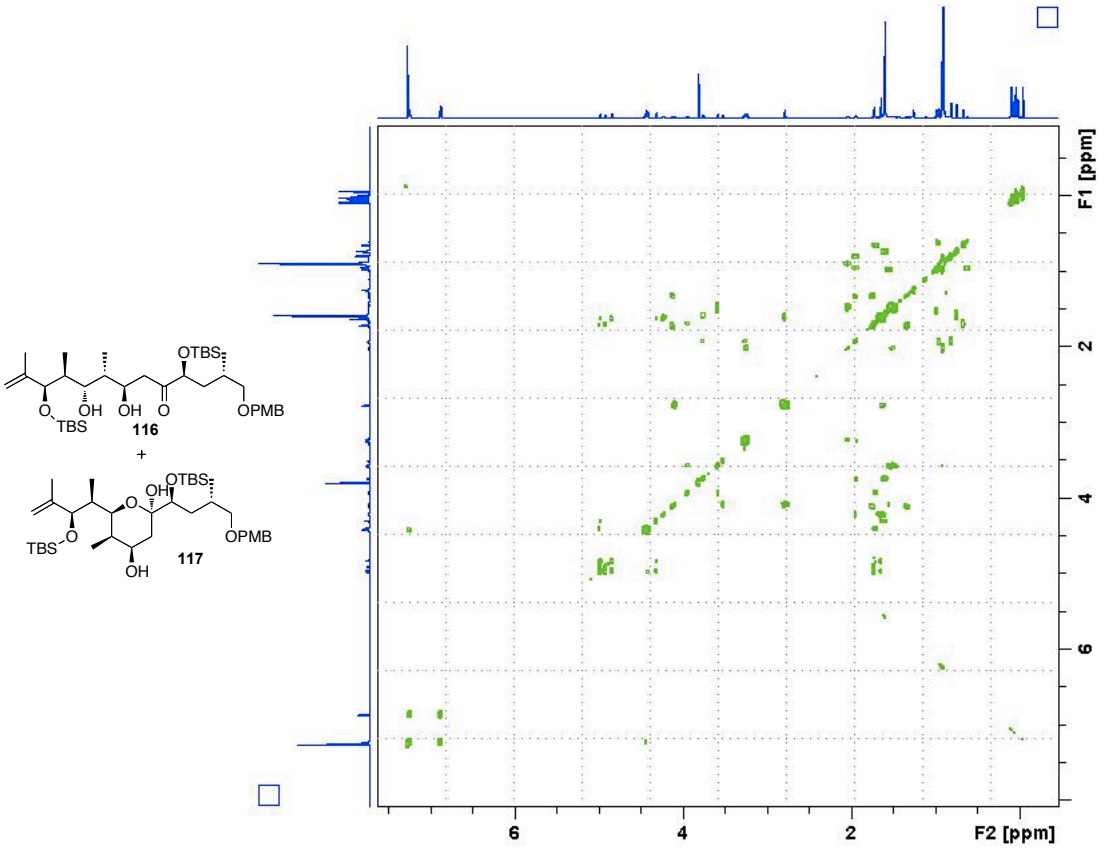

Figure A13: 600 MHz COSY spectrum of mixture of diol **116** and hemiacetal **117** in $CDCl_3$.

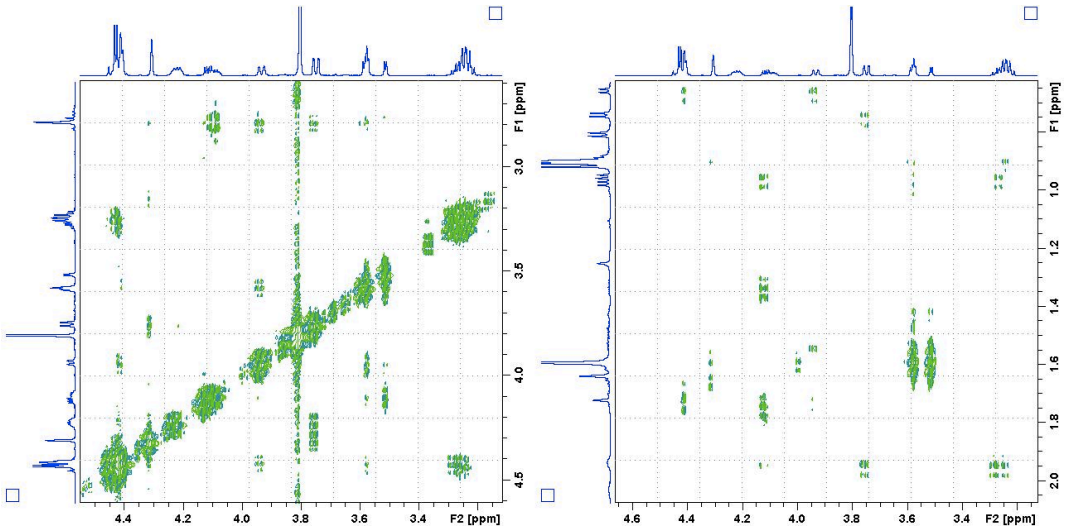

Figure A14: 600 MHz NOESY spectrum of mixture of diol **116** and hemiacetal **117** in $CDCl_3$.

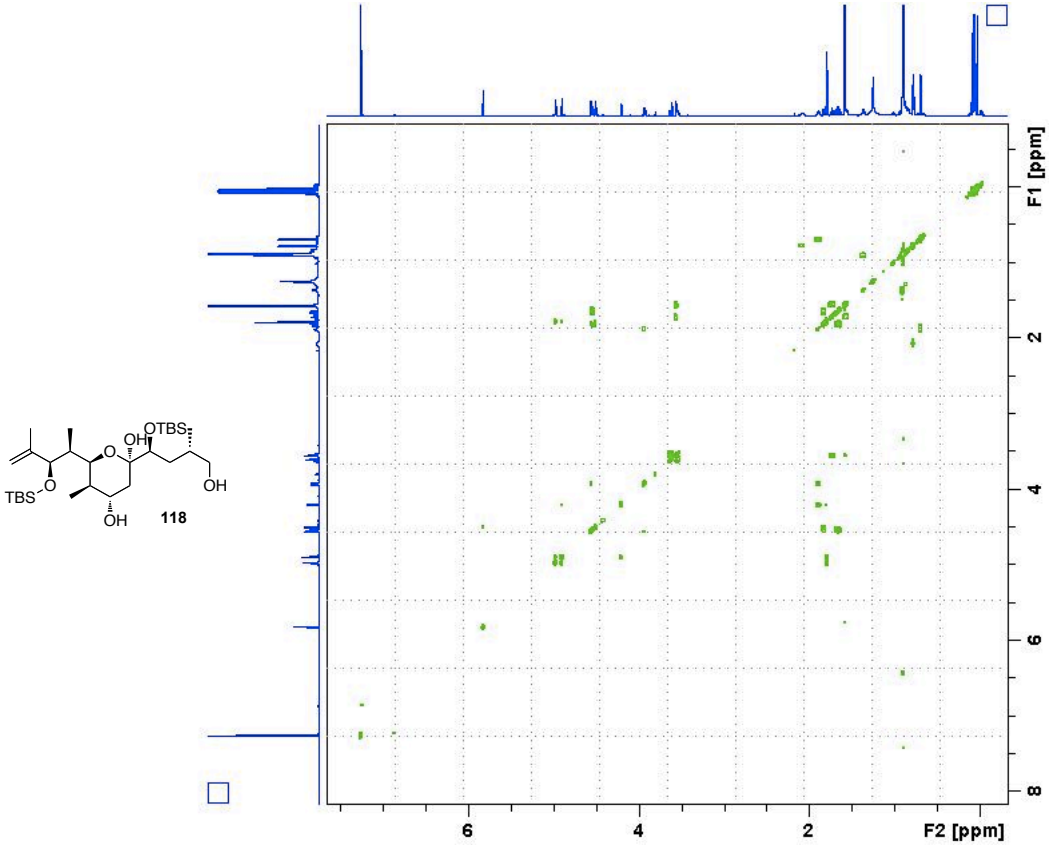

Figure A15: 600 MHz COSY spectrum of hemiacetal **118** in $CDCl_3$.

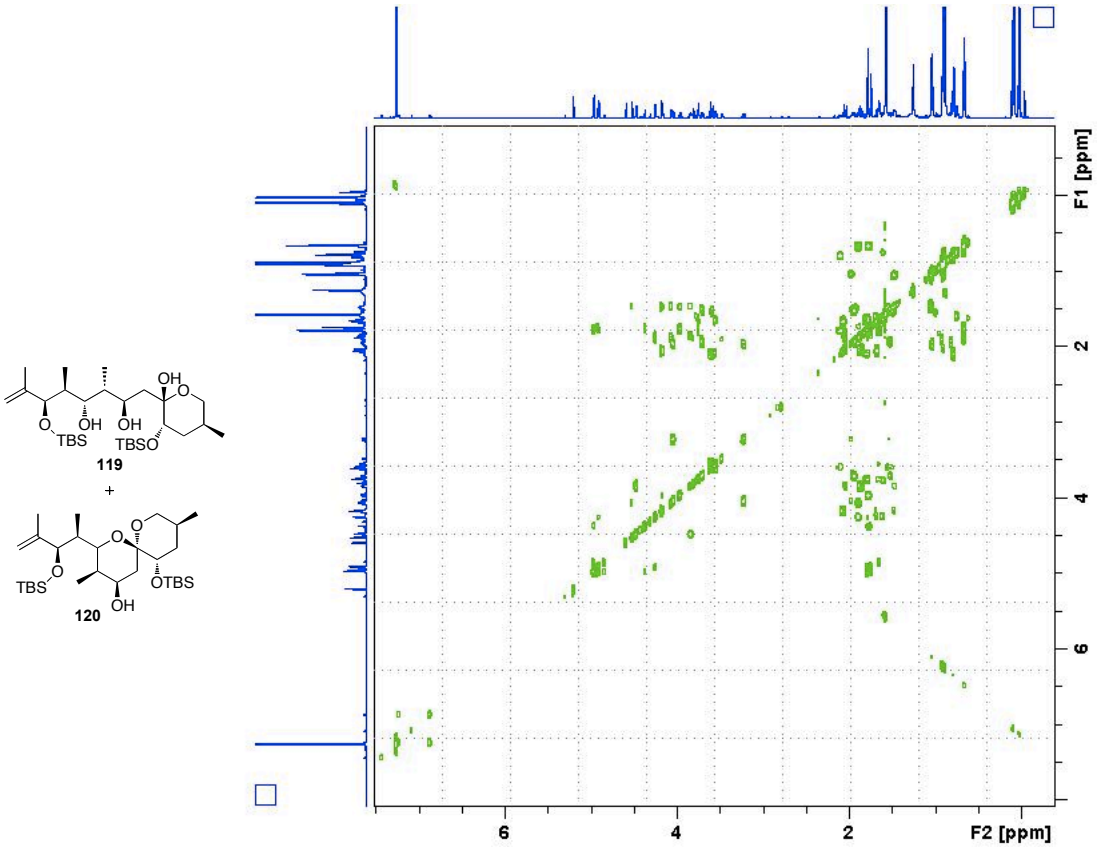

Figure A16: 600 MHz COSY spectrum of mixture of hemiacetal **119** and spiroacetal **120** in $CDCl_3$.

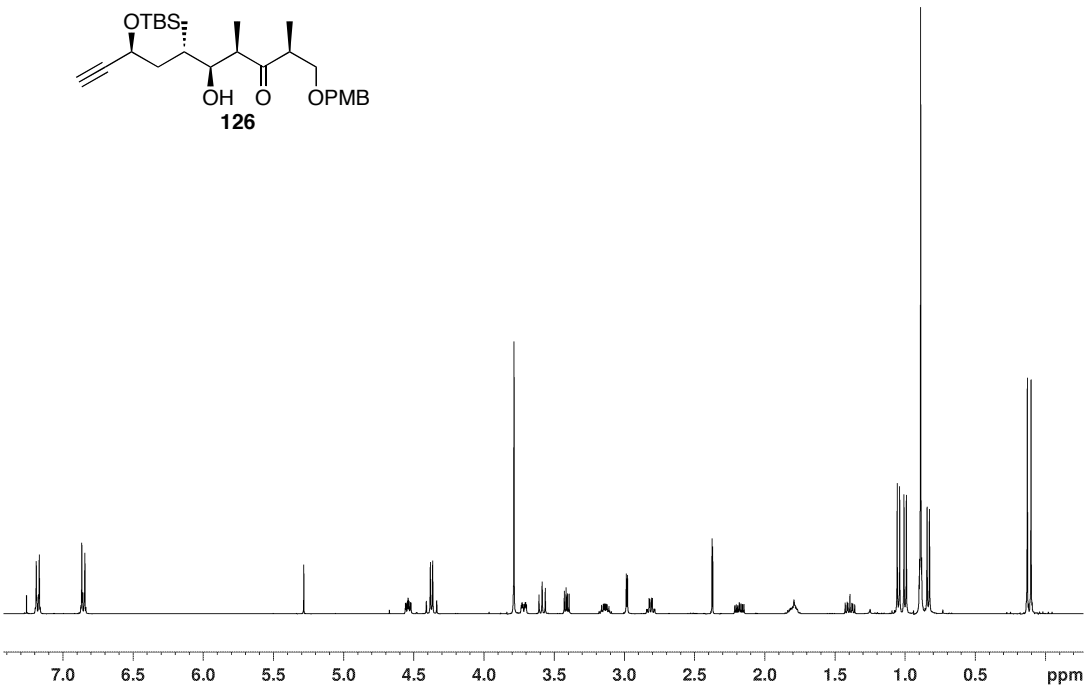

Figure A17: 400 MHz ^{1}H NMR spectrum of aldol adduct **126** in $CDCl_3$.

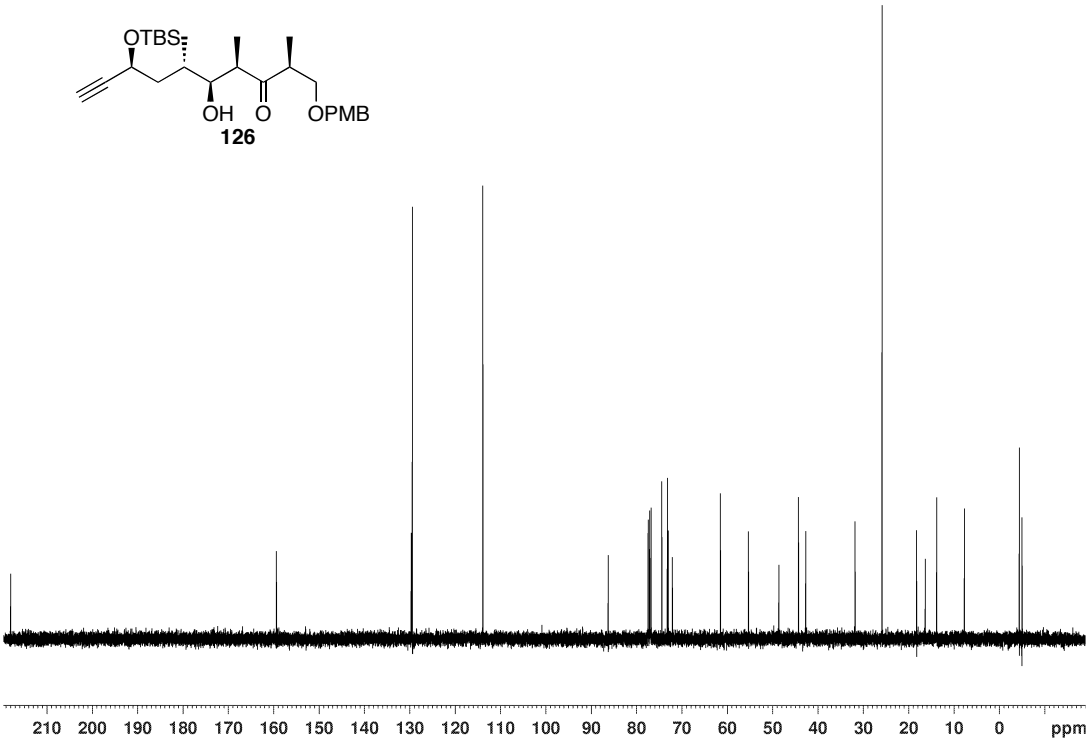

Figure A18: 100 MHz ^{13}C NMR spectrum of aldol adduct **126** in $CDCl_3$.

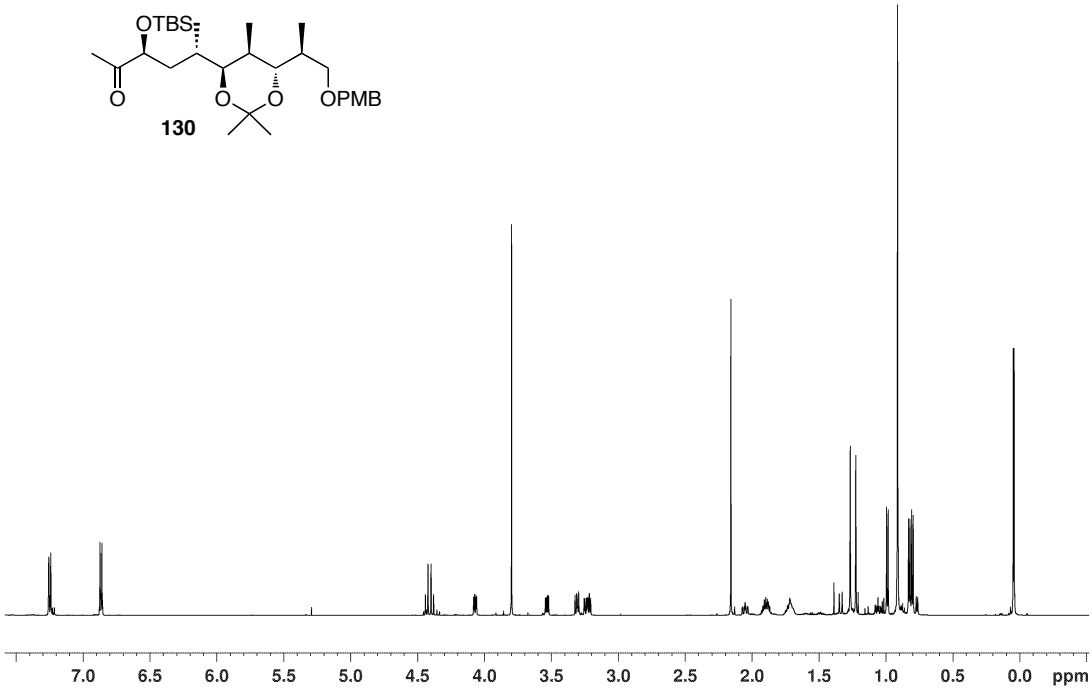

Figure A19: 600 MHz ^{1}H NMR spectrum of methyl ketone **130** in $CDCl_3$.

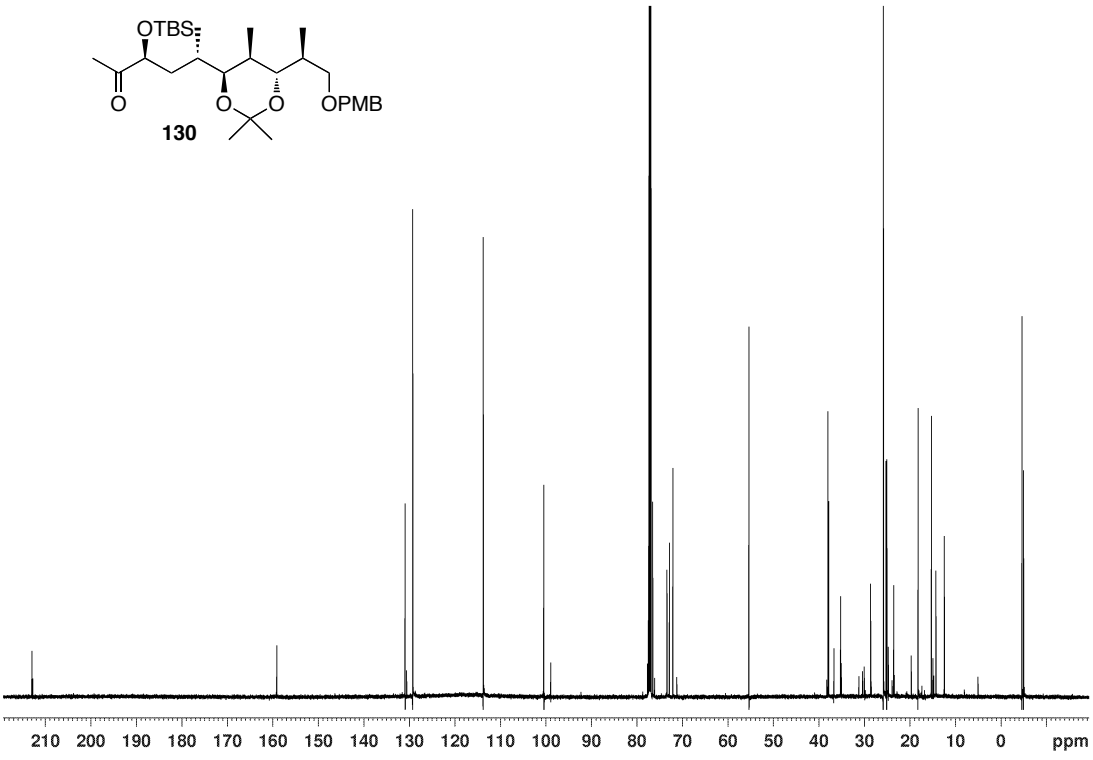

Figure A20: 151 MHz ^{13}C NMR spectrum of methyl ketone **130** in $CDCl_3$.

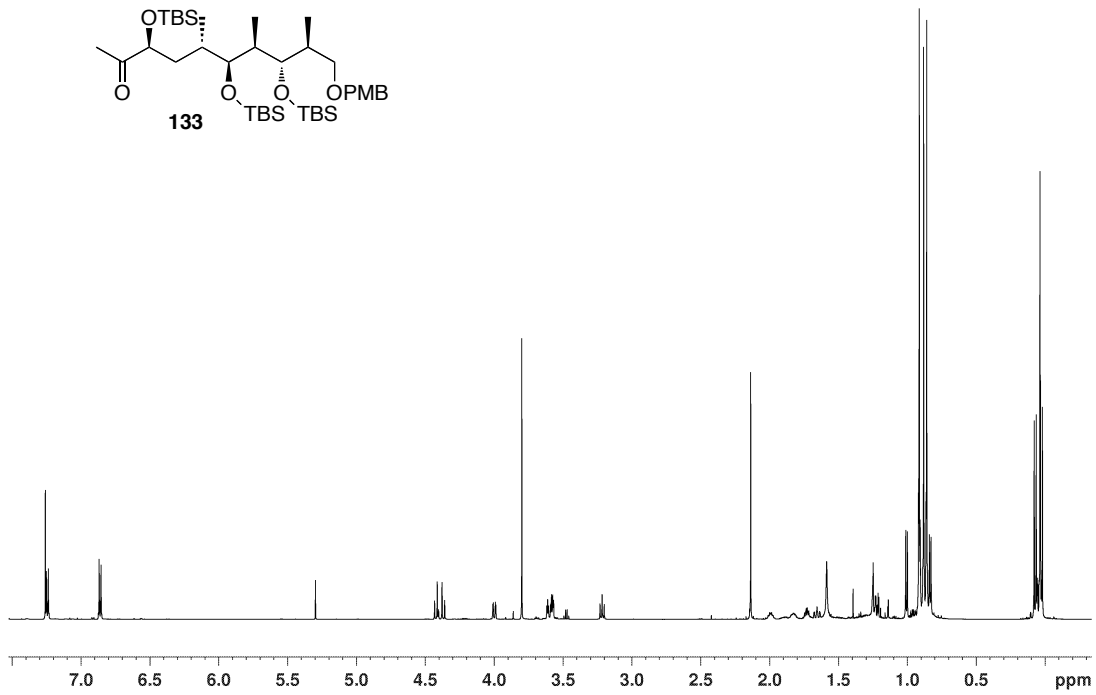

Figure A21: 600 MHz ^{1}H NMR spectrum of methyl ketone **133** in $CDCl_3$.

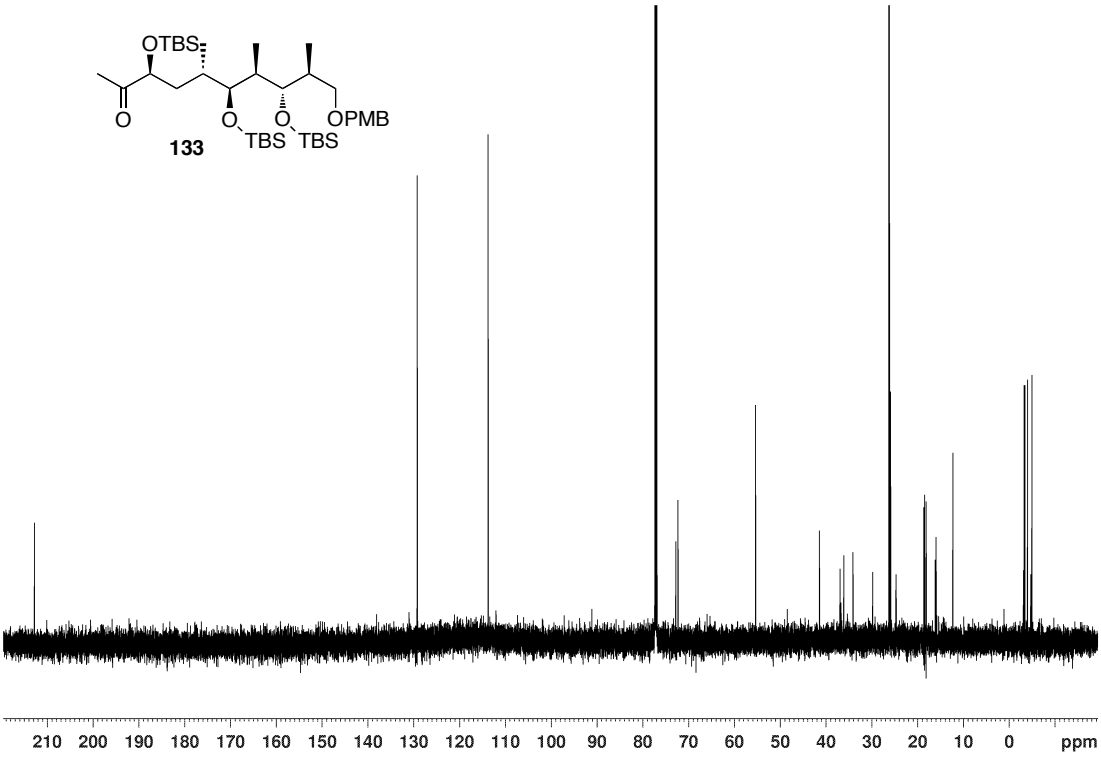

Figure A22: 151 MHz ^{13}C NMR spectrum of methyl ketone **133** in $CDCl_3$.

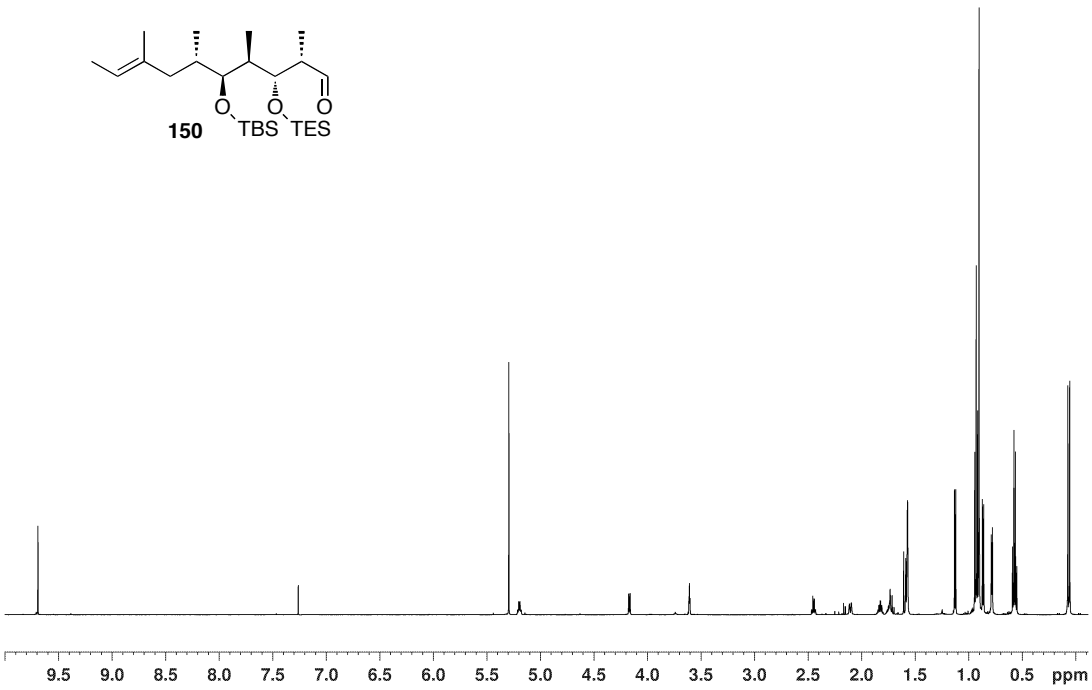

Figure A23: 600 MHz ^{1}H NMR spectrum of aldehyde **150** in $CDCl_3$.

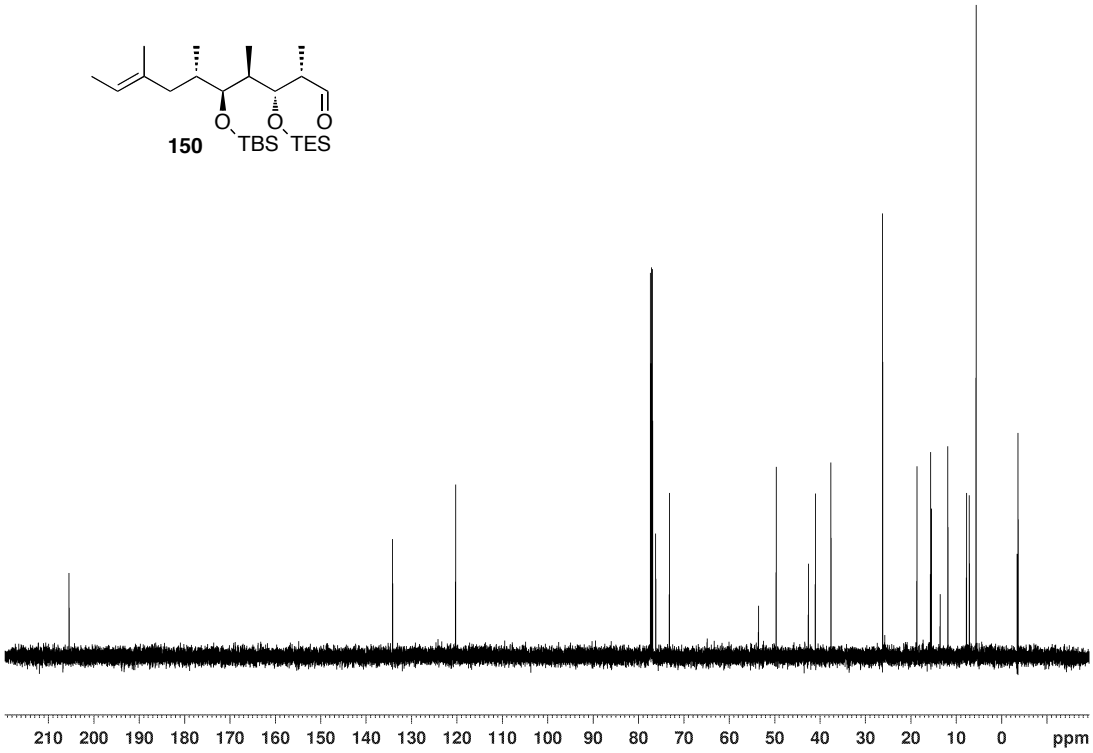

Figure A24: 151 MHz ^{13}C NMR spectrum of aldehyde **150** in $CDCl_3$.

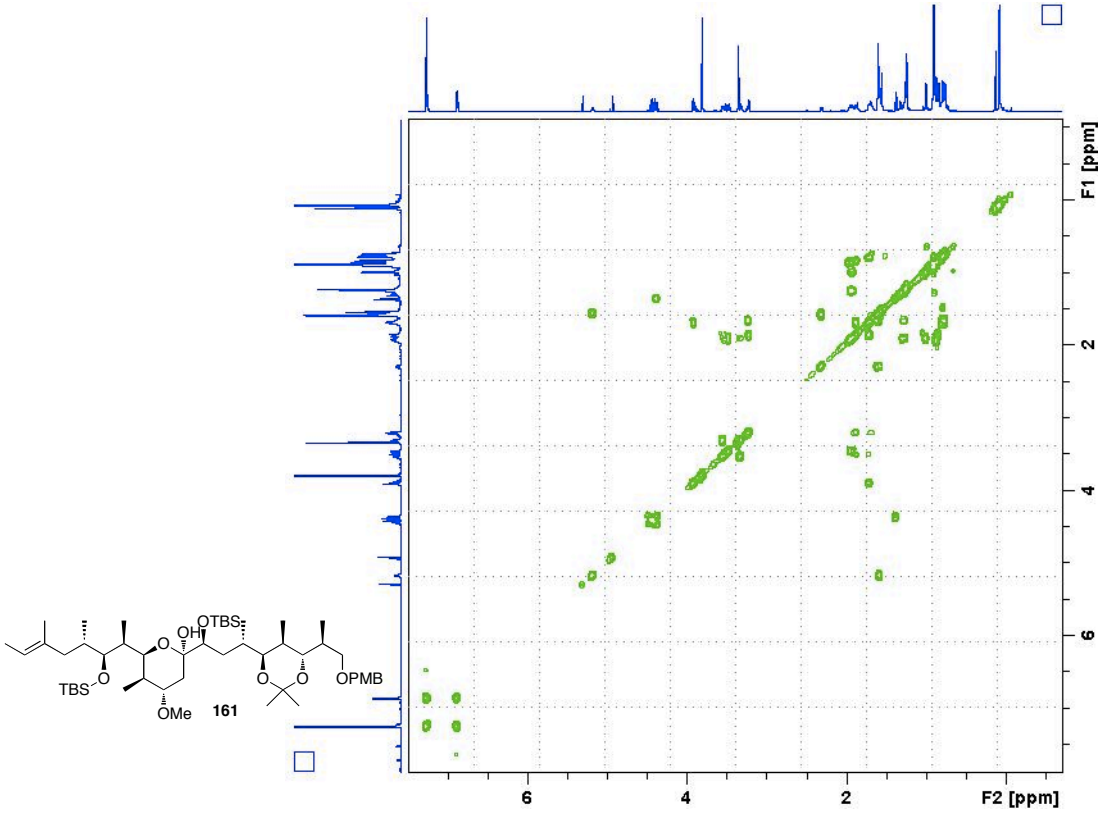

Figure A25: 600 MHz COSY spectrum of hemiacetal **161** in $CDCl_3$.

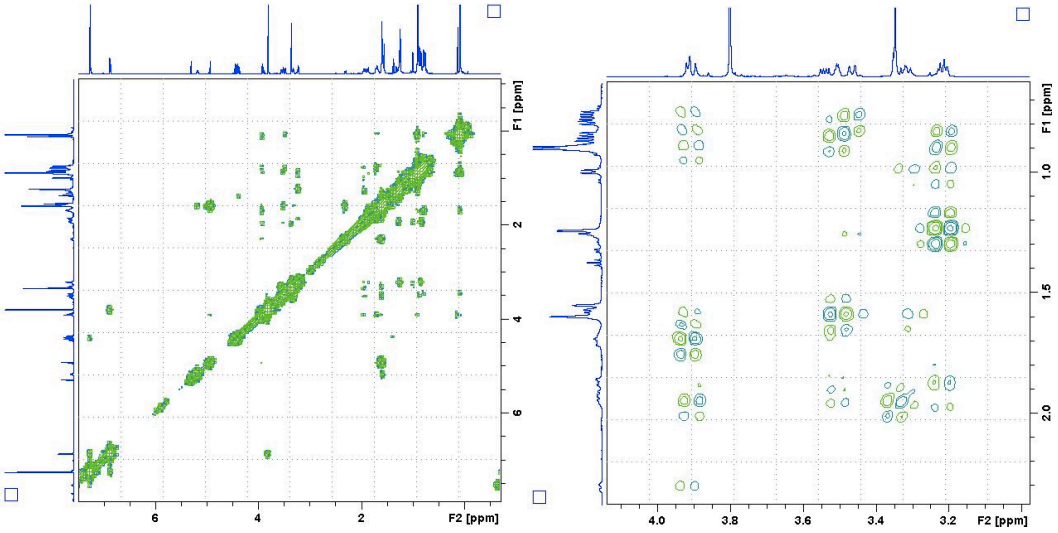

Figure A26: 600 MHz NOESY spectrum of hemiacetal **161** in $CDCl_3$.

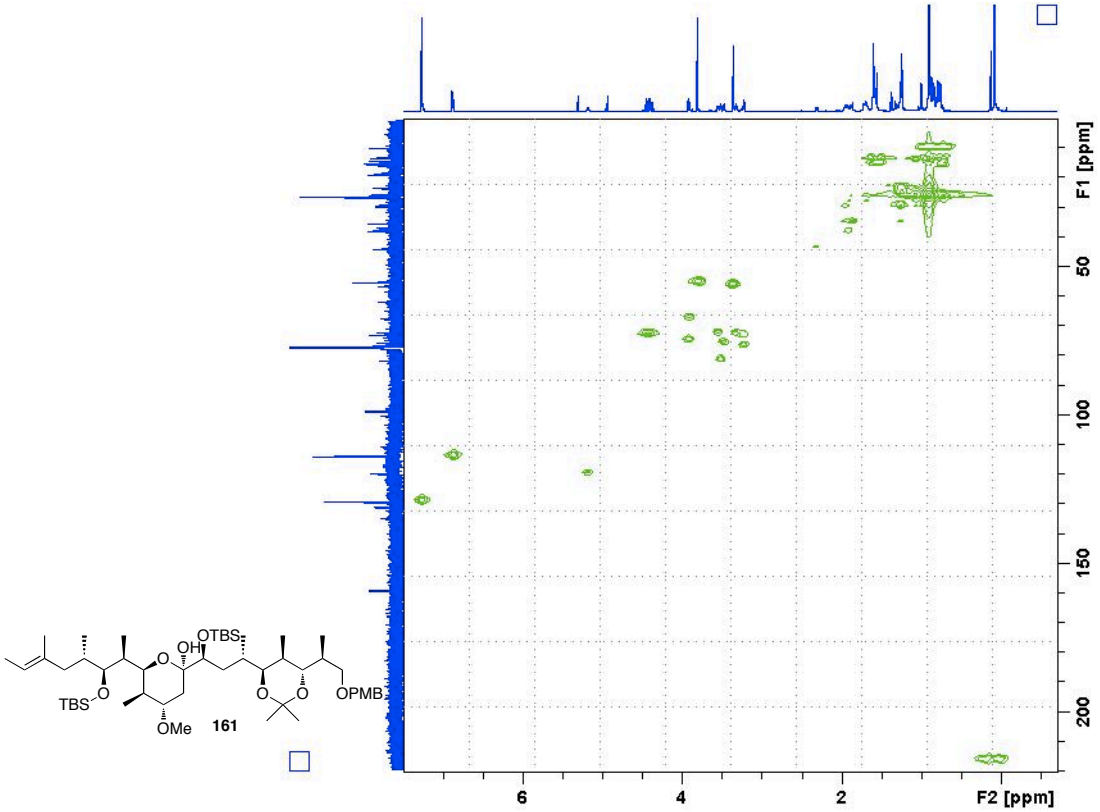

Figure A27: 600 MHz HMQC spectrum of hemiacetal **161** in $CDCl_3$.

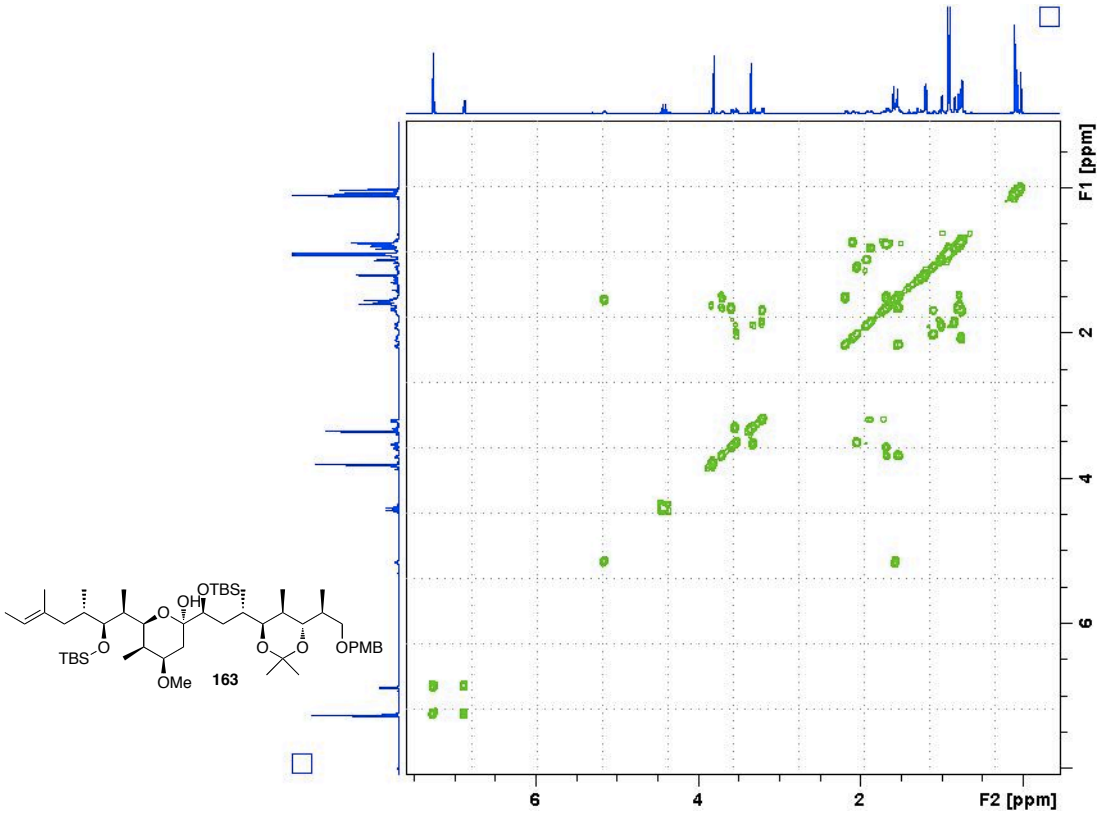

Figure A28: 600 MHz COSY spectrum of hemiacetal **163** in $CDCl_3$.

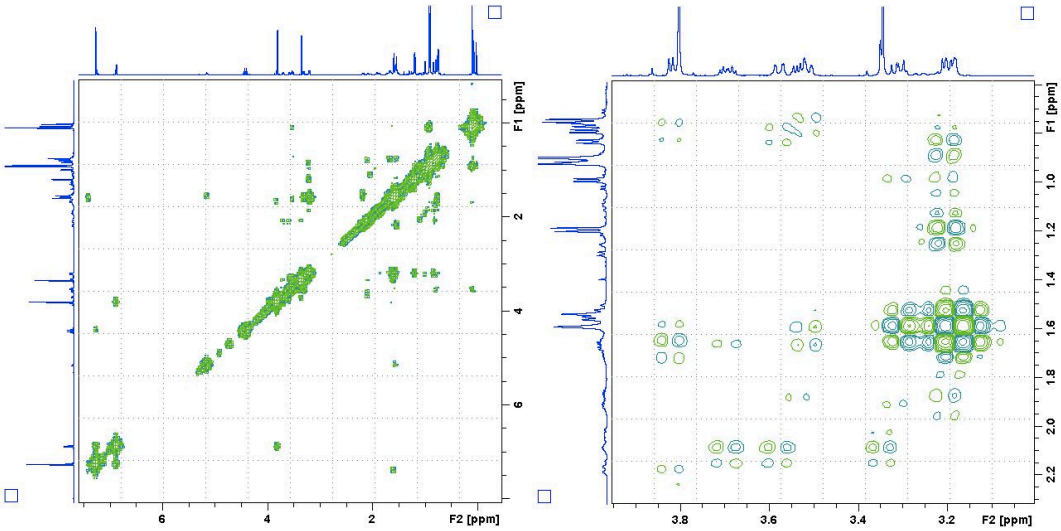

Figure A29: 600 MHz NOESY spectrum of hemiacetal **163** in $CDCl_3$.

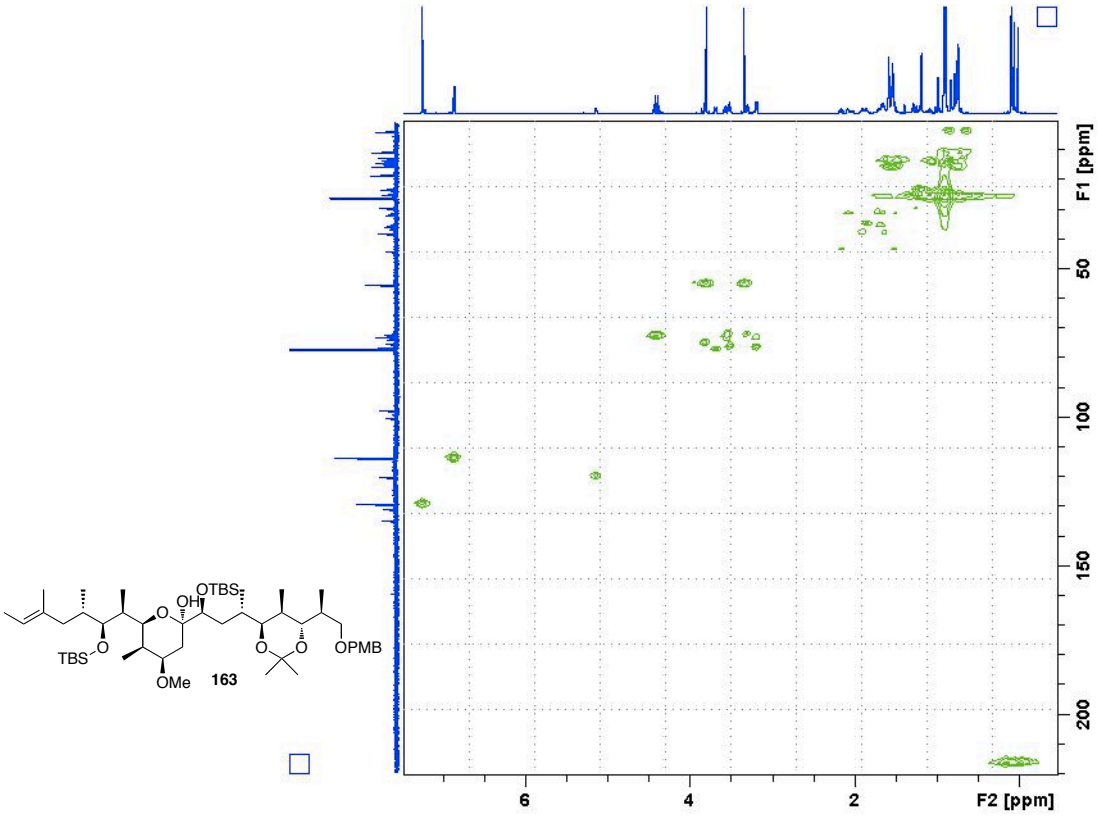

Figure A30: 600 MHz HMQC spectrum of hemiacetal **163** in $CDCl_3$.

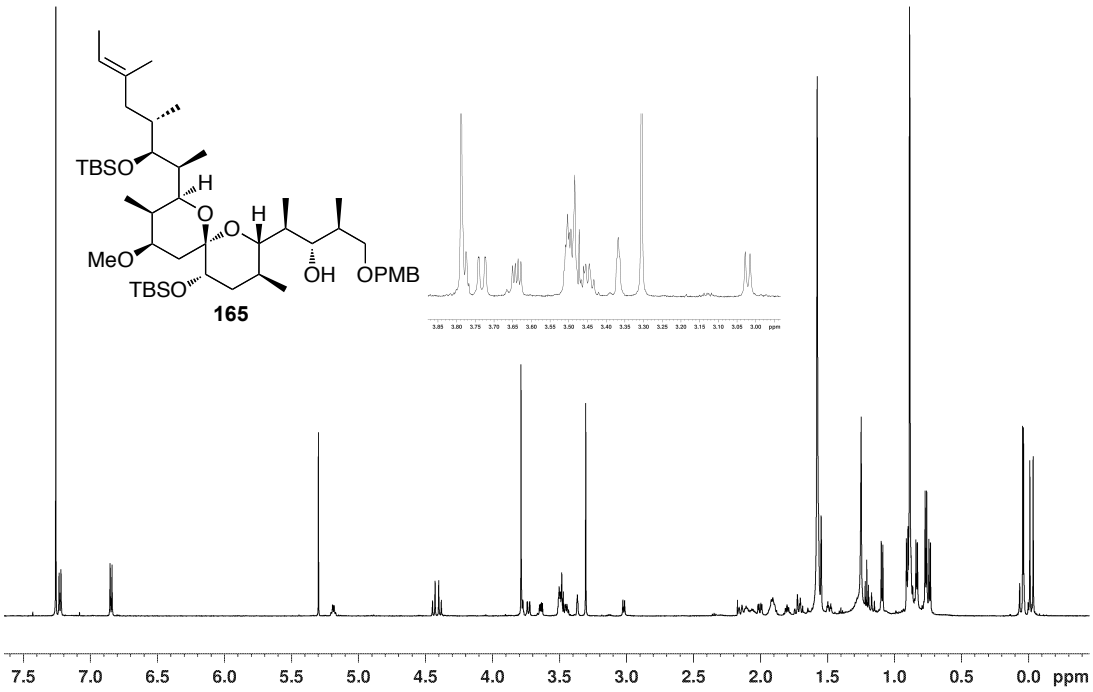

Figure A31: 600 MHz ^{1}H spectrum of spiroacetal **165** in $CDCl_3$.

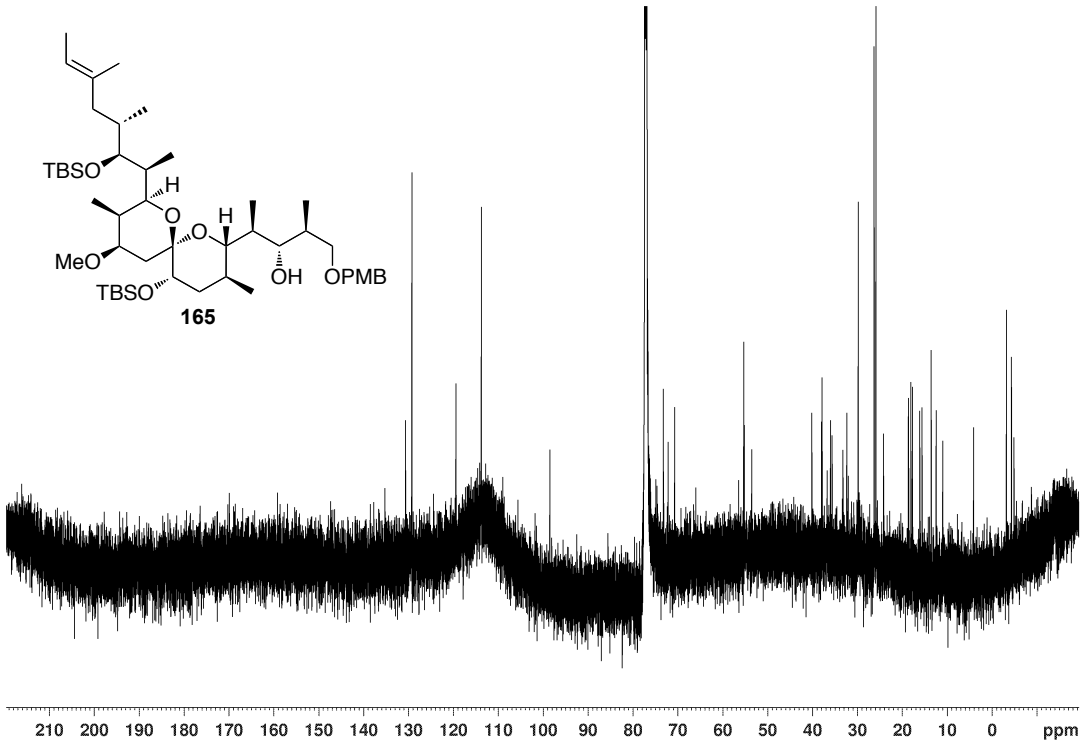

Figure A32: 151 MHz ^{13}C spectrum of spiroacetal **165** in $CDCl_3$.

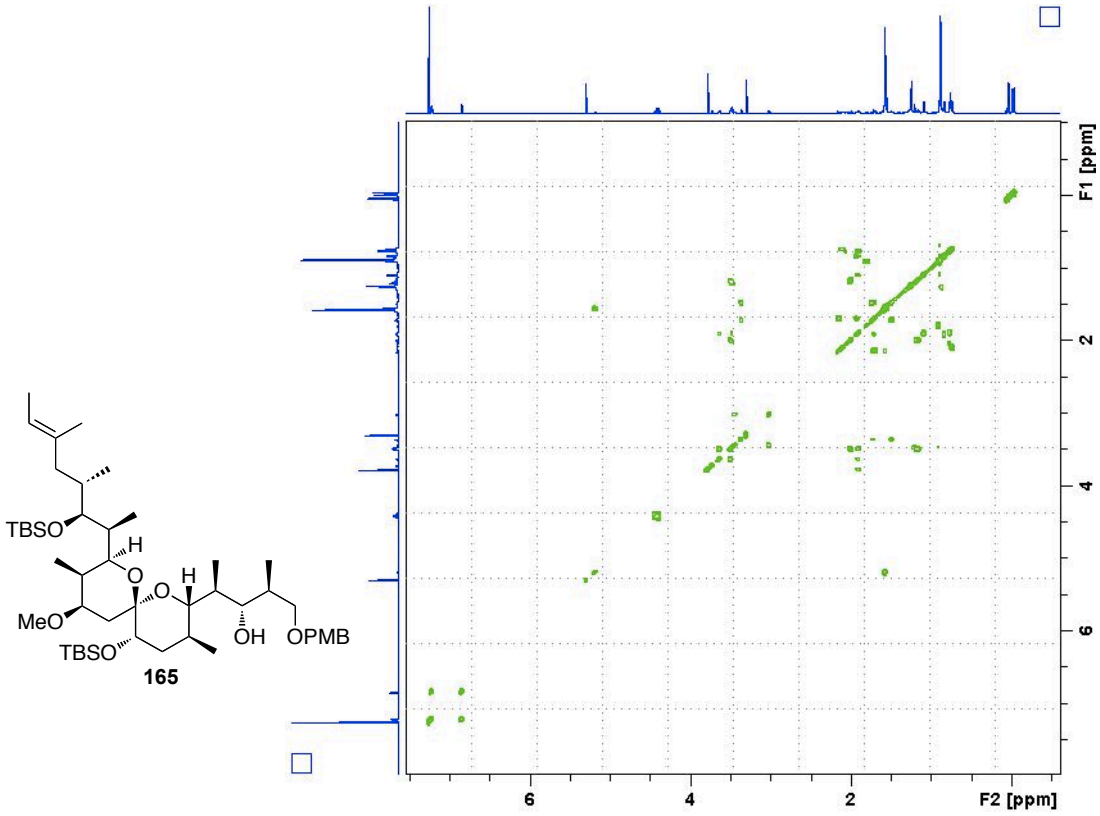

Figure A33: 600 MHz COSY spectrum of spiroacetal **165** in $CDCl_3$.

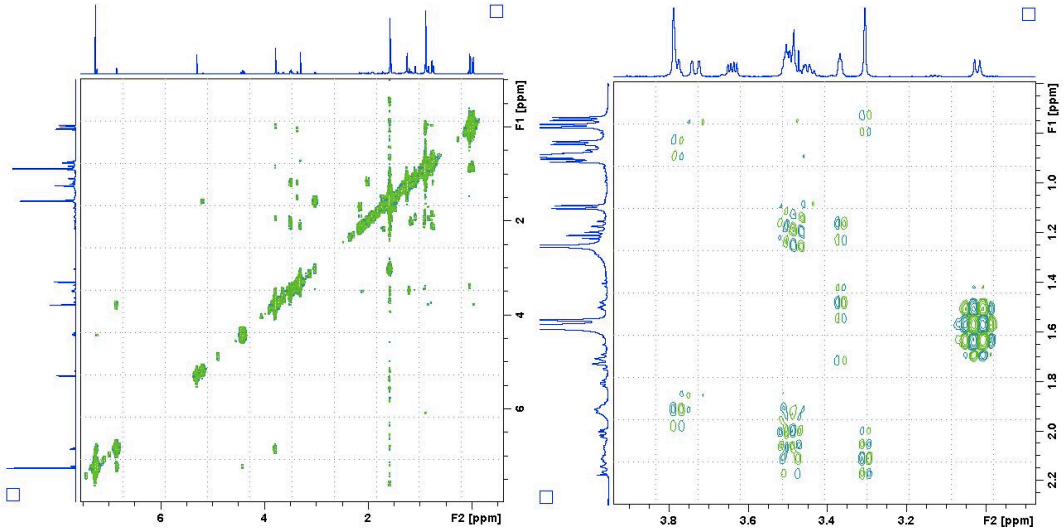

Figure A34: 600 MHz NOESY spectrum of spiroacetal **165** in $CDCl_3$.

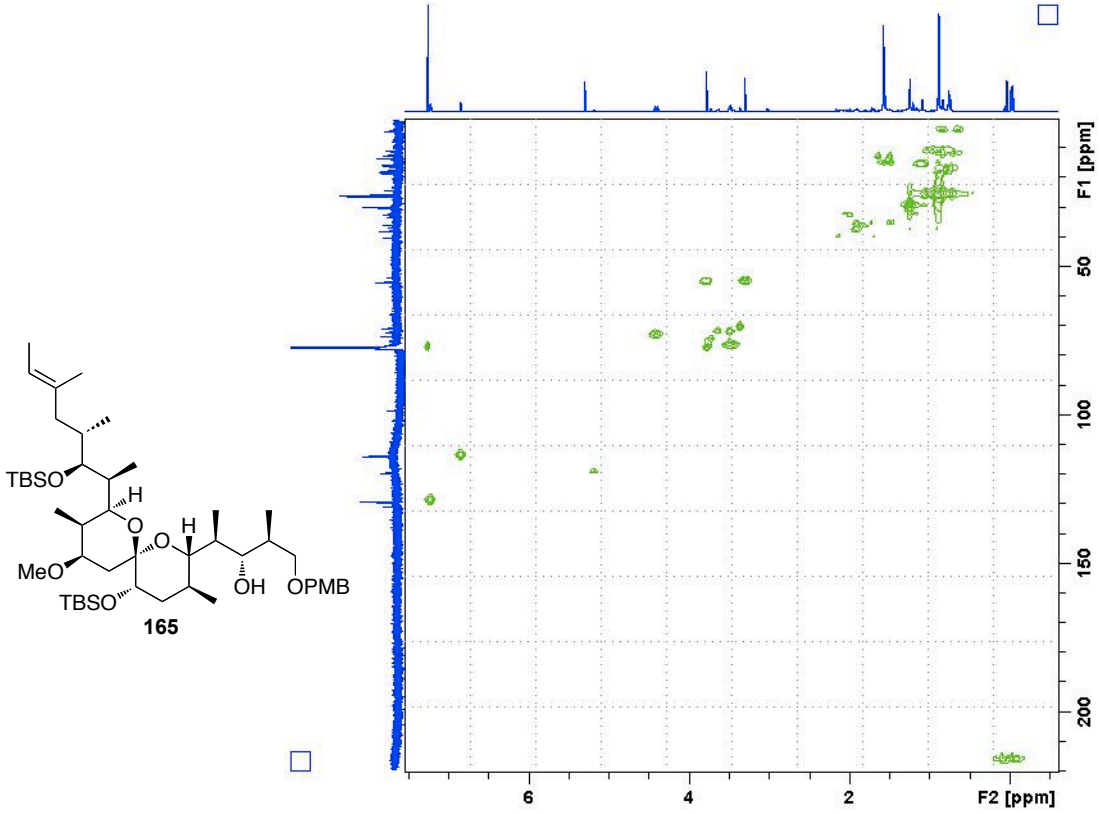

Figure A35: 600 MHz HMQC spectrum of spiroacetal **165** in $CDCl_3$.

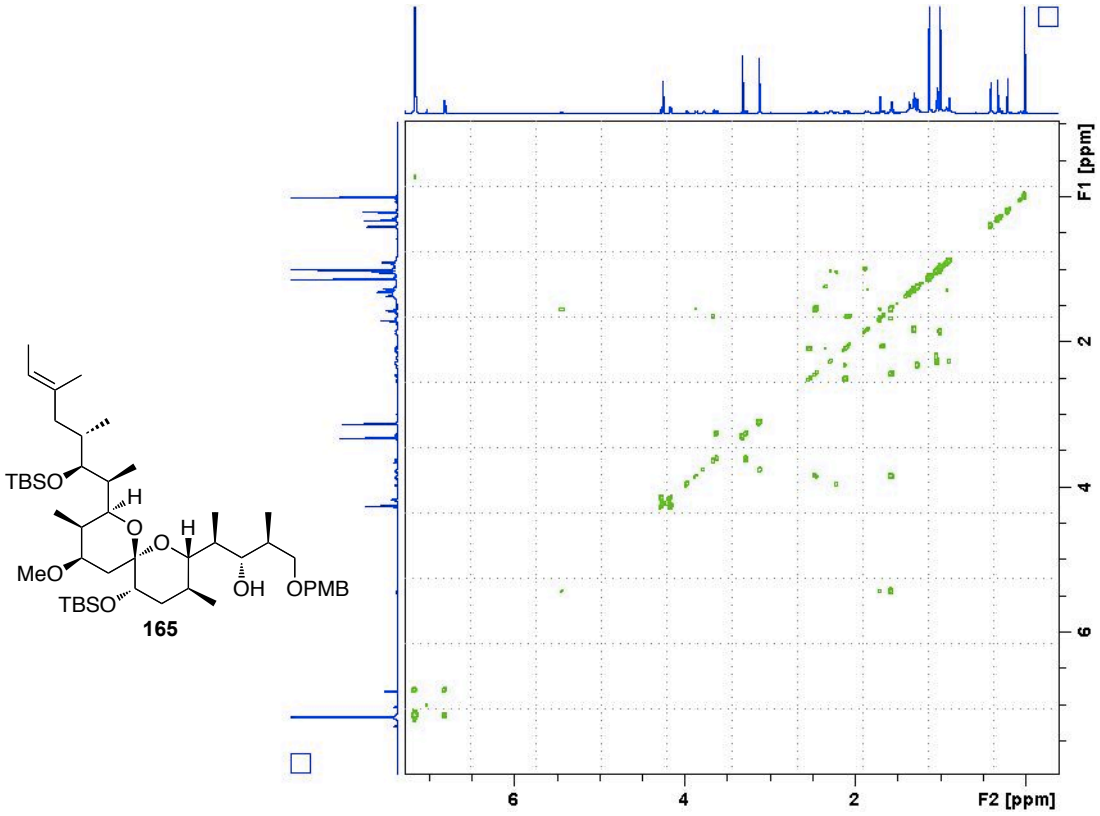

Figure A36: 600 MHz COSY spectrum of spiroacetal **165** in C_6D_6.

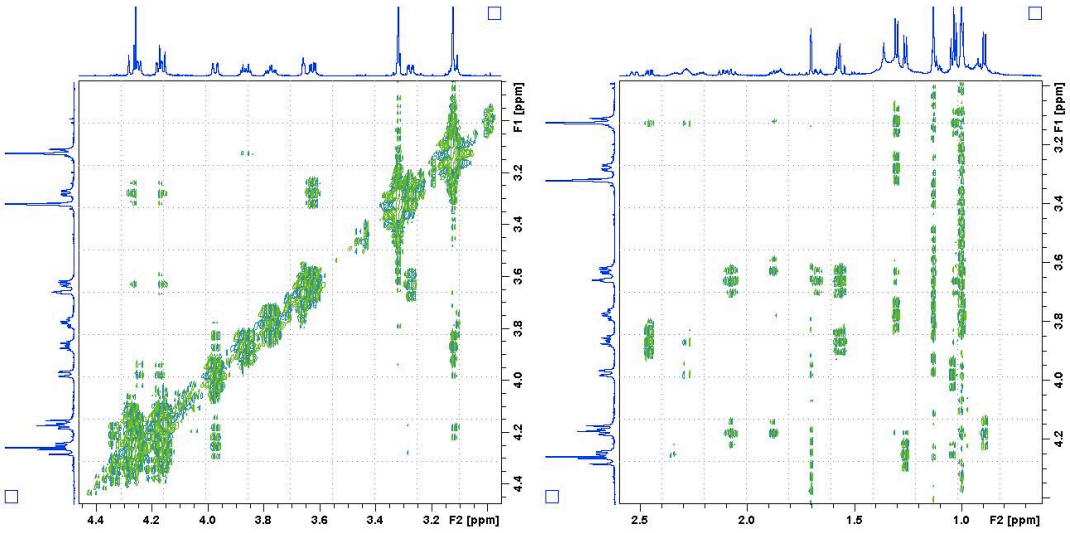

Figure A37: 600 MHz NOESY spectrum of spiroacetal **165** in C_6D_6.

Appendix B. Additional Spectral Data for Chapter Three

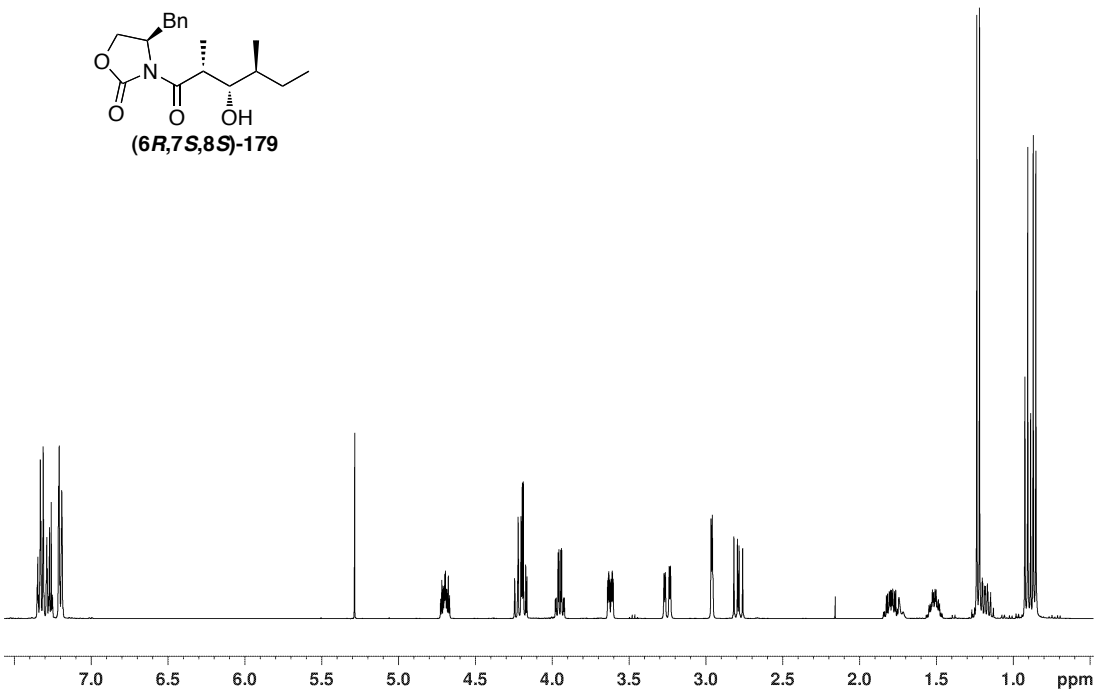

Figure B1: 400 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-179** in $CDCl_3$.

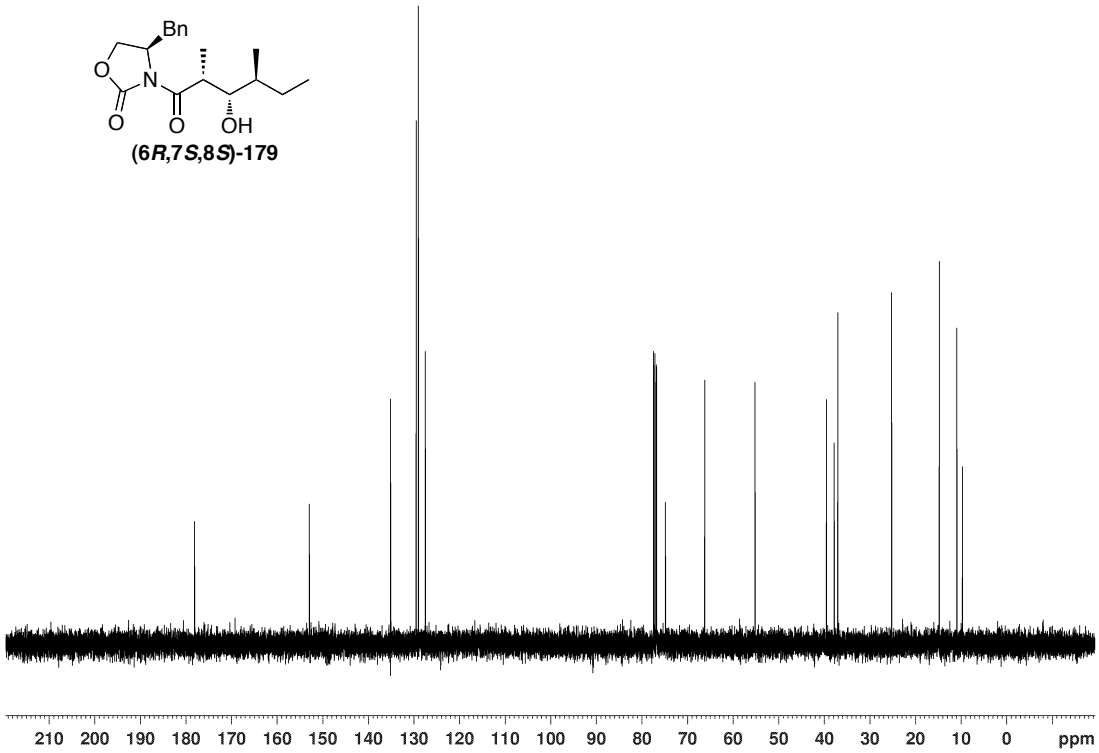

Figure B2: 100 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-179** in $CDCl_3$.

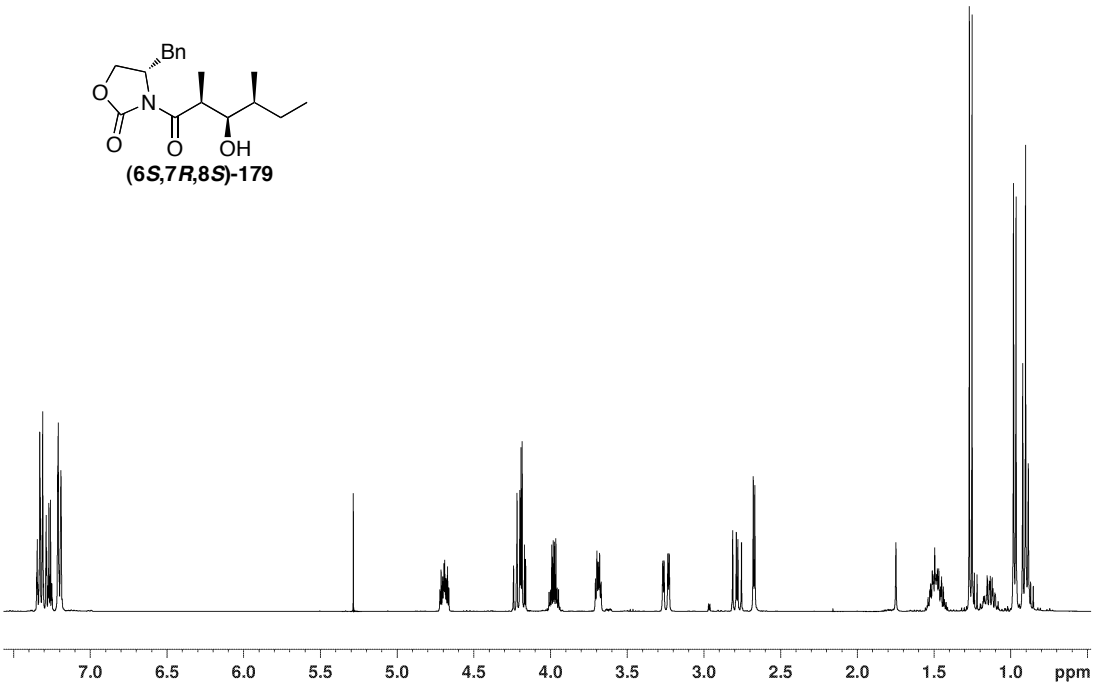

Figure B3: 400 MHz ^{1}H NMR spectrum of **(6*S*,7*R*,8*S*)-179** in $CDCl_3$.

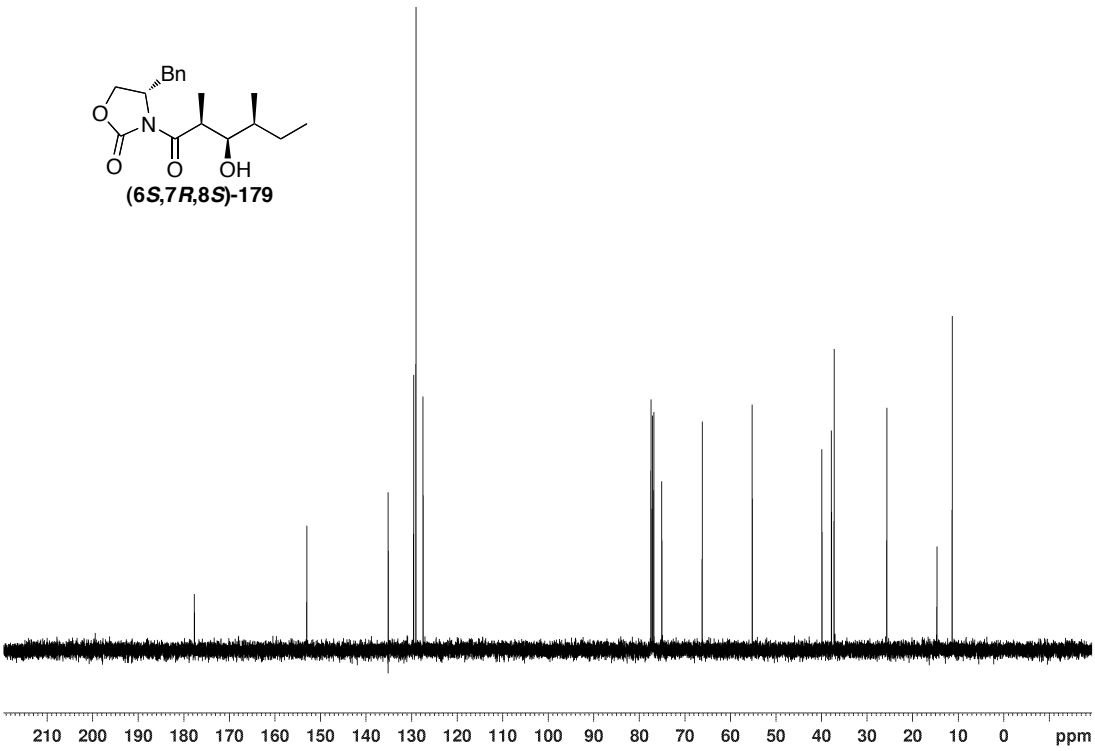

Figure B4: 100 MHz ^{13}C NMR spectrum of **(6*S*,7*R*,8*S*)-179** in $CDCl_3$.

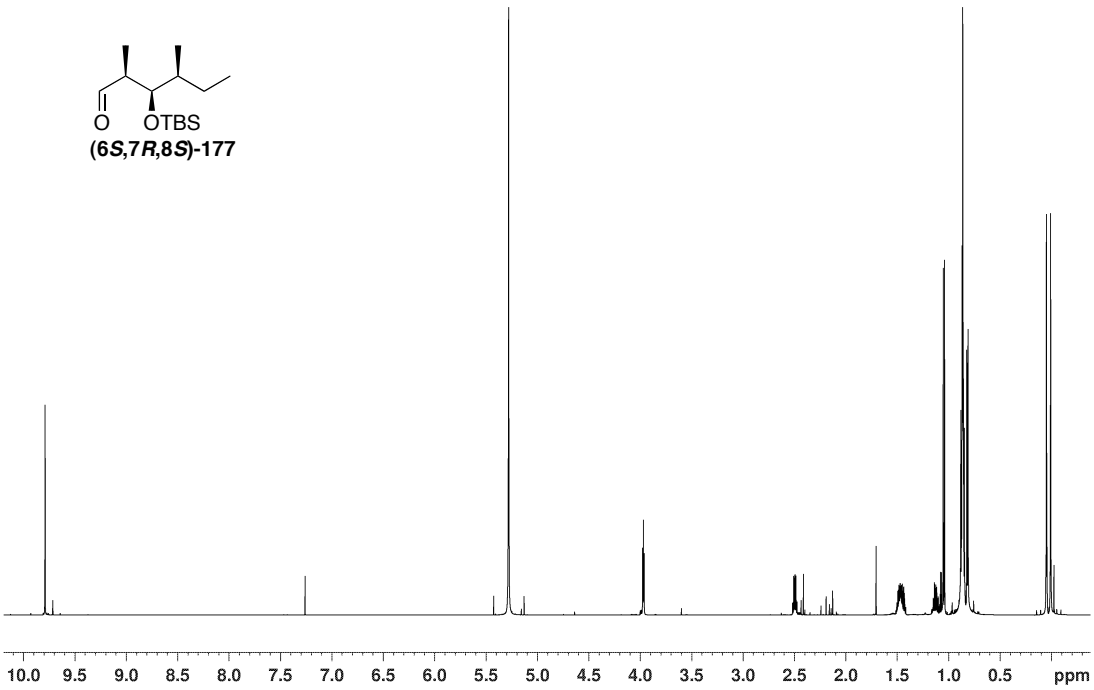

Figure B5: 400 MHz ^{1}H NMR spectrum of **(6*S*,7*R*,8*S*)-177** in $CDCl_3$.

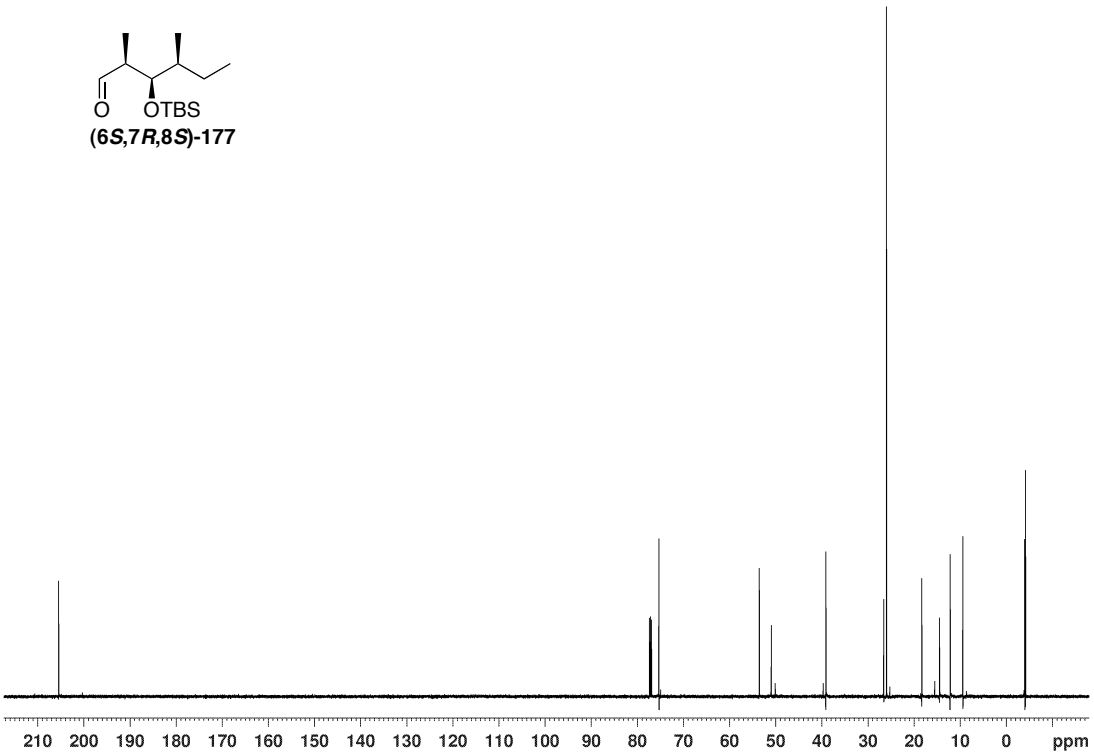

Figure B6: 100 MHz ^{13}C NMR spectrum of **(6*S*,7*R*,8*S*)-177** in $CDCl_3$.

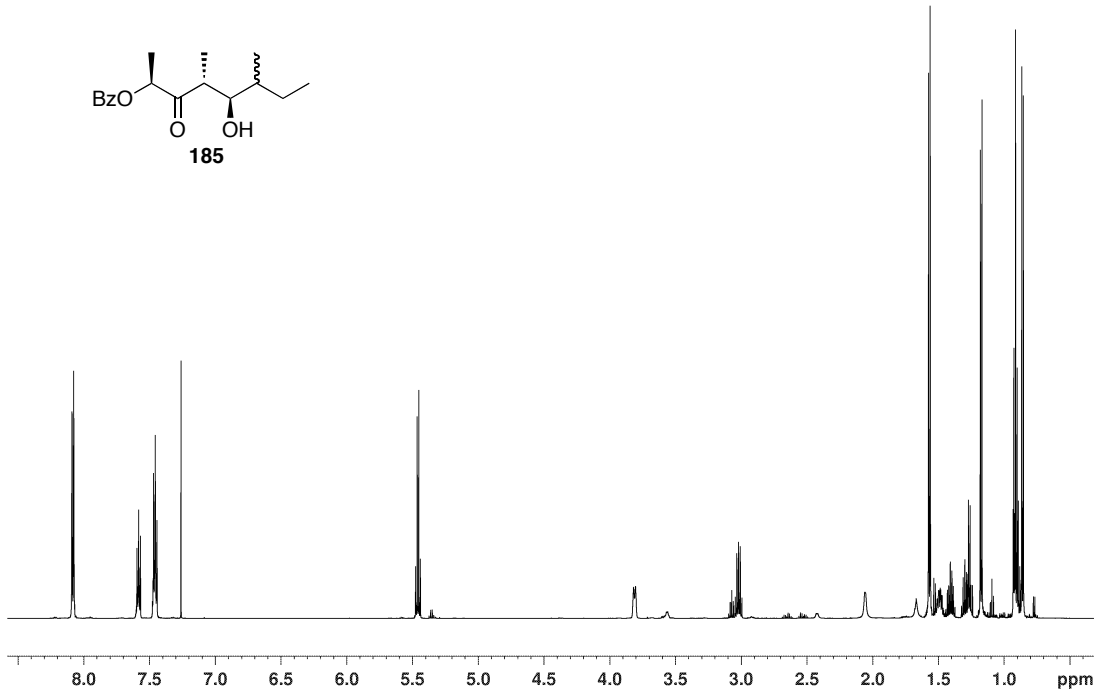

Figure B7: 600 MHz ^{1}H NMR spectrum of aldol adduct **185** in $CDCl_3$.

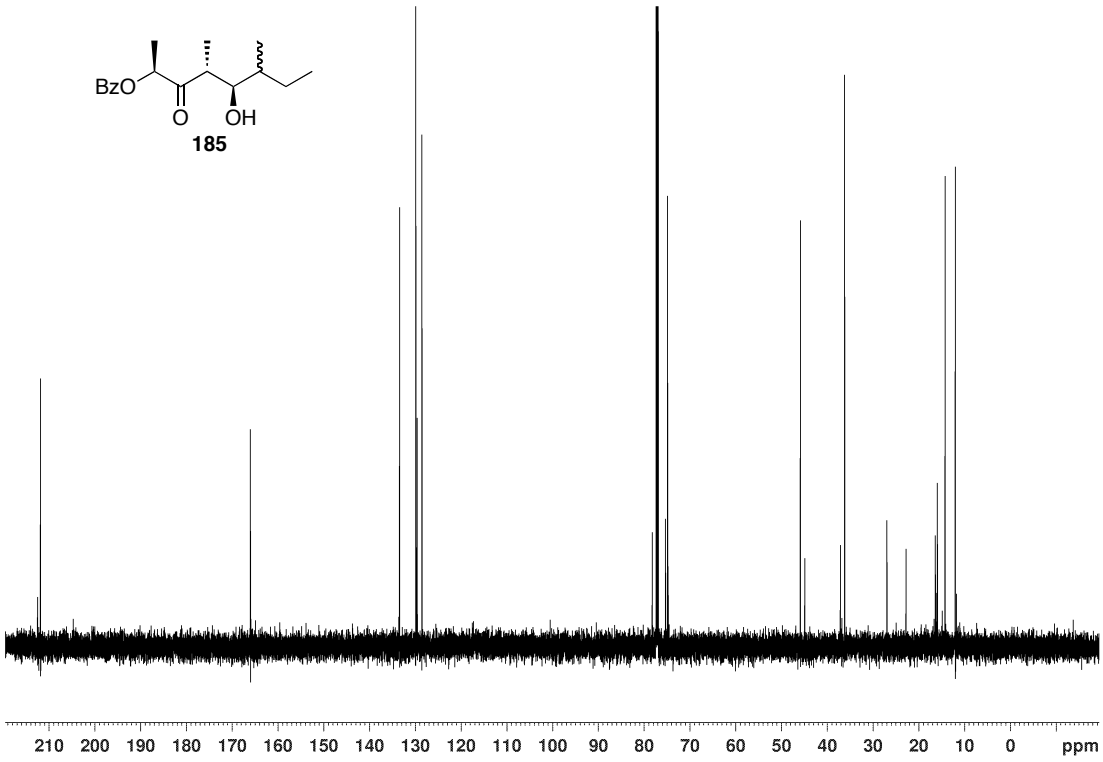

Figure B8: 151 MHz ^{13}C NMR spectrum of aldol adduct **185** in $CDCl_3$.

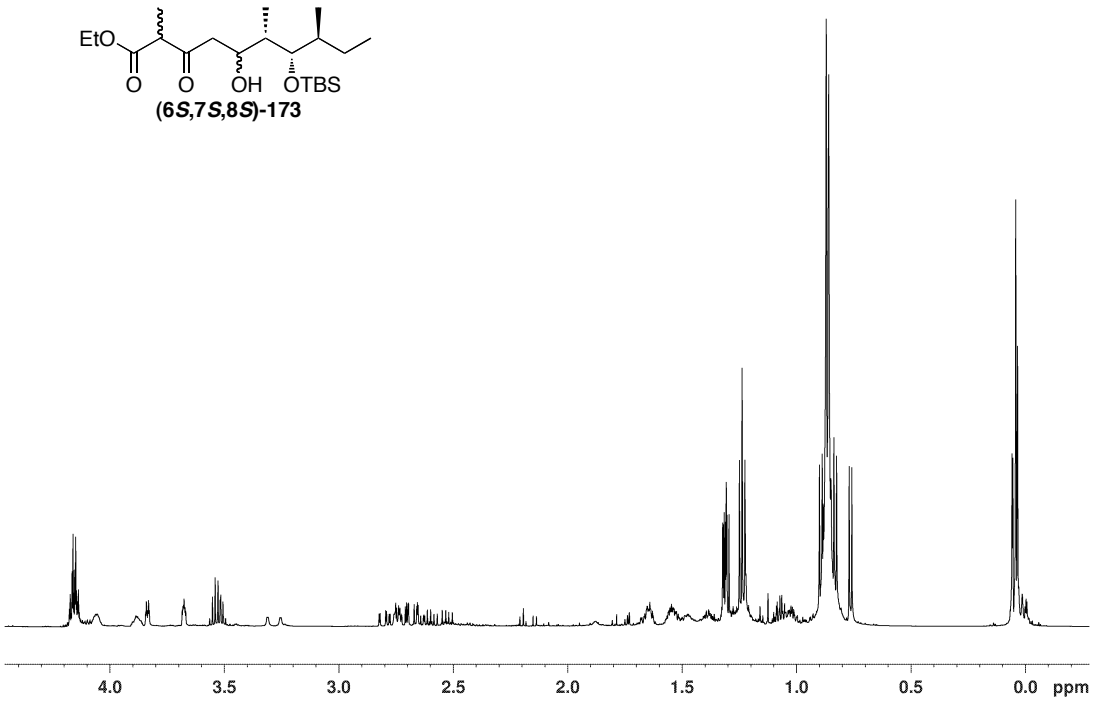

Figure B9: 600 MHz ^{1}H NMR spectrum of **(6*S*,7*S*,8*S*)-173** in $CDCl_3$.

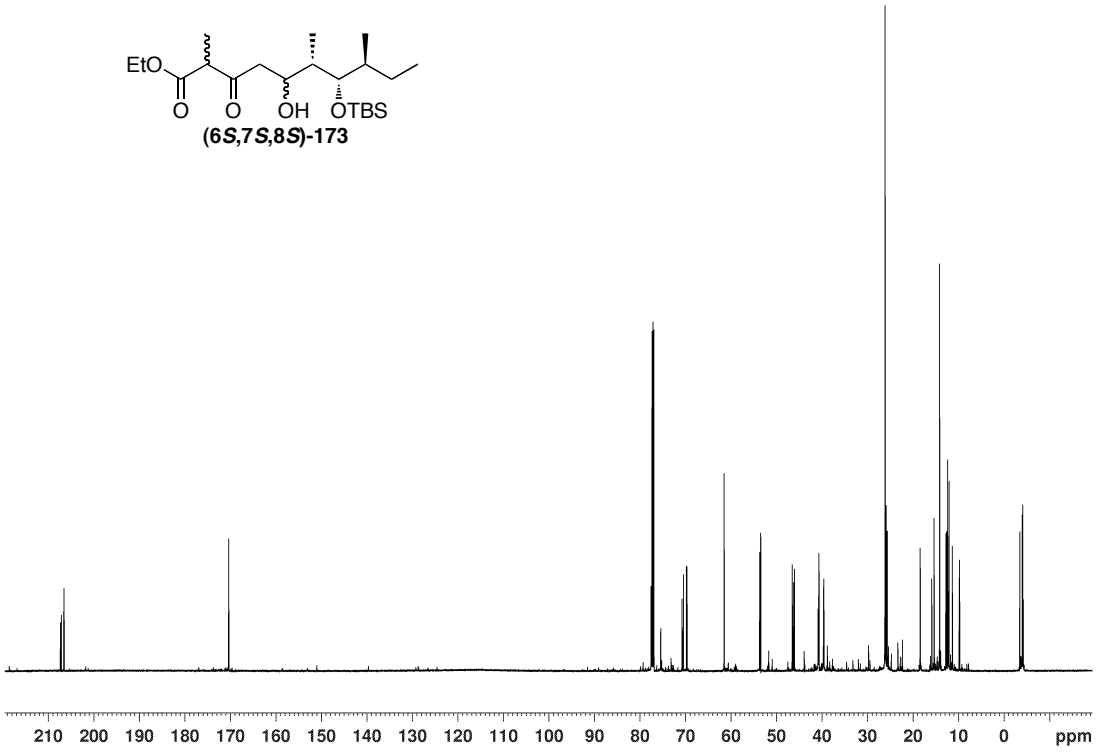

Figure B10: 151 MHz ^{13}C NMR spectrum of **(6*S*,7*S*,8*S*)-173** in $CDCl_3$.

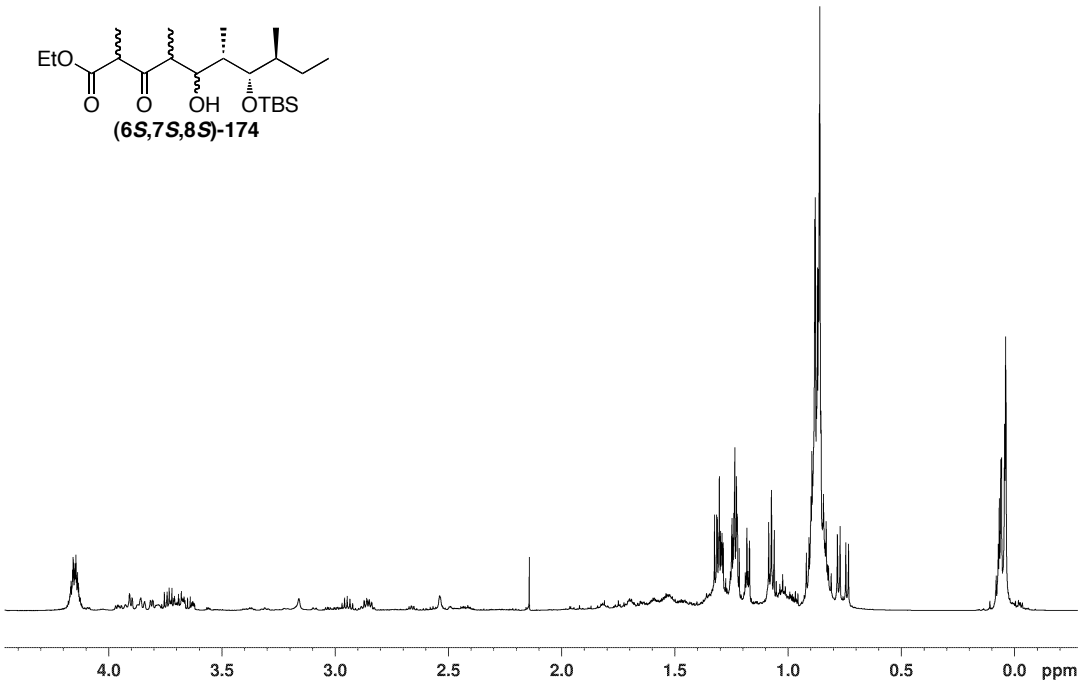

Figure B11: 600 MHz ^{1}H NMR spectrum of **(6*S*,7*S*,8*S*)-174** in $CDCl_3$.

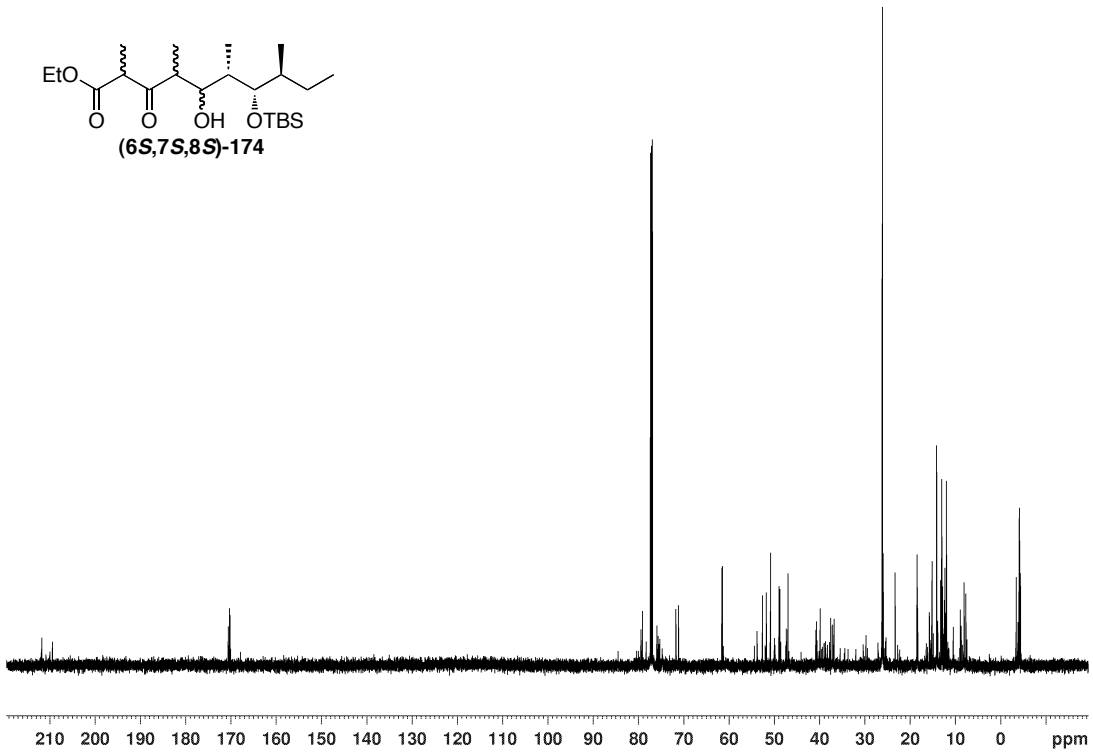

Figure B12: 151 MHz ^{13}C NMR spectrum of **(6*S*,7*S*,8*S*)-174** in $CDCl_3$.

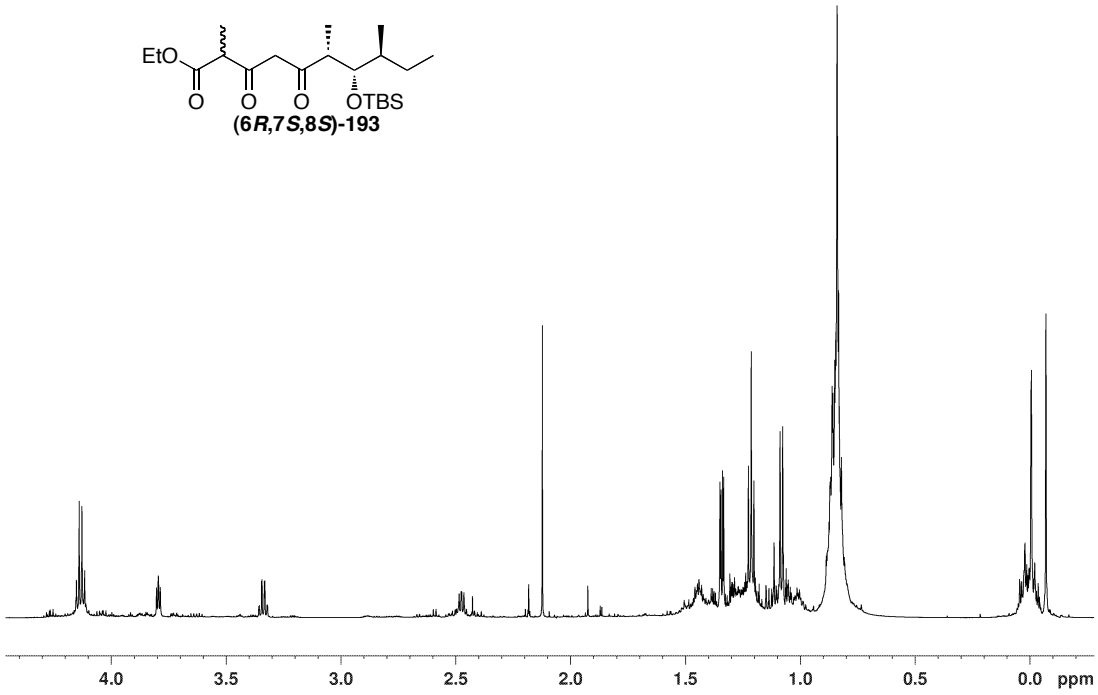

Figure B13: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-193** in $CDCl_3$.

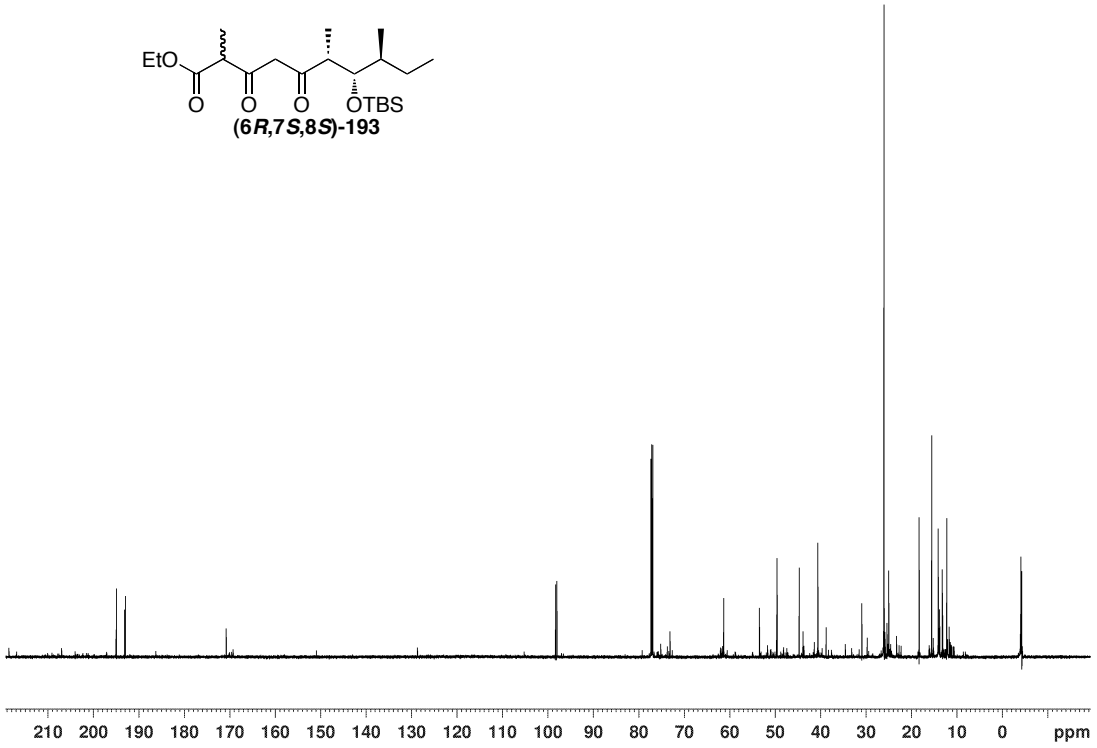

Figure B14: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-193** in $CDCl_3$.

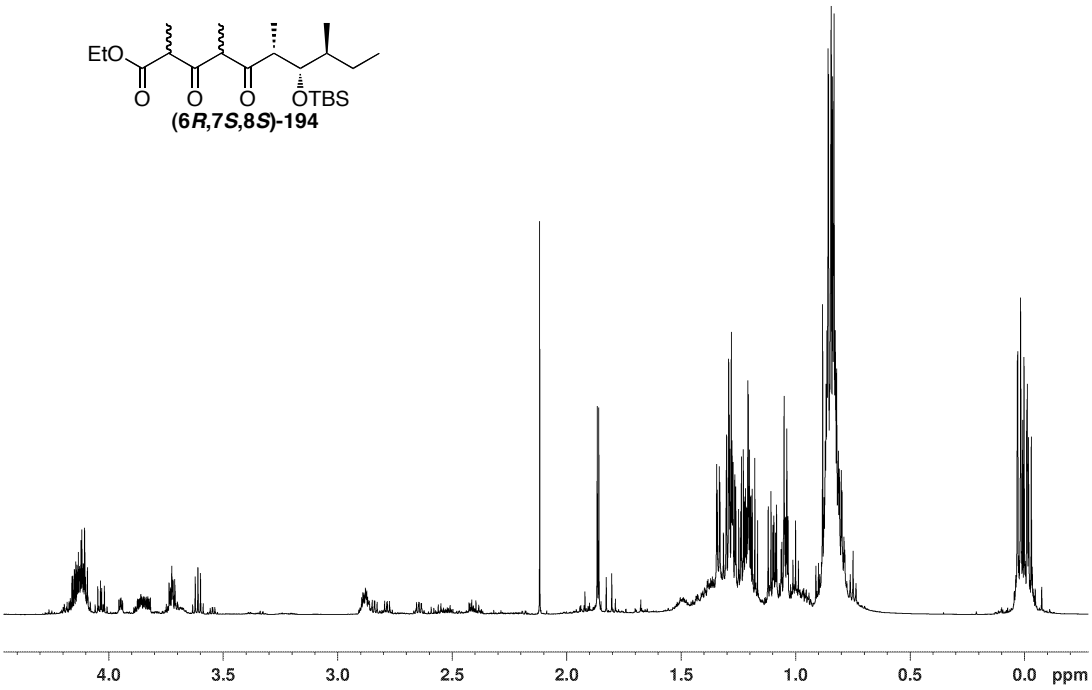

Figure B15: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-194** in $CDCl_3$.

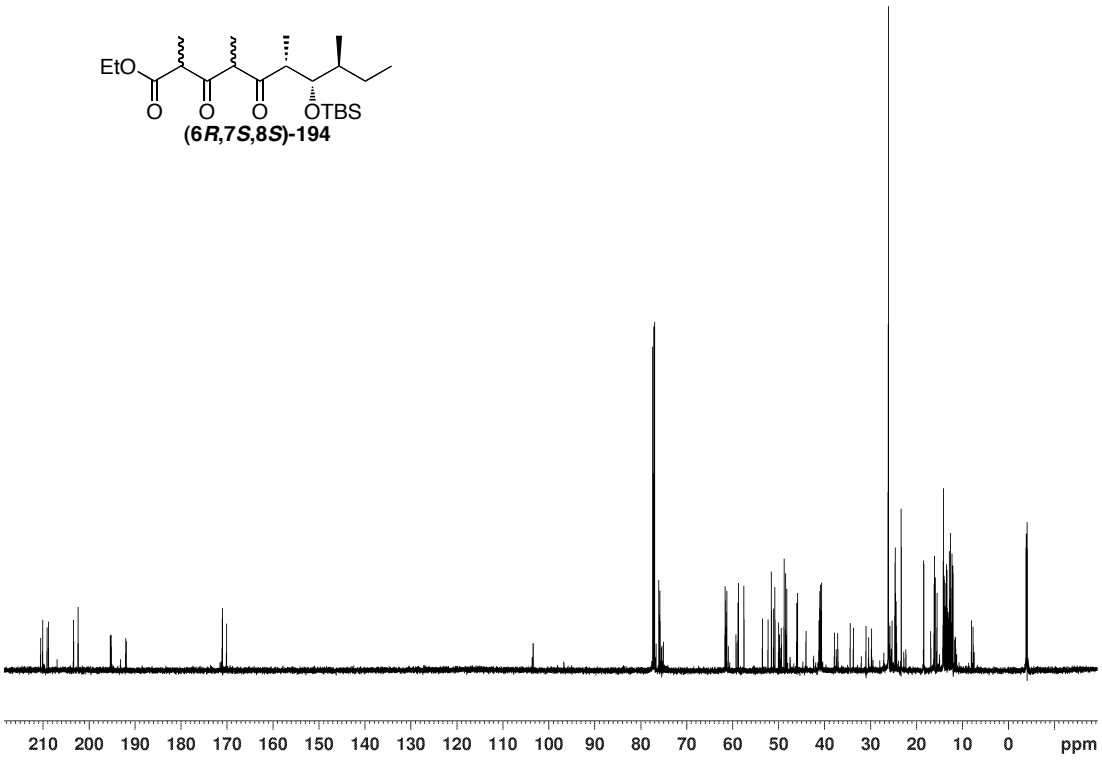

Figure B16: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-194** in $CDCl_3$.

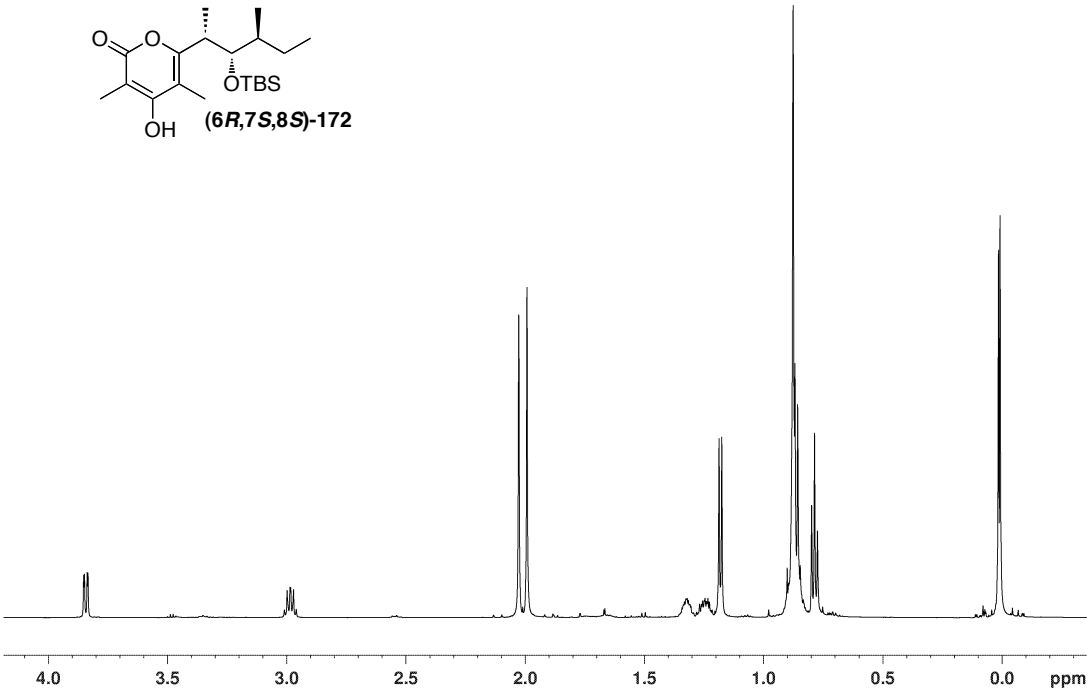

Figure B17: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-172** in $CDCl_3$.

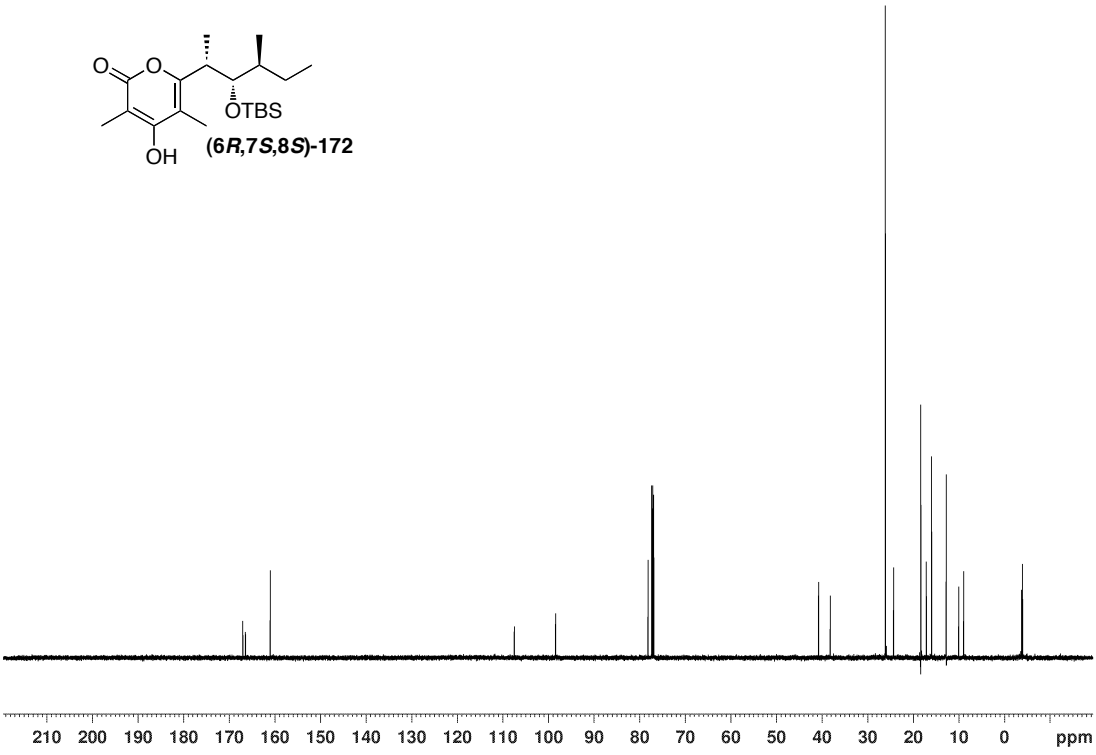

Figure B18: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-172** in $CDCl_3$.

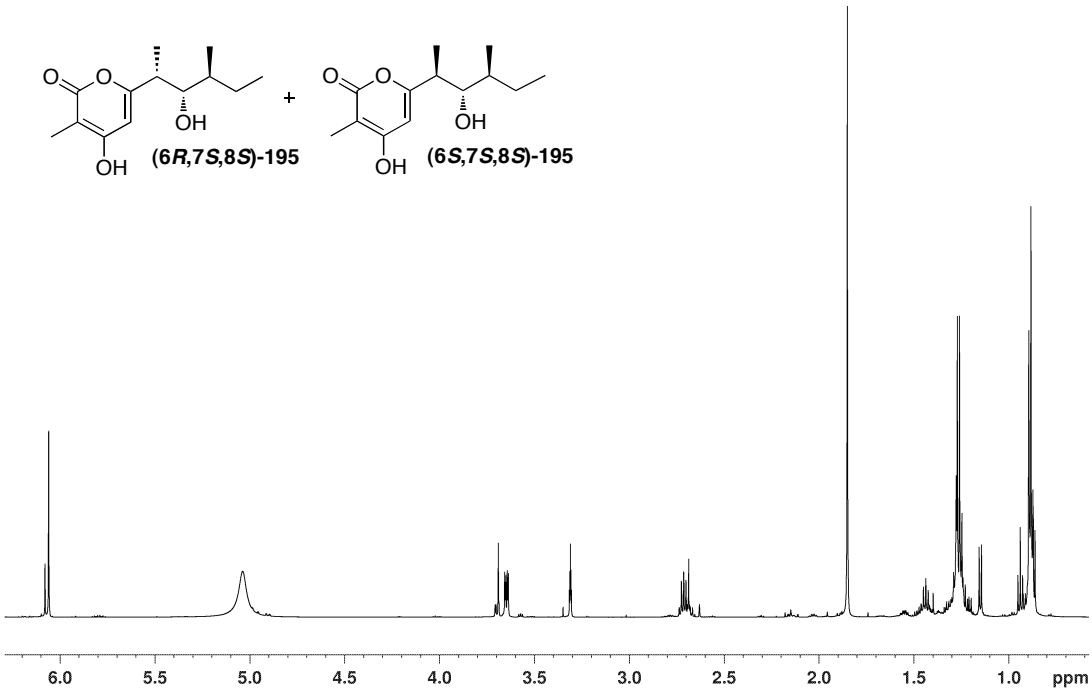

Figure B19: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-195**/**(6*S*,7*S*,8*S*)-195** in MeOD.

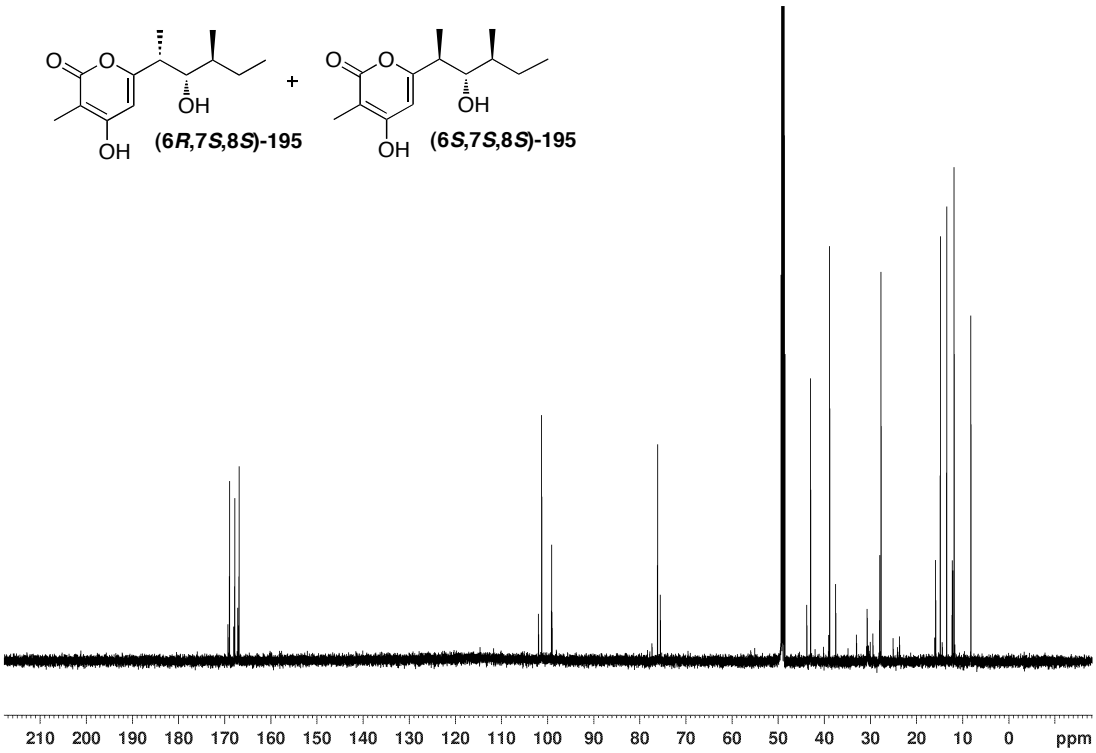

Figure B20: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-195**/**(6*S*,7*S*,8*S*)-195** in MeOD.

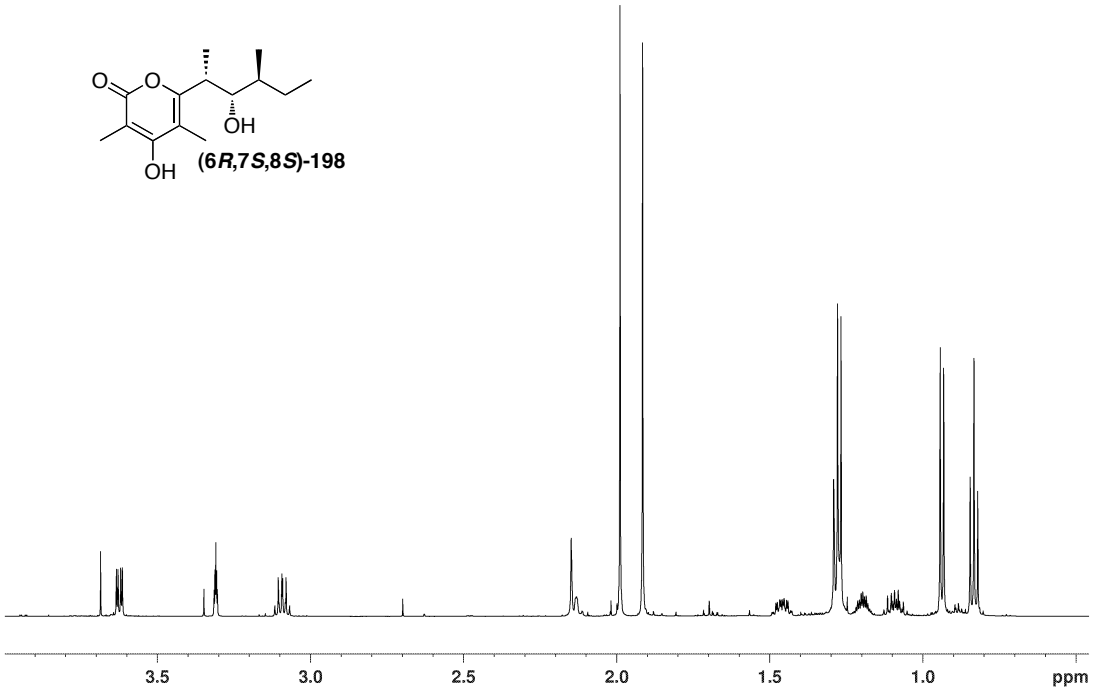

Figure B21: 600 MHz ^{1}H NMR spectrum of **(6*R*,7*S*,8*S*)-198** in MeOD.

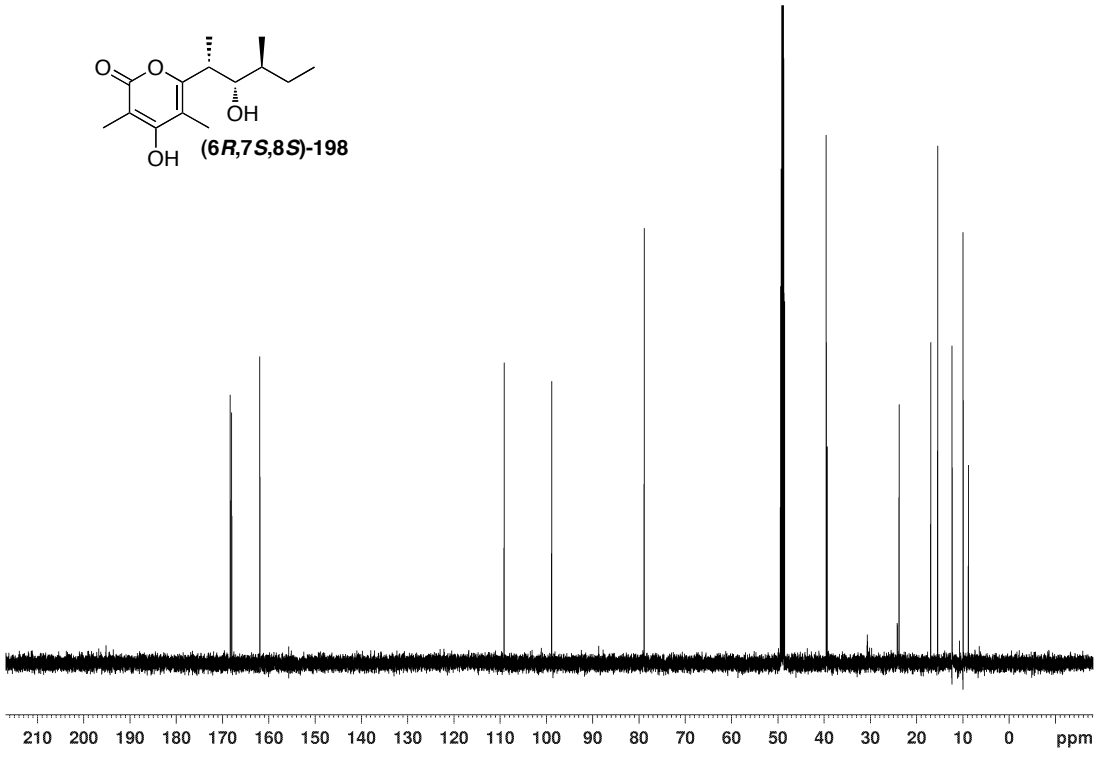

Figure B22: 151 MHz ^{13}C NMR spectrum of **(6*R*,7*S*,8*S*)-198** in MeOD.