Total Synthesis of Auripyrone A and Related Metabolites

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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Declaration

I declare that the material presented in this thesis is the culmination of original work conducted by the author and that none has been previously submitted for any other degree at any university. To the best of my knowledge, this thesis does not contain any material previously published, or written, by any person except where acknowledgment by citation of the original publication is made in the text.

Troy Lister

24th February 2006

"We act as though comfort and luxury were the chief requirements of life, when all that we need to make us happy is something to be enthusiastic about."

Albert Einstein

Acknowledgements

I wish to first and foremost sincerely thank my supervisor, Dr. M.V. Perkins. After completing my honours degree under his guise, I had no hesitation in deciding to continue my education through research in his lab. The past few years have been tremendously enjoyable and fulfilling and I thank 'Dr. Mike' for the opportunity he has given me to grow and succeed in a field which I am passionate to be a part of. As a man of boundless wisdom and a contagious smile, Dr. Perkins was seemingly never short of advice and support when things went awry. I am very grateful for the freedom I have been given to explore and grasp the subtleties of organic synthesis, but also for the wealth of knowledge and ability that Dr. Mike has passed on to me. It is testament to his teachings, support and profound understanding of natural product synthesis that I am able to submit the dissertation that follows in under three years.

Many thankyous must also go to the various academic staff whose teachings and support during my years as an undergraduate student have given me the foundation and skills in chemistry that enabled my pursuit of a PhD. In particular, Prof. Rolf Prager, who has followed my research career closely and whose endless knowledge has been invaluable. Also, Dr. Martin Johnston, Dr. Gordon Elsey, Prof. Kevin Wainwright and Prof. Bill Adcock for their many contributions.

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I wish to thank my loving family and friends for their boundless support and encouragement that has enabled me to pursue a dream. I especially wish to thank Mum and David, whose love and support have given me the opportunity and ability to make my dreams come true and Kate and Bryan for their love, friendship and smiling faces.

The following list represents publications that have resulted from research outlined in this thesis and presentations that were given at various symposia.

Publications[📖]

1. Total Synthesis of a Hemiacetal Polypropionate from *Siphonaria australis*. Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004**, 57(8), 787-797.

2. Total Synthesis of Auripyrone A
Lister, T.; Perkins, M. V. *Angew. Chem. Int. Ed.* **2006**, 45(16), 2560-2564.

3. A retro-Claisen Approach to Dolabriferol
Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, 8(9), 1827-1830.

Presentations

The Synthesis of Two Marine Polypropionates from *Siphonaria australis*.
Poster presentation at the 19th RACI Organic Conference, Lorne, VIC, 6th-11th July, 2003.

Towards a Total Synthesis of Dolabriferol.
Oral presentation delivered at the Adelaide Organic Symposium, Adelaide, SA, December 2003.

Forays in Total Synthesis: The retro-Claisen Rearrangement of Marine Natural Products.
Poster presentation at the 39th National Organic Chemistry Symposium, Salt Lake City, Utah, 12th-16th June, 2005.

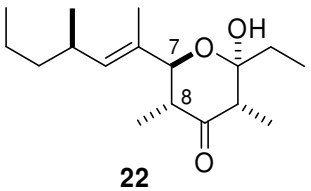
Adventures in the Synthesis of Polypropionate Natural Products
Oral presentation delivered at RACI Connect 2005, Sydney, NSW, 3rd-7th July, 2005.

📖 Reprints (and/or preprints) are contained within Appendix C.

Abstract

In recent decades the emergence of marine polypropionate natural products as compounds of diverse structural complexity and intriguing biological activity has influenced the advancement of asymmetric synthesis and predicated detailed studies of marine ecology. The introductory chapter of this thesis explores the nature of marine natural products, including their structure, biological activity and biosynthesis. Additionally, a brief review of the aldol reaction is presented. This well established biomimetic chemical transformation underpins polyketide synthesis and was utilised extensively in the research contributing to this dissertation.

Chapter Two describes the first asymmetric total synthesis of the two marine polypropionates isolated from specimens of *Siphonaria australis* by Hochlowski *et al.* in 1984. Spectroscopic analysis revealed hemiacetal **22** and ester **23** to be identical to the secondary metabolites extracted from the marine pulmonate. The synthetic approach to hemiacetal **22** utilised lactate derived ketone (*S*)-**67** to control the configuration of the C7 and C8 stereocentres and involved the discovery of a mild protocol for the synthesis of trimethylsilyl enol ether **109**, which was employed for a Mukaiyama aldol homologation reaction. Additionally, ester **23** was synthesised from hemiacetal **22** *via* a retro-Claisen fragmentation.



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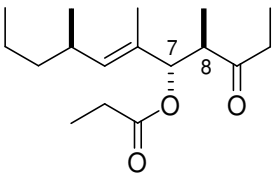

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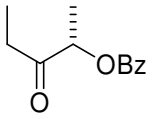
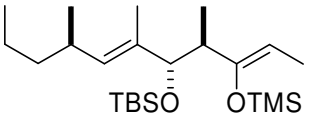


(*S*)-**67**



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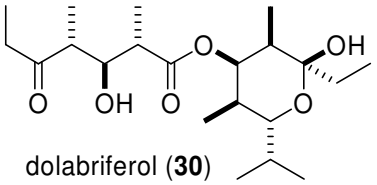
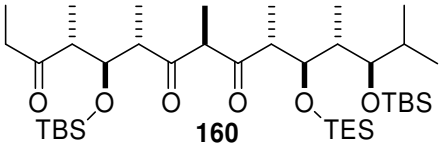
The retro-Claisen approach utilised in the synthesis of ester **23** was extended in Chapter Three to serve as the pivotal transformation in an attempted total synthesis of the unusual marine polypropionate dolabriferol (**30**). The strategy toward

dolabriferol (**30**) involved an iterative homologation of chiral ketone (*S*)-**67** to install all but one of the requisite stereocentres in the natural product. Chemoselective deprotection of acyclic precursor **160** gave the elaborate 2,4,6-trioxaadamantane **167**, whose participation as a protecting group mimic lead to the formation of ester **169** after reaction of the polycycle **167** with base. The synthesis of ester **169**, which represents a direct precursor to dolabriferol (**30**), was achieved in 16 steps with an overall yield of 24%. Unfortunately, a robust protecting group on ester **169** prohibited a synthesis of dolabriferol (**30**), but intriguingly in one deprotection of ester **169** with aqueous hydrofluoric acid, spiroacetal **172** was isolated.



dolabriferol (**30**)



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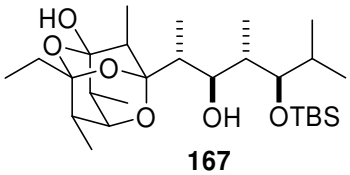

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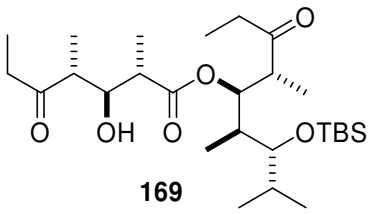

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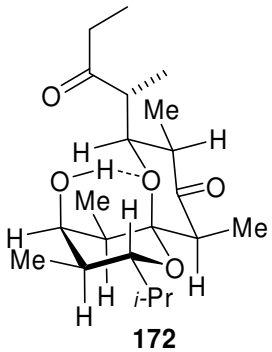
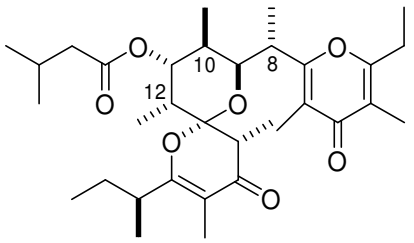


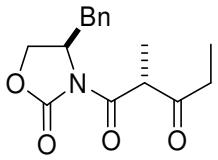
172

Chapter Four describes the first total synthesis of cytotoxic marine polypropionate auripyrone A (**78**) and establishes the absolute configuration of this important natural product as that depicted for compound **78**. The requisite C8-C12 stereopentad of auripyrone A (**78**) was formulated from Evans' dipropionate equivalent **53** in a double stereodifferentiating aldol reaction, followed by *syn*-reduction to give diol **206**. Differentiation of the secondary alcohols in compound **206** was achieved by migration of the PMB protecting group and protection at C11 with the requisite acyloxy group of auripyrone A (**78**). Differential protection was critical to achieving

selective spiroacetalisation to afford the unique spiroacetal dihydropyrone core of the natural product. The utility of LiHMDS for highly selective double stereodifferentiating aldol homologations of sensitive fragments is also discussed. This mild aldol protocol was pivotal to forming the carbogenic skeleton of auripyrone A, in particular, elaborate adduct **278**.



auripyrone A (**78**)



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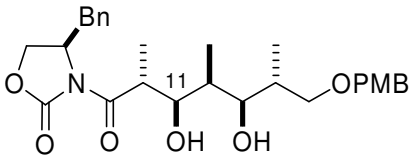

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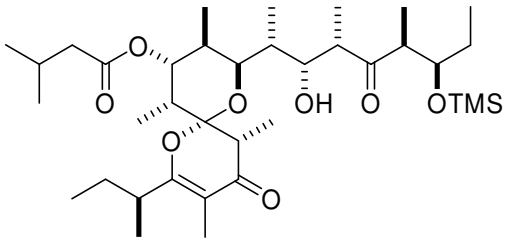

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Glossary

°C	degrees Celsius
Δ	heat
4Å	4 angstroms
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
app	apparent (^{1}H NMR spectra)
APT	attached proton test (^{13}C NMR spectroscopy)
aq	aqueous
atm	atmosphere
$BF_3{\cdot}OEt_2$	boron trifluoride-diethyl ether complex
$BH_3{\cdot}SMe_2$	borane-dimethyl sulfide complex
Bn	benzyl
bp	boiling point
Bu_2BOTf	dibutylboron triflate
tert-BuOH	*tertiary*-butanol
n-BuLi	butyllithium
Bz_2O	benzoic anhydride
c	concentration (g/100 mL)
ca.	*circa* (approximately)
Calcd.	calculated
cat.	catalytic
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
COSY	correlation spectroscopy
δ	chemical shift (parts per million)
de novo	from the beginning
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
$^c Hex_2BCl$	dicyclohexylboron chloride
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMP	Dess-Martin Periodinane
	1,1,1-triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1*H*)-one
DMSO	dimethylsulfoxide
ds	diastereoselectivity
E	*entgegen* (opposite)
e.e.	enantiomeric excess
e.g.	*exempli gratia* (for example)
EI	electron impact
EIMS	electron impact mass spectroscopy (spectrum)
eq	equivalents
ESI	electrospray ionisation
et al.	*et alia* (and others)
Et	ethyl
ether or Et_2O	diethyl ether
EtCOCl	propionyl chloride
EtMgBr	ethylmagnesium bromide
Et_3N	triethylamine
$(EtO)_2CO$	diethyl carbonate
EtOH	ethanol
FGI	Functional Group Interconversions
HF	hydrofluoric acid
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy (spectrum)
Hünig's Base	*N*,*N*-diisopropylethylamine
Hz	hertz
i.e.	*id est* (that is)

^{i}Pr	*iso*-propyl
^{i}PrMgCl	*iso*-propylmagnesium chloride
IR	infrared
J	coupling constant (Hz)
$KBrO_3$	potassium bromate
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
lit.	literature
$LiAlH_4$	lithium aluminium hydride
$LiBH_4$	lithium borohydride
LSI	liquid secondary ionisation
M^+	molecular ion (mass spectrum)
Me	methyl
MeCN	acetonitrile
Me_2NEt	dimethylethylamine
MeOH	methanol
MHz	megahertz
mmol	millimole
mol	mole
m.p.	melting point
MS	mass spectrum
m/z	mass-to-charge ratio
$NaBH_4$	sodium borohydride
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
ν_{max}	infrared absorption maxima (cm^{-1})
OTf	trifluoromethanesulfonate (triflate)
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzyl chloride
PMP	*para*-methoxyphenyl

PPh_3	triphenylphosphine
ppm	part per million
PPTS	pyridinium *para*-toluenesulfonate
pyr	pyridine
R_f	retention factor
rt	room temperature
sat.	saturated
SiO_2	silica gel
SmI_2	samarium(II) iodide
SO_3	sulfur trioxide
$Sn(OTf)_2$	tin(II) trifluoromethanesulfonate
TAS-F	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
tlc	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
™	trade mark
p-TsOH	*para*-toluenesulfonic acid
Z	*zusammen* (together)
<	less than
>	greater than

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Chapter One

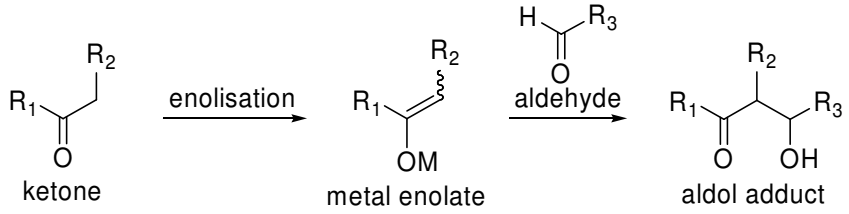
Introduction: Marine Natural Products: Biological Activity, Structure and Synthetic Approaches

Chapter One

Introduction: Marine Natural Products: Biological Activity, Structure and Synthetic Approaches

The following chapter introduces marine natural products, with a particular focus on the biosynthesis, biological activity and structure of polypropionate derived secondary metabolites. The strategies employed by the organic community that underpin natural product synthesis will also be discussed, with a strong emphasis on the aldol reaction which is the pivotal technique for efficient, asymmetric polypropionate assemblage.

The Aldol Reaction



1.1 Investigating Marine Natural Products

Natural product chemistry remains the principal driving force for progress in organic chemistry. The dominance of this discipline continues, due in part to Nature's boundless supply of inspiringly complex, structurally challenging molecules that require constant innovation in methodology to facilitate their synthesis. For many years terrestrial species were the primary source of natural products. However, in recent decades the focus has shifted to the oceans, which are providing an abundance of structurally unique natural products, accumulated in marine invertebrates such as sponges, tunicates, bryozoans and molluscs. Indeed, from relatively humble beginnings the isolation and study of marine natural products has escalated and now

exceeds 10000 (as of 2001),[1] with 656 compounds being reported in the literature for the year 2003 alone.[2]

Significant numbers of marine natural products are reported to display biological activity, often at potent levels. This intriguing aspect is habitually hindered by the sparing quantities of material isolated from the natural source (milligram to microgram amounts), which prohibits harvesting for thorough evaluation and testing. Additionally, ambiguous relative and absolute stereochemistry of such compounds motivates targeted syntheses.

1.2 Biological Activity of Marine Natural Products

The serious search for pharmacologically useful compounds from marine organisms probably began in 1969 with Weinheimer and Spraggins discovery of significant quantities of prostaglandins in the gorgonian *Plexaura homomalla*.[3] Indeed, from 1969-1999, almost 300 patents were issued on biologically active marine natural products.[1] It thus comes as no surprise that the main support for research on marine natural products over the past 30 years has come from the study of biologically active compounds of potential therapeutic use.[4]

The range of biological activity associated with marine natural products is broad, encompassing both life-threatening toxicity and beneficial preventative activity. While the study of potentially fatal paralytic and diarrhetic properties of some toxic marine compounds is of importance to prevent illness or death arising from accidental ingestion or contact with the toxic organism, much of the focus in bioactive marine natural products is on compounds with potential pharmacological applications. Many compounds have shown potent antimicrobial and antifungal, cytotoxic or antiviral, antibiotic or anti-inflammatory and immunomodulatory activity, making them prime candidates for medical trials. Although a marketable bioactive marine natural product has yet to come to fruition, several contenders have reached advanced human clinical trials. For example, ecteinascidin 743 (**1**),[5] an anti-cancer drug isolated from *Ecteinascidia turbinata* (tunicate), has reached phase III

clinical trials,[1] which is the most advanced stage of testing of any marine derived compound. Dolastatin-10 (**2**),[6] an anti-cancer drug isolated from *Dolabella auricularia* (sea hare), discodermolide (**3**),[7] an anti-cancer drug isolated from *Discodermia dissoluta* (sea sponge) and bryostatin 1 (**4**),[8] an anti-cancer drug isolated from *Bugla neritina* (bryozoan), have all entered phase II clinical trials[1] (Figure 1.1). Significantly, all the material required for the clinical trials of discodermolide (**3**) has come from total synthesis.[9] This reflects the contribution that total synthesis makes to pharmacology, but also highlights the limiting factor in the use of marine secondary metabolites in pharmacological studies, namely the availability of the biomass from which the metabolite is isolated.

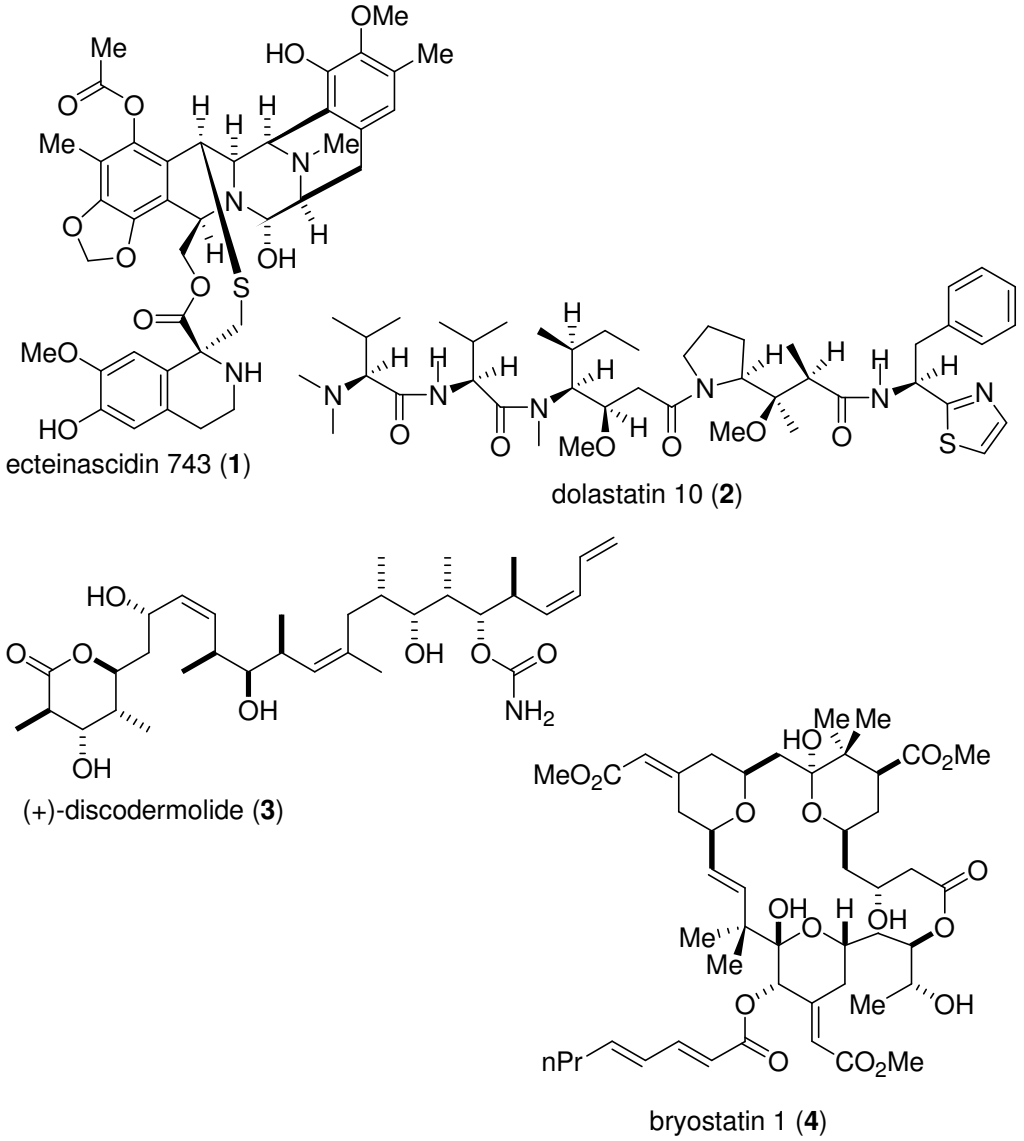


Figure 1.1: *Biologically active secondary marine metabolites.*

While the activity of many secondary metabolites towards human cell lines can be explained through the study of structure activity relationships (SAR), it is unclear what advantage, if any, such compounds exhibit for the source organism. It is suspected that some bioactive compounds play a role in chemical defence. For instance, opisthobranchs (marine sea hares) show a surprising immunity to predation, despite having partial, and in some cases total evolutionary loss of the protective shell.[10] As such, the array of secondary metabolites isolated from these organisms may act as a defence mechanism to aid survival. It is also suggested that micro-organisms play a crucial role in marine ecology, such that potent bioactive metabolites are produced from symbiotic relationships between marine organisms and micro-organisms.[11] In general, the confusion surrounding the activity of many secondary metabolites stems from an incomplete understanding of their biosynthetic origin.

1.3 Biosynthesis of Marine Natural Products

While many secondary marine metabolites display inherent bioactivity, numerous compounds have also been isolated from marine organisms that exhibit no biological function toward human cell lines. Of course this doesn't mean that the metabolite is inactive in the source organism, but the origin and purpose of such metabolites is unclear. In general metabolites, whether active or inactive, are acquired through bioaccumulation, biotransformation or biosynthesis.

The principal source of natural products in marine organisms appears to be dietary (bioaccumulation).[10] For example, high concentrations of algal secondary metabolites have been isolated from the digestive glands of *D. auricularia*.[12] And, despite the geographic constancy displayed in the metabolite profile of Siphonariids,[13] the connection between molluscan predators and their algal or invertebrate diet has been confirmed.[10] Often the indicator for secondary metabolite bioaccumulation is the confinement of such metabolites to the digestive glands, where they would appear to be unable to aid the organism in defence.

It has been shown that marine organisms are able to acquire secondary metabolites by either modifying metabolites sequestered from their specific prey or requisitioning micro-organisms for symbiotic metabolite production. For instance, chloroplasts sequestered from algae by sacoglossan molluscs remain active for several days, synthesising molecules useful to the mollusc for both nutrition and diet.[10]

Although *de novo* biosynthetic metabolite production in marine organisms has been demonstrated,[10] such studies are hindered by the limited understanding of metabolic processes in the marine environment. A meticulous biosynthetic experiment to confirm the *de novo* production of metabolites from *Siphonaria denticulata* will be presented below in the context of polypropionate biosynthesis (Section 1.4.1).

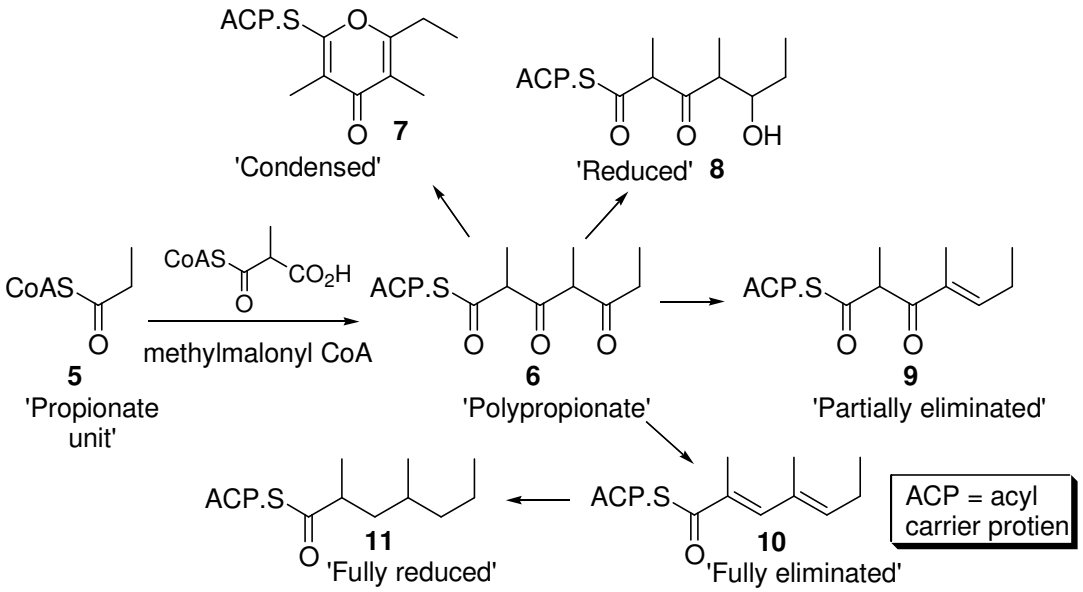
Ascertainment of the existence of *de novo* biosynthesis of metabolites in marine organisms continues to influence studies in marine ecology. To this end, it has been suggested that it may be possible to predict the origin of secondary metabolites in nudibranch molluscs by probing their geographical variations in a given species. Hence, molluscs that contain identical chemical constituents regardless of their geographic residence are probably capable of *de novo* biosynthesis, where as those that demonstrate significant variation in their metabolite composition likely obtain these from nutritional resources.[10]

1.4 Polypropionate Marine Natural Products

Polypropionate metabolites are common products of metabolism in bacteria, insects and fungi.[14] Indeed, macrolide and polyether derived metabolites from terrestrial organisms represent important sources of commercial antibiotics. Structurally and biosynthetically similar, these two classes of bioactive metabolites use propionate units as a biosynthetic building block.[14] In recent decades, the emergence of structurally distinctive polypropionate metabolites from marine organisms has instigated detailed studies to probe their biosynthetic origin and to produce a pharmacologically useful drug. While various marine polypropionate compounds are

inherently bioactive, generally the metabolites exhibit no apparent activity toward human cell lines. It is believed however, that even the inactive compounds impart an ecological influence on the organism that produces them. Despite a wealth of compounds possessing polypropionate fragments, wholly polypropionate derived natural products are comparatively rare, with the Mollusca proving to be the primary source.[10] Indeed, these compounds appear to characterise the metabolism of many opisthobranchs and pulmonates.[15]

The polypropionate motif, represented as tricarbonyl **6** in Scheme 1.1, is proposed to evolve from enzymatic condensation of propionate units (**5**).[15] This leads to the characteristic structural feature of polypropionate metabolites, namely a linear carbon chain possessing alternating methyl bearing and oxygen bearing carbon centres. Biosynthetic propionate homologation is routinely accompanied by transformation of the growing chain as depicted in Scheme 1.1. Condensation of the polypropionate motif leads to pyrone **7**, which is thought to be an important structural feature for bioactivity in polypropionate metabolites. Compound **8** arises from reduction of the polypropionate motif. This common transformation introduces the 'aldol' motif. Subsequent elimination of the alcohol groups from reduced compound **8** leads to partially eliminated **9** or fully eliminated **10**. This in turn gives rise to fully reduced **11**, after reduction of the double bonds in **10**.



Scheme 1.1: *Potential processive transformations of the polypropionate motif* ***6****.*

It has been suggested that modification of the polypropionate chain is *via* a processive strategy rather than a post-chain elongation event.[13] These various functionalisation tactics lead to compounds of immense structural diversity, high levels of oxygenation and elaborate stereochemical arrays, some of which are depicted in Figure 1.2. Denticulatin A (**12**) and B (**13**)[16] exhibit examples of reduced, eliminated and fully reduced motifs in addition to a hemiketal moiety. Siphonarins A (**14**) and B (**15**)[17] possess a γ-pyrone ring and an intricate spiroacetal, while diemenensin A (**16**)[18] displays further evidence of eliminated and full reduced transformations, as well as a β-pyrone ring.

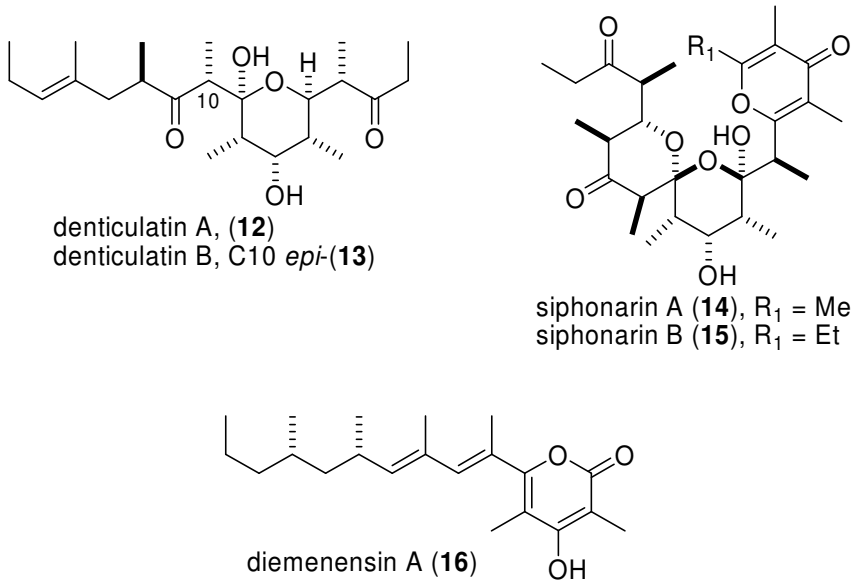
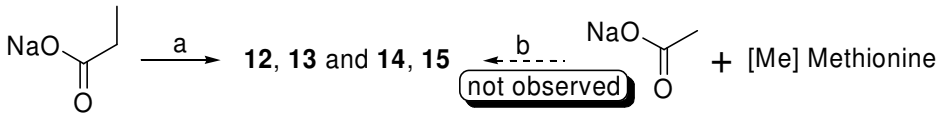


Figure 1.2: *Structural diversity in marine polypropionate metabolites.*

Cyclic ketals are a common motif in polypropionate derived secondary metabolites and arise from nucleophilic attack of a hydroxyl group on a carbonyl carbon centre further down the linear chain. However, it has been suggested that such cyclic polypropionates represent thermodynamic, i.e. non-enzymatic, cyclisation products of unstable acyclic precursors.[13] As such, it has been proposed that these acyclic compounds may constitute the true marine natural product, meaning that many ketal containing 'metabolites' are isolation artefacts.[13] This point will be elaborated below.

1.4.1 Polypropionate Biosynthesis

The study of polypropionate biosynthesis centres on determining both the origin of the secondary metabolites (from epibionts, endobionts or *de novo* biosynthesis) and the nature of polypropionate assemblage (from propionate or from acetate plus methionine units). This research is primarily conducted by exposing the marine organism to ^{14}C radio-labelled material for periods of time and subsequently determining the extent of ^{14}C fixation (if any) in the isolated metabolites. Early work by Ireland and Scheuer[19] and also Cimino and co-workers[20,21] involved placing molluscs in a habitat that contained ^{14}C-labelled sodium hydrogen carbonate. Analysis of the isolated polypropionates revealed they contained the radioactive label. Meticulous studies by Garson *et al.* determined the nature of polypropionate assembly in two specimens of mollusc. Specimens of *Siphonaria denticulata* injected with [1-^{14}C]propionate, were found to produce denticulatins A (**12**) and B (**13**) that incorporated the radioactive label.[22] In contrast, exposure to [1-^{14}C]acetate failed to produce similarly labelled metabolites.[22] An analogous study showed that ^{14}C fixation was observed in siphonarins A (**14**) and B (**15**) after injection of [1-^{14}C]propionate into the foot tissue of *S. zelandica*.[15] These results showed that molluscs were capable of synthesising polypropionate metabolites *de novo* and that the propionate unit (C_3) (path a) and not acetate (C_2) plus methionine (C_1) units (path b) were used in the biosynthetic pathway (Scheme 1.2).[15]



Scheme 1.2: *Alternative biosynthetic pathways to polypropionates denticulatin A (**12**) and B (**13**) and siphonarin A (**14**) and B (**15**).*

1.4.2 Cyclisation Modes of Polypropionates

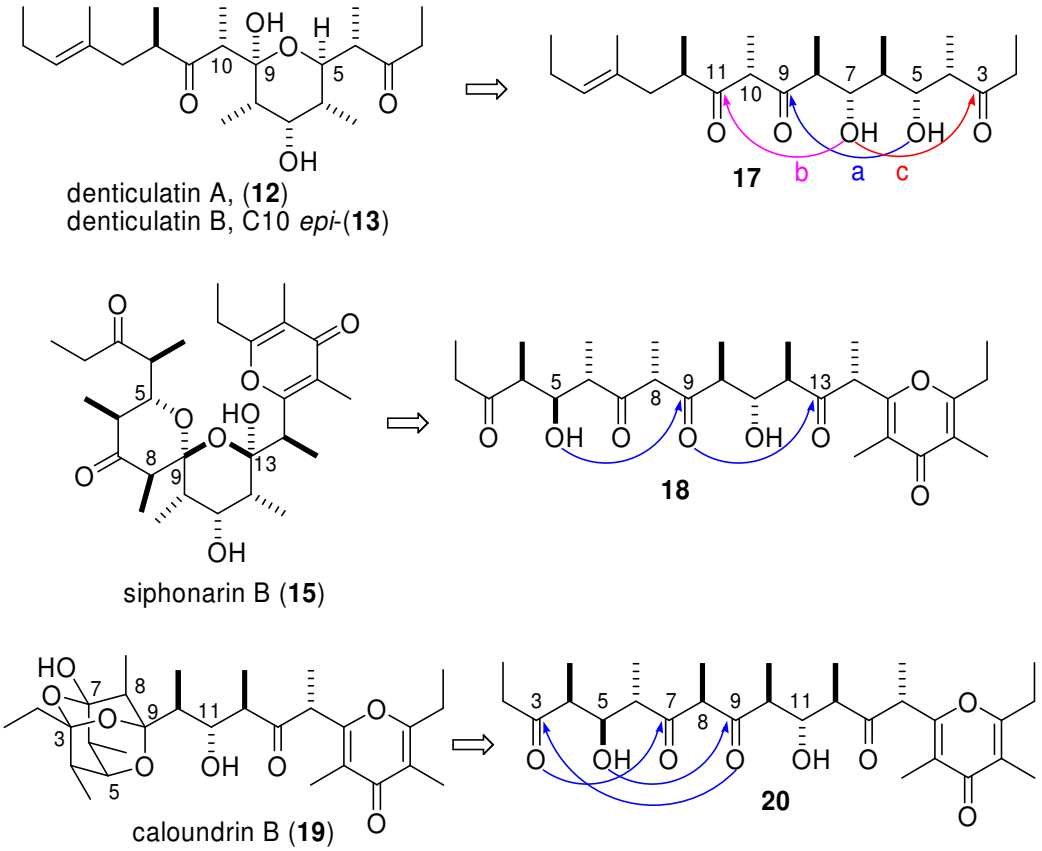
Polypropionate derived marine natural products, particularly those from Siphonariids, frequently display ketal or pyrone functionality.[13] This propensity for yielding cyclic compounds predicates an understanding of the modes of their formation, which is best achieved by unravelling the cyclic moieties to reveal the putative acyclic precursors. Often performing this retro-'biosynthetic' analysis

uncovers an acyclic precursor with potential myriad of cyclisation modes *i.e.* multiple nucleophilic (hydroxyl) and electrophilic (carbonyl) sites for cyclisation. It has been well established that the formation of cyclic polypropionates is determined by thermodynamic factors related to the oxidation state of the carbon centres and the absolute configuration of the hydroxyl and methyl groups in the acyclic precursor. This infers that in cases where more than one cyclisation mode is possible, the mode leading to the most thermodynamically favoured product will prevail. Six membered ketals dominate the cyclic secondary metabolites, and as such the least energetic product will adopt a chair conformation that has the largest alkyl groups in the sterically least demanding equatorial positions and where stabilising anomeric influences are maximised *i.e.* acetal hydroxyl groups are axially substituted. The cyclisation modes of several known polypropionate natural products are shown in Scheme 1.3, where cyclisation is depicted as nucleophilic intramolecular attack of a hydroxyl group upon a carbonyl group further down the chain of the acyclic precursor.

Unravelling denticulatin A (**12**) and B (**13**) reveals acyclic precursor **17**, which could cyclise *via* three different hemiacetal-forming modes; (a) the C5 hydroxyl adding to the ketone at C9, (b) the C7 hydroxyl attacking the C11 carbonyl, or (c) the C7 hydroxyl adding to the C3 carbonyl (Scheme 1.3).[23] Denticulatin A (**12**) and B (**13**) form as a result of cyclisation mode (a), which is the most thermodynamically favoured pathway as the ring alkyl groups occupy the equatorial positions and the axial C7 hydroxyl participates in stabilising hydrogen bond interactions with the anomeric oxygen.

Siphonarin B (**15**)[17] and caloundrin B (**19**)[13] exemplify the influence that product thermodynamic stability and the relative configuration of the stereocentres in the acyclic precursor has on the potential cyclisation modes. Acyclic precursors **18** and **20** leading to siphonarin B (**15**) and caloundrin B (**19**), respectively, are identical, other than the configuration of the stereocentre at C8 (they are epimeric at C8). The cyclisation mode leading to siphonarin B (**15**) utilises a cascade process, with the hydroxyl at C5 adding to the ketone at C9, followed by attack of the nucleophile generated at C9 upon the carbonyl at C13. This leads to formation of a highly

substituted spiroacetal in which all the alkyl substituents adopt the thermodynamically favoured equatorial position and the two ring oxygens, anomeric alcohol and C11 alcohol are all axially substituted.



Scheme 1.3: *Cyclisation modes of several marine polypropionates.*

The cyclisation mode leading to formation of the unusual 2,4,6-trioxaadamantane ring system in caloundrin B (**19**) also involves a cascade process. In this instance cyclisation occurs through attack of the hydroxyl at C5 upon the ketone at C9, followed by addition of the hydroxyl produced at C9 to the C3 carbonyl and finally coupling of the hydroxyl at C3 to the ketone at C7. This elaborate polycycle has all the ring oxygens in the anomerically stabilising axial position and the C3, C4 and C6 alkyl groups equatorially substituted. The methyl group at C8 adopts the axial position to avoid a destabilising *syn*-pentane interaction with the C6 methyl substituent. Energy calculations conducted by Garson *et al.*[24] showed that the formation of the 2,4,6,-trioxaadamantane in caloundrin B (**19**) requires less energy than the alternate spirocyclisation to give the C8 epimer of siphonarin B. Similarly,

additional calculations[24] showed that formation of the spiroacetal moiety in siphonarin B (**15**) is considerably more favourable than cyclisation to give the 2,4,6,-trioxaadamantane corresponding to the C8 epimer of caloundrin B. The 2,4,6,-trioxaadamantane moiety formed from precursor **18** would be destabilised by *syn*-pentane interactions between the C6 and C8 methyl substituents. Thus, the thermodynamic preference in these systems seems to be directly related to the *syn* vs. *anti* relationship between the C6 and C8 methyl groups in acyclic precursors **18** and **20**.[24] Given that siphonarin B (**15**) and caloundrin B (**19**) were isolated as co-metabolites from *S. zelandica*,[13] it is likely that epimerisation of the C8 methyl bearing centre (plausible given its location between two carbonyl groups) occurs at a rate comparable to cyclisation.

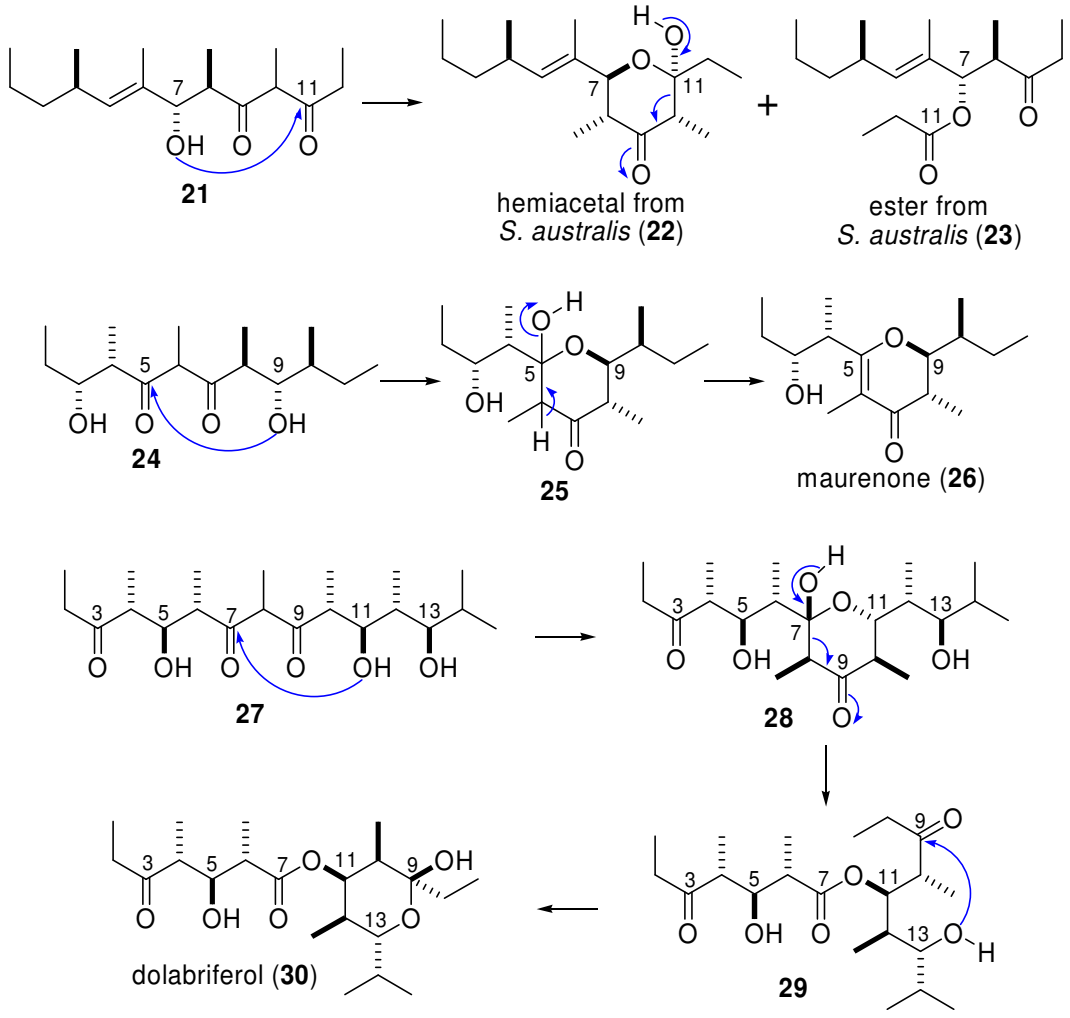
Despite recent propositions that the true nature of marine polypropionate metabolites is more closely related to the open chain precursor than the cyclic isolates, it is apparent that acetal moieties (particularly spiroacetals) are frequently characterised by the exhibition of biological activity and as such, a number of these cyclic compounds may in fact represent true secondary metabolites.

1.4.3 The Fate of Cyclic Polypropionates

While analysing the formation of acetal moieties of cyclic marine polypropionates in a retro-'biosynthetic' sense allows the synthetic chemist to accurately gauge a suitable strategy for controlled synthesis, including protecting group and oxidation state selection, in some instances such endeavours identify additional ambiguities. For instance, the formation of a hemiacetal moiety from an acyclic precursor is readily understood and in situations where multiple cyclisation modes exist, consideration of the thermodynamic requirements of the product can be invoked to explain why one particular mode dominates. However, on occasions it appears that the initially formed hemiacetal is prone to further manipulation. Scheme 1.4 illustrates this point with three examples.

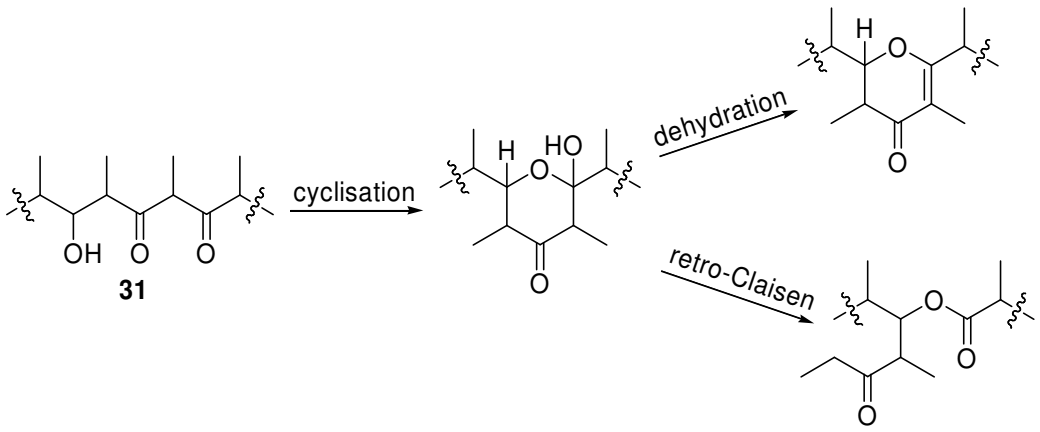
Hemiacetal **22** and ester **23** were co-isolates of the marine mollusc *S. australis*.[25] This fact seems to indicate that after cyclisation of precursor **21** to give the hemiketal **22**, subsequent retro-Claisen fragmentation of the cyclic moiety gave ester **23**.

Conversely, the dihydropyrone containing maurenone (**26**), isolated from *S. maura*,[26] appears to form from initial selective cyclisation of precursor **24** to give hemiacetal **25**, followed by subsequent dehydration to yield enone **26**. While not an unexpected result, given the propensity for *anti*-periplanar β-hydroxy ketones to undergo dehydration, this transformation is intriguing when compared to the previous and final examples (see below). Dolabriferol (**30**), isolated from *Dolabrifera dolabrifera*,[27] is one of the rare, non-contiguous marine polypropionates that have been unearthed in recent years.[28] The disruption of the polypropionate backbone in dolabriferol (**30**) appears to eventuate from retro-Claisen fragmentation of precursor hemiacetal **28** (which forms from selective cyclisation of acyclic compound **27**) to give acyclic ester **29**. Subsequent hemiketalisation of the alcohol at C13 onto the carbonyl carbon at C9 gives dolabriferol (**30**).



Scheme 1.4: *Hemiketal modification in several marine polypropionates.*

Interestingly, the fate of hemiacetal **25** in the maurenone pathway is different to that encountered for hemiacetals **22** and **28**. For reasons that are not clear, hemiacetal **25** undergoes exclusive dehydration, with no retro-Claisen product detected, while hemiacetal **22** shows partial fragmentation to ester **23** and hemiacetal **28** shows complete conversion to ester **29**. Hemiacetals **22** and **28** show no signs of dehydration. One might presume that the compounds were isolated differently, thus accounting for the different reactivity, but the extraction and purification techniques used in these examples, and generally for marine natural product isolation, were essentially the same. These results suggest that the fate of β-hydroxy-β-dicarbonyl systems, such as **31** (Scheme 1.5), is difficult to predict and seemingly uncertain in nature.



Scheme 1.5: *Ambiguous fate of β-hydroxy-β-dicarbonyl moieties such as* ***31****.*

1.5 Methods for Polyketide Synthesis

The wealth of polyketide derived natural (and non-natural) products, coupled with the emergence of this class of compounds as potentially potent therapeutic drugs, has motivated the advancement of polyketide synthesis. The pivotal requirement that all chiral drugs be formulated as optically pure compounds has lead to a recent renaissance in asymmetric organic synthesis. With a specific application to polyketide synthesis, vast research programs have been dedicated to improving the control (both regio- and stereochemical) and efficiency with which carbon-carbon bonds are formed and carbonyl moieties are reduced or reacted with nucleophiles.

The asymmetric reduction of carbonyl compounds (and indeed olefins) has been extensively reviewed, and given the limited examples of such transformations in this dissertation will not be elaborated. However, the aldol reaction, which is essentially a simultaneous carbon-carbon bond forming reaction and carbonyl reduction, was pertinent to the research presented herein and as such is discussed below.

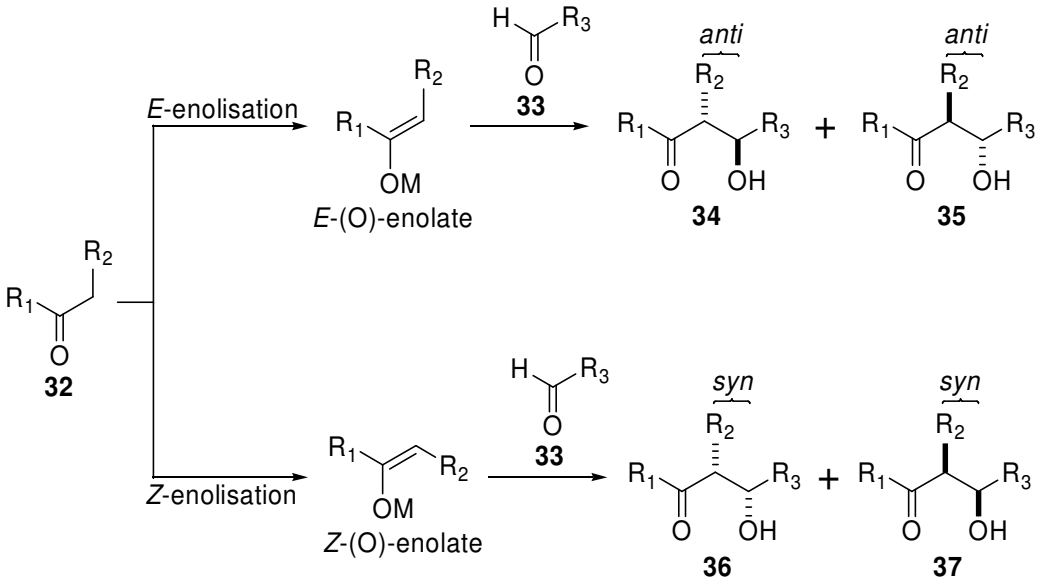
1.5.1 The Aldol Reaction

While several methods have emerged over the past 30 years to provide access to acyclic polyketide derived compounds with high levels of stereocontrol, i.e. pericyclic Claisen and Cope rearrangements, hetero-Diels-Alder reactions, crotyl- and allylmetallation and conjugate additions, the aldol reaction has prevailed as one of the most popular and influential means for carrying out stereoselective polyketide synthesis. To this end, extensive research programs have been dedicated to understanding and controlling the level and nature of stereoinduction exhibited by the aldol reaction.

The crossed aldol reaction (reaction between an acyclic ketone and acyclic aldehyde) emerged from the traditional aldol reaction/condensation (reaction between enolisable aldehydes) and the Claisen-Schmidt condensation as a biomimetic approach to polyketide synthesis. The biosynthesis of polypropionate metabolites is known to occur *via* the condensation of propionate (and/or acetate) equivalents, giving rise to the characteristic linear carbon chain with alternating centres of methylation and oxygenation. Given this, and the elaborate stereochemical arrays that result from this biosynthetic pathway, the crossed aldol reaction has been developed to provide strategies for predictable stereocontrolled chain elongation.

The modern aldol reaction utilises a stoichiometric, acyclic enolate formed by the treatment of a carbonyl compound (usually a ketone) with a strong base, or more recently with a combination of a Lewis acid and a weaker base. The nucleophilic enolate reacts with carbonyl compounds (typically aldehydes) to form a carbon-carbon bond and up to two new stereocentres. If the enolate is generated from an ethyl-type ketone (**32**), then reaction with an aldehyde (**33**) can give one of (or a mixture of) four possible products, namely the *anti* **34** and **35** and *syn* **36** and **37**

adducts shown in Scheme 1.6. If R_1, R_2 and R_3 are achiral then the reaction affords two sets of enantiomeric pairs (**34/35** and **36/37**). If any of R_1, R_2 and R_3 is chiral then all four products are diastereomers.



Scheme 1.6: *Possible products from reaction of the enolate of ketone* ***32*** *with aldehyde* ***33****.*

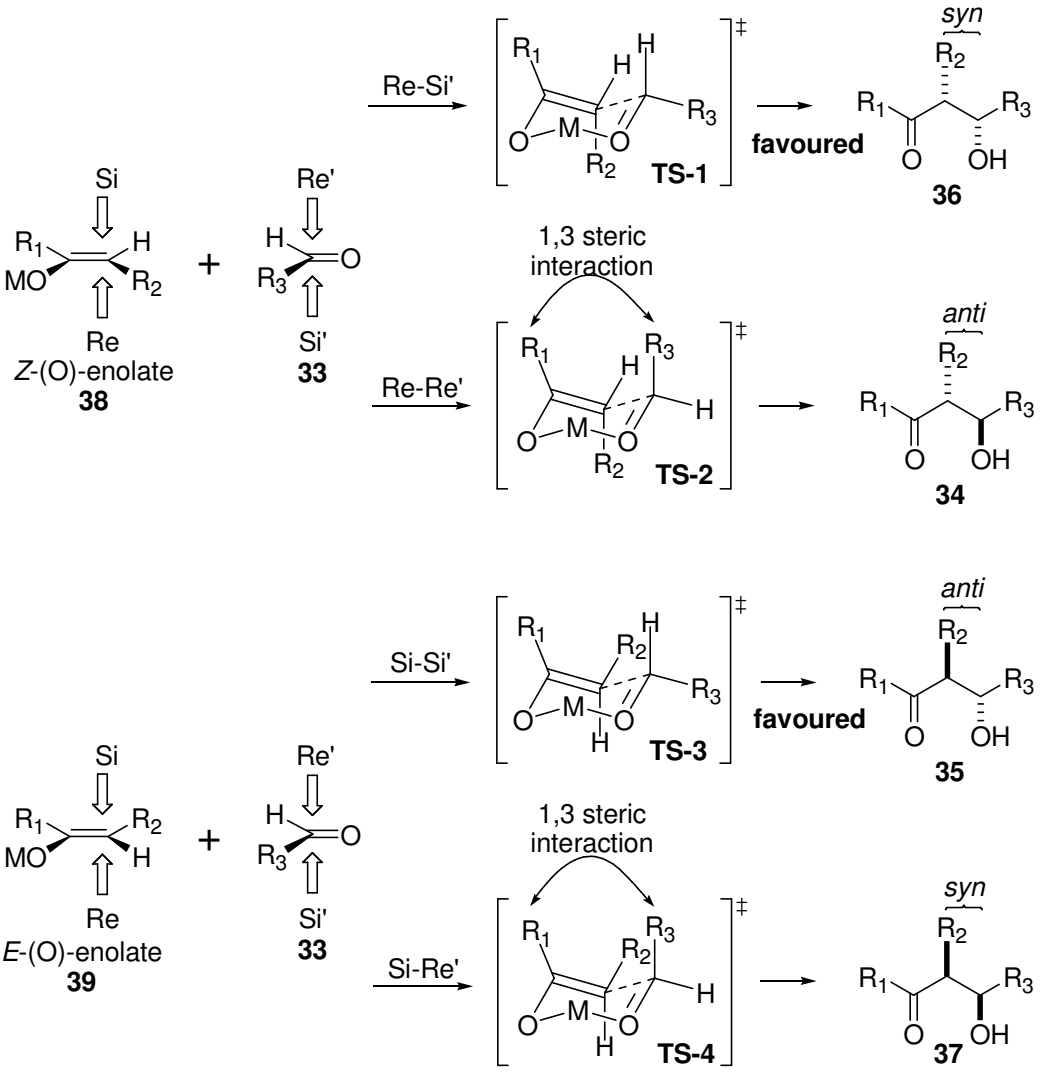
The directed aldol reaction has advanced significantly from the early discoveries. The primary focus has been controlling the inherent stereoinduction exhibited by this reaction to enable one of the four possible products to be synthesised selectively. A pivotal aspect in controlling the stereochemistry of aldol adducts is controlling the geometry of the enolate.

1.5.2 Controlling Enolate Geometry

Extensive research has shown that the *syn* vs. *anti* selectivity exhibited by the mixed aldol reaction can be directly related to the geometry of the enolate.[29-35] Thus, control of the enolate geometry is crucial for achieving efficient stereocontrol. In general, for reactions of achiral ethyl enolates with achiral aldehydes, *Z*-(O)-enolates* give *syn*-aldol adducts and *E*-(O)-enolates give *anti*-aldol adducts. This situation is also generally applicable to the equivalent reaction of chiral fragments,

* The naming of enolates relates to *Z*(*cis*)- or *E*(*trans*)-geometry, where the oxygen-metal substituent is designated higher priority than R_1.

but in such cases additional stereochemical features require consideration (see Section 1.5.3 for discussion).



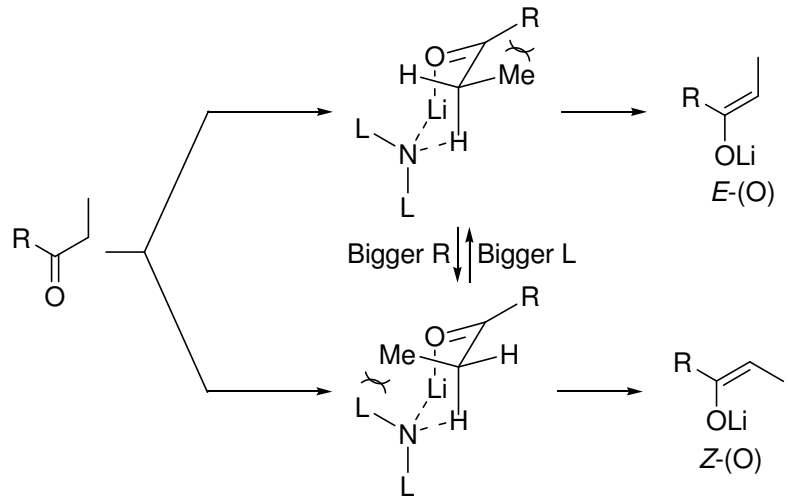
Scheme 1.7: *Stereochemistry of products from aldol reactions between Z-(O)- and E-(O)-enolates and aldehydes.*

Closed, six-membered cyclic Zimmermann-Traxler transition states[36] have been invoked to rationalise this stereochemical phenomenon. Scheme 1.7 shows that reaction of the *Re* face of *Z*-(O)-enolate **38** with the *Si'* face of aldehyde **33** will proceed *via* **TS-1** to give *syn*-aldol product[Φ] **36** (plus its enantiomer from the

[Φ] The '*syn*' and '*anti*' convention for assigning the stereochemistry of aldol products was introduced by Masumane.[37] With the main carbon chain drawn in a 'zig-zag' conformation, a *syn* relationship is defined where the two substituents in question are drawn both pointing into or out of the plane of the paper. By contrast, an *anti* relationship has the two substituents pointing to opposite sides of the plane of the paper.

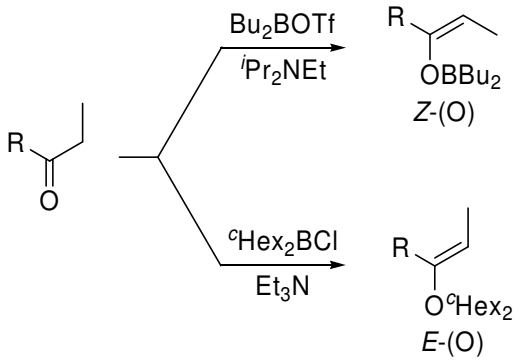
enantiomeric transition state). Alternatively, reaction of the *Re'* face of aldehyde **33** with the *Re* face of enolate **38** will proceed *via* **TS-2** to give *anti*-adduct **34** (plus its enantiomer from the enantiomeric transition state). The pathway leading to the *syn*-adduct is favoured because **TS-1** exists in a conformation where the alkyl group (R_3) of the aldehyde is in the favoured equatorial position. Conversely, transition state **TS-2**, leading to *anti*-aldol adduct **34**, experiences a destabilising 1,3 steric interaction between the alkyl group (R_1) of the enolate and the axial alkyl group (R_3) of the aldehyde. This destabilising interaction causes the energy barrier to **TS-2** to be higher than that to **TS-1**, which accounts for the fact that *Z*-(O)-enolates predominantly give *syn*-aldol products. Similarly, the preference of *E*-(O)-enolates (**39**) to react with aldehydes (**33**) through transition state **TS-3** over transition state **TS-4**, giving *anti*-adduct **35** and not *syn*-adduct **37**, is rationalised on the grounds that transition state **TS-4** is destabilised by 1,3 steric interactions between R_1 and R_3.

Given the critical role enolate geometry plays in determining the stereochemical outcome of mixed aldol reactions, significant research has probed not only conditions for selective enolate formation but also definitive confirmation of the enolates geometry. The wealth of experimental data shows that enolate geometry is dictated by: 1) the base employed; 2) the Lewis acid employed (and thus the metal coordinated to the oxygen of the enolate); 3) the substituents on the ketone; 4) the ligands attached to the Lewis acid metal and 5) the reaction conditions. However, not all enolates can be studied directly to determine their geometry and as such the geometry is often derived from the stereochemistry of the respective aldol adducts. The ability to 'capture' lithium enolates with trimethylsilyl chloride (TMSCl) to form stable silyl enol ethers has enabled the study of lithium enolate geometry through ^{1}H NMR spectroscopy.[38,39] In general it has been observed that more *E*-(O)-enolate is formed as the size of the ligands of the lithium amide base increase and more *Z*-(O)-enolate is formed as the R group of the ketone becomes larger (see Scheme 1.8).[40]



Scheme 1.8: *Controlling the geometry of lithium enolates.*

The geometry of boron enolates is similarly predictable and has also been confirmed from direct enolate analysis. In general, the combination of small ligands (ethyl, n-butyl) and a good leaving group on boron (triflate) and a bulky amine base (diisopropyl ethyl amine) gives *Z*-(O)-enolates, while bulky ligands (cyclohexyl) and a poor leaving group on boron (chloride) and a smaller amine base (triethylamine) leads to *E*-(O)-enolates (Scheme 1.9).

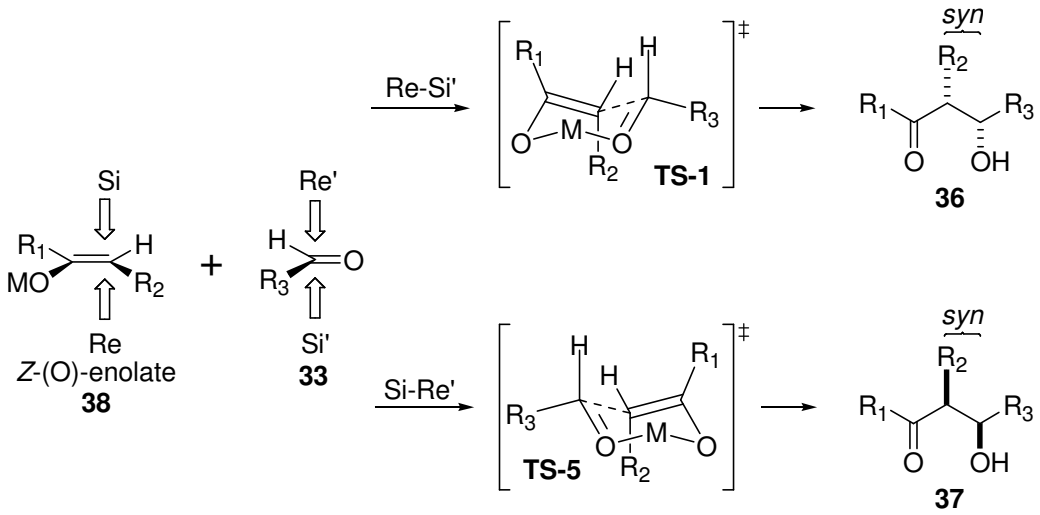


Scheme 1.9: *Controlling the geometry of boron enolates.*

With regard to titanium enolates, the enolate geometry has not been directly observed but it is generally suspected that the *Z*-(O)-geometry dominates, given the high *syn*-selectivity inherently exhibited in aldol reactions of Ti(IV) enolates.[41,42] In practice the wealth of data concerning enolate geometry allows this critical element of aldol chemistry to be manipulated in a predictable fashion.

1.5.3 π-Facial Selectivity

Although the ratio of *syn* to *anti* products in aldol reactions can be influenced by controlling the enolate geometry, it is clear that in situations where R_1, R_2 and R_3 are achiral, the transition states leading to the products will be accompanied by enantiomeric transition states. This causes the products to be generated as racemic mixtures (as shown for *syn*-aldol adducts **36** and **37** in Scheme 1.10).



Scheme 1.10: *Transition states depicting the formation of an enantiomeric pair of adducts from the reaction between a Z-(O)-enolate and an aldehyde.*

Selectively controlling the formation of one *syn* (or *anti*) product over the other requires π-facial discrimination on the behalf of the enolate and/or the aldehyde. Facial selectivity eventuates when one face of either the enolate or the aldehyde reacts preferentially, thus preventing reactivity *via* the enantiomeric transition state. In general, π-facial discrimination can be achieved by introducing asymmetry into the reaction through one of (or a combination of) the following: 1) reagent control; 2) substrate control or 3) auxiliary control.

Reagent control is required when an aldol reaction is scheduled between two achiral fragments. In these situations asymmetry is introduced as an external source of chirality in the form of a chiral reagent, a chiral catalyst or a chiral solvent. In practice, reagent control is most readily employed in boron mediated aldol reactions, where the asymmetry is introduced as chiral ligands attached to the boron atom of

the Lewis acid used to generate the enolate. Boron has a much shorter bond length with oxygen than other metals employed in aldol reactions (i.e. Li, Ti, Sn, Mg or Al). Thus, the cyclic transition states in boron mediated aldol reactions are tighter and result in enhanced levels of π-facial discrimination.[43] Figure 1.3 displays several chiral boron Lewis acids that have been developed for enantioselective aldol reactions and which have been shown to translate exceptional levels of enantiomeric excess. Borolanes **40** and **41** were developed by Masamune *et al.*[44-46] and Reetz *et al.*,[47-49] respectively, while the menthone derived **42** and diazaborolidine **43** were introduced by Gennari *et al.*[50-53] and Corey *et al.*,[54-56] respectively. The diisopinocamphenylboranes (−)-**44** and (+)-**44** were developed by Brown *et al.* as reagents for stereoselective hydroboration and asymmetric reduction[57,58] and have been employed by Paterson in numerous asymmetric aldol reactions.[59-66]

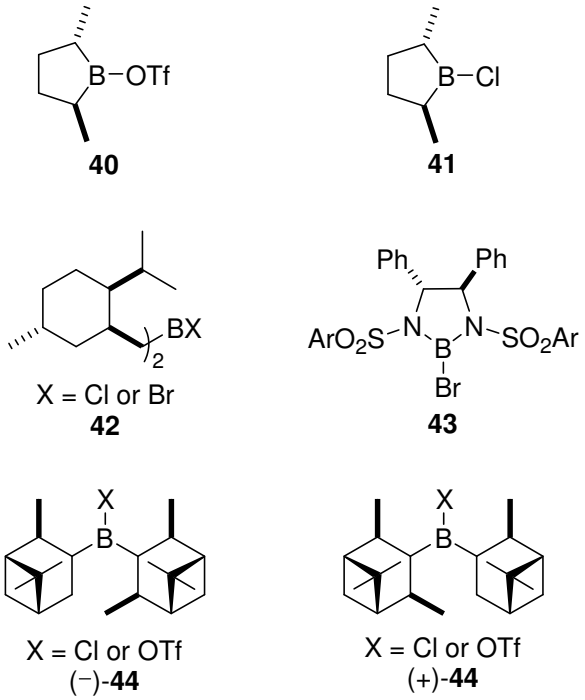
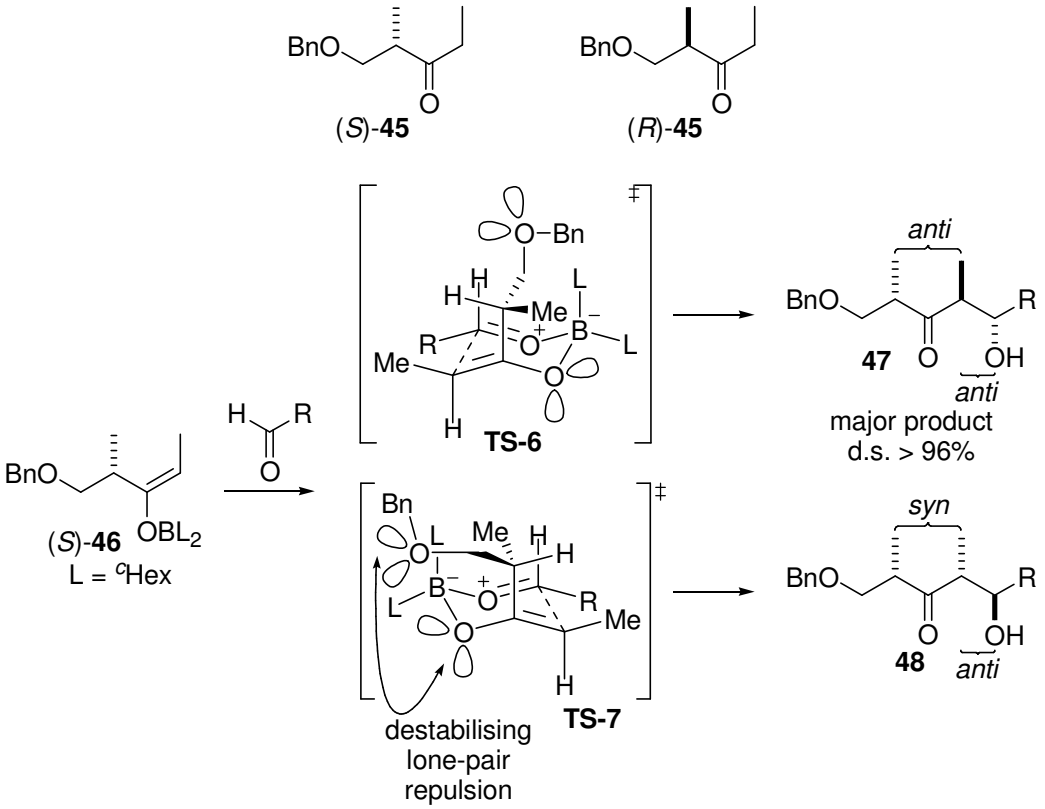


Figure 1.3: *Chiral boranes used in asymmetric aldol reactions.*

Highly selective π-facial discriminating aldol reactions can also be achieved by employing chiral ketones (and to a lesser extend chiral aldehydes) in substrate controlled aldol reactions. These reactions are said to be diastereoselective as the chirality possessed by the substrate (ketone or aldehyde) is retained in the product and is incorporated into the stereochemistry of the final target compound. The

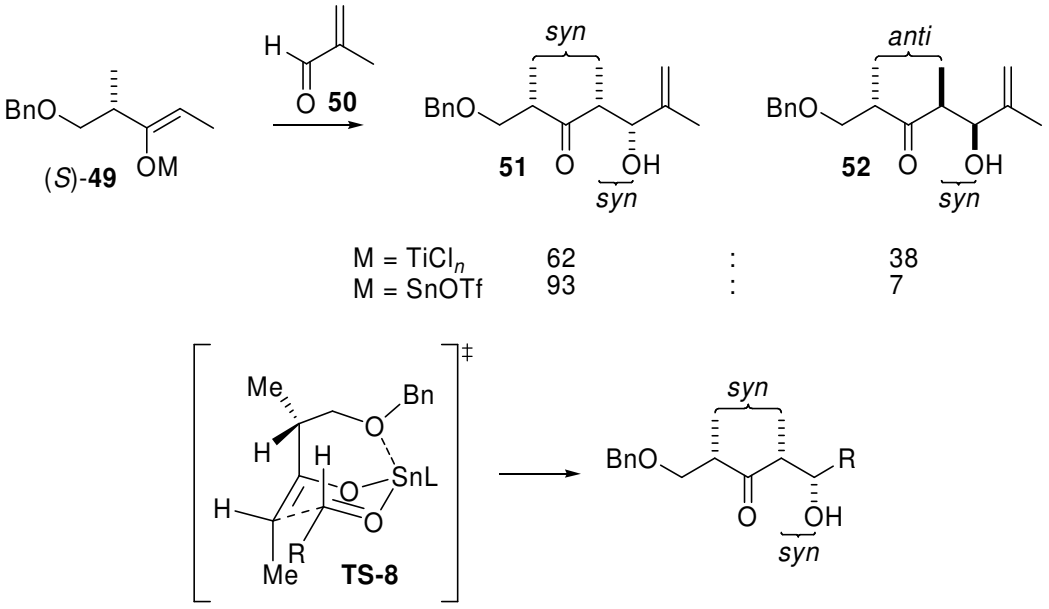
asymmetric substrate influences π-facial selectivity by differentiating the competing transition states through stabilising intramolecular bonds or destabilising steric or lone pair interactions. This point is exemplified in the following two examples.

In 1989, Paterson introduced α-methyl substituted chiral ketones (*S*)-**45** and (*R*)-**45**.[66] The *E*-(O) boron enolates [(*S*)-**46**] of these dipropionate equivalents can be generated selectively ($^{c}Hex_2BCl/Et_3N$) and react with aldehydes in highly selective *anti*,*anti*-aldol reactions.[66-68] Paterson has rationalised the exceptional selectivity exhibited by these substrate controlled processes by invoking the competing transition states[69] depicted in Scheme 1.11. Interestingly, transition state **TS-6**, leading to the favoured *anti*,*anti*-product **47** would appear to be contra-steric, with the demanding benzyloxymethylene unit directed toward the centre of the transition state. However, this particular rotamer of the α-enolate bond has the hydrogen eclipsing the enolate methyl, thus minimising A(1,3) allylic strain. The competing transition state **TS-7** leading to the *syn*,*anti*-adduct **48** appears to be disfavoured due to electrostatic repulsion of the lone-pairs on the benzyloxy oxygen and enolate oxygen.



Scheme 1.11: *Paterson's dipropionate equivalent chiral ketones (S)-**45** and (R)-**45**.*

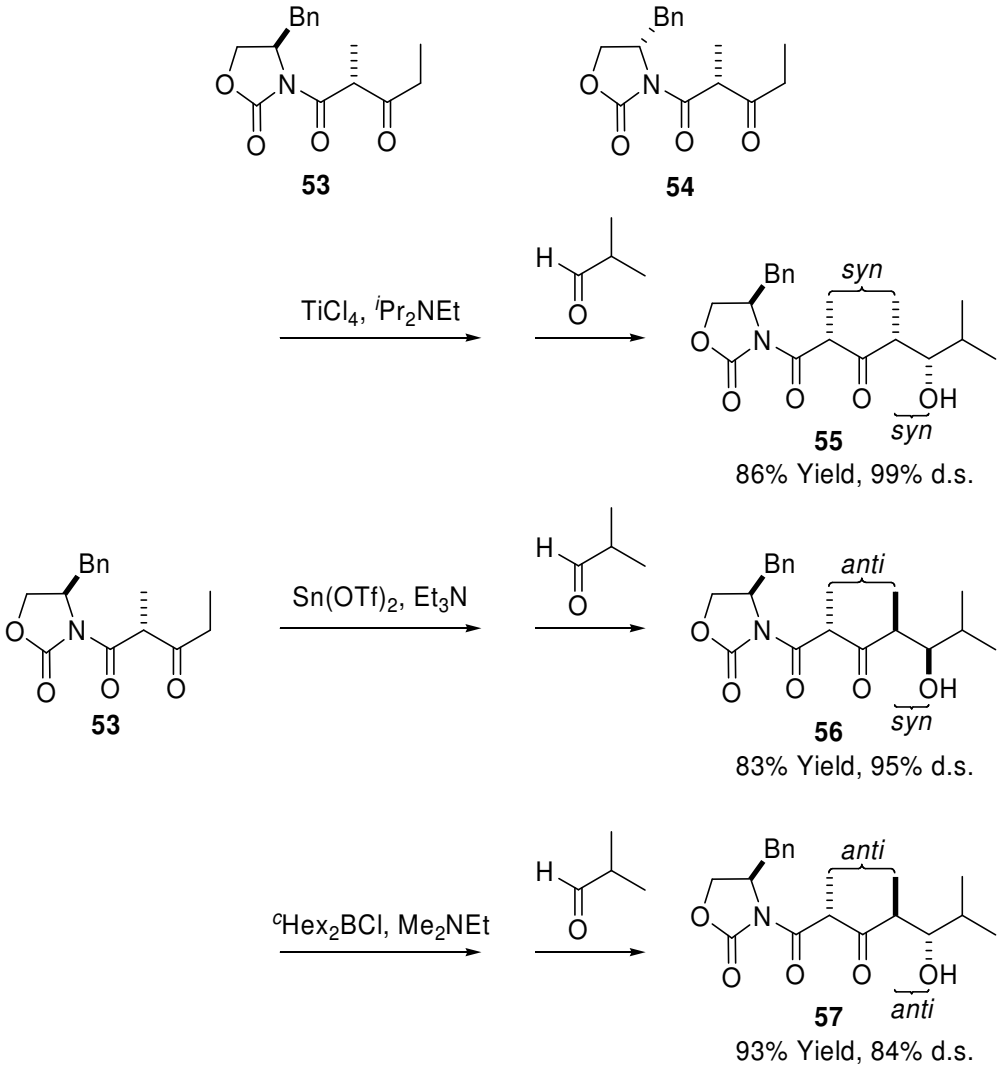
Ketones (*S*)-**45** and (*R*)-**45** also display high levels of diastereoselectivity in the corresponding *syn*-aldol reactions.[70] Scheme 1.12 delineates the observed diastereoselection of analogous aldol reactions between the titanium(IV) and tin(II) enolates [(*S*)-**49**] of ketone (*S*)-**45** with methacrolein (**50**), giving adducts **51** and **52**. The data indicates that both enolates display the same sense of induction, giving the *syn*,*syn*-product **51** as the major isomer, although the Sn(II) variant exhibits much higher levels of diastereoselection. Paterson postulates that chelation of the benzyloxy oxygen to the tin (see **TS-8**) is responsible for the high level of selectivity.[70]



Scheme 1.12: *Syn aldol reactions of Paterson's chiral ketone (S)-**45**.*

In 1992, David Evans of Harvard University extended his research on oxazolidinone compounds as chiral auxiliaries[71] to develop β-ketoimides **53** and **54** as dipropionate mimics for highly selective aldol reactions (Scheme 1.13).[72,73] While the example leading to *anti*,*anti*-aldol adduct **57**,[73] depicted in Scheme 1.13, closely resembles the analogous reaction with Paterson's dipropionate equivalents, the *syn*-aldol variants show significant differences. Evans *et al.* has shown[41] that the titanium(IV) and tin(II) enolates of β-ketoimide **53** exhibit an opposing sense of stereoinduction, such that the titanium(IV) enolate leads to all *syn*-adduct **55**, whereas the tin(II) enolate gives the *anti*,*syn*-product **56**. This is in stark contrast to the analogous reactions of

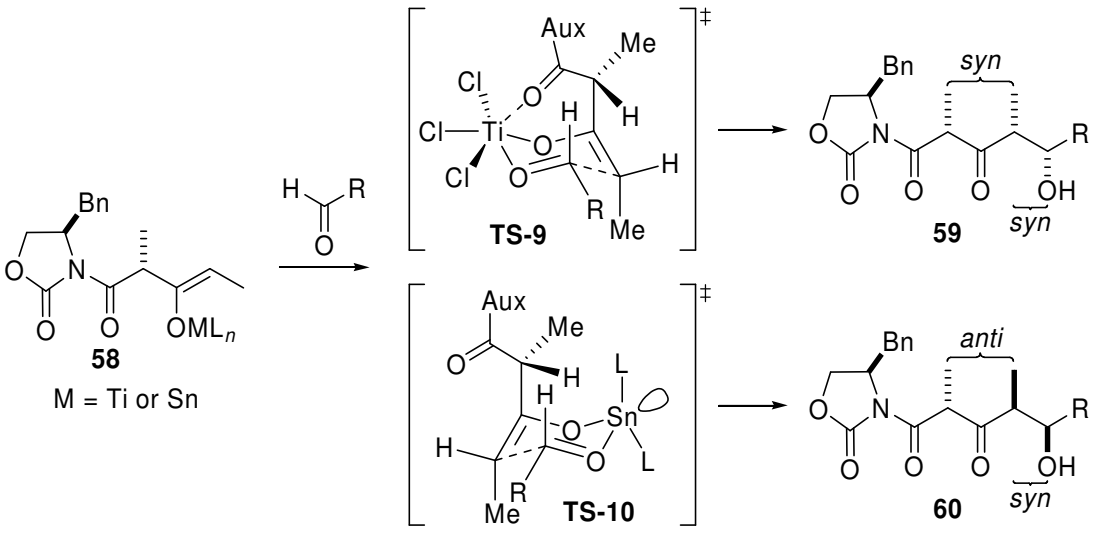
Paterson's chiral ketones, which display the same sense of stereoinduction for the titanium(IV) and tin(II) enolates favouring the all *syn*-adduct. The ability to access *anti*,*syn*-adducts using Evans' dipropionate technology was a critical factor in the decision to employ this strategy for the synthetic studies presented in Chapter 4 of this thesis.



Scheme 1.13: *Evans' dipropionate equivalent chiral ketones* ***53*** *and* ***54****.*

Scheme 1.14 depicts the transition states invoked by Evans *et al.*[41] to rationalise the stereoselectivity exhibited by their dipropionate equivalent chiral ketones. In the case of the Ti(IV) enolate of **58** leading to the all *syn*-adduct **59**, the carbonyl of the ketoimide coordinates to the titanium (see **TS-9**). Evans' explanation of the tin variant depicts transition state **TS-10**, leading to the *anti*,*syn*-product, where the α-

enolate bond adopts a rotamer such that the least sterically demanding hydrogen is directed toward the centre of the transition state. The fact that chelation does not appear to occur in the Evans tin variant suggests that either the tin enolates of Paterson's and Evans' chiral ketones display contravening behaviour, or some other explanation is required to account for the observed selectivity.

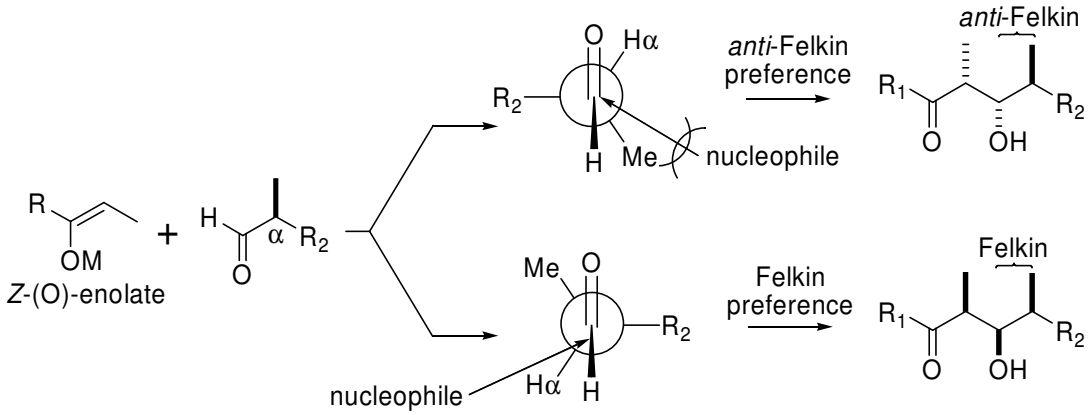


Scheme 1.14: *Opposing induction for Ti(IV) and Sn(II) enolates* ***58****.*

The chiral ketones developed by Paterson and Evans display dominating π-facial stereoselection, such that any stereoinduction exhibited by chiral aldehydes in double stereodifferentiating aldol reactions is usually overwhelmed.[67,74] To this end the stereochemical outcome in such reactions is highly predictable. This faithful translation of stereochemistry has seen these ketones used extensively in asymmetric aldol reactions and in the total synthesis of a number of polyketide derived natural products.[23,68,75-77]

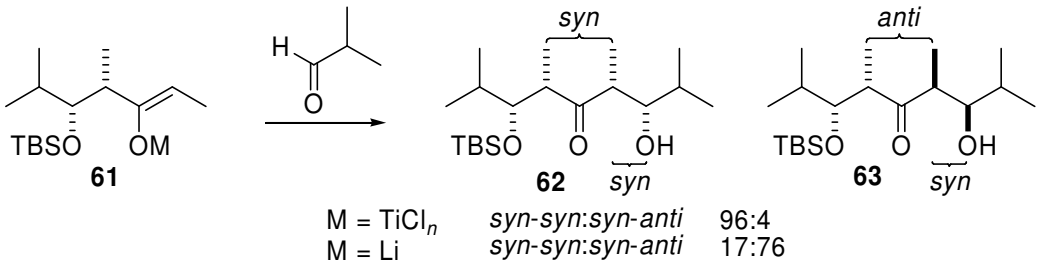
In more general terms, all chiral ketones and aldehydes will impart some sense of π-facial diastereoselection on the aldol reactions in which they participate. When only one of the coupling partners is chiral, predicting and subsequently rationalising the observed stereoselection is possible based on the attributes of that fragment *i.e.* the configuration of α and β stereocentres on aldehydes and ketones and the nature of the enolate. For instance, using α-methyl aldehydes to control the selectivity of aldol

reactions with achiral ketones is possible due to the fact that the approach of α-methyl aldehydes involves competition between Felkin-Anh and *anti*-Felkin preference (Scheme 1.15).[78-80] In general, *E*-(O)-enolates display inherent Felkin selectivity, whereas *Z*-(O)-enolates prefer *anti*-Felkin approach of the electrophile. Generally, the use of α-methyl aldehydes to influence stereoselection is not a popular choice as these compounds typically exhibit substandard selectivity.



Scheme 1.15: *Competing Felkin and anti-Felkin preferences displayed by chiral α-methyl aldehydes.*

With respect to the selectivity exhibited by chiral ketones, Evans *et al.* has shown that reaction of titanium(IV) enolate **61** with isobutyraldehyde leads to a 96:4 ratio of *syn*,*syn*:*syn*,*anti*-adducts **62** and **63** (Scheme 1.16).[42] Conversely, McCarthy found that reaction of lithium enolate **61** with the same aldehyde afforded a 17:76 ratio of *syn*,*syn*:*syn*,*anti*-adducts **62** and **63** (Scheme 1.16).[81] These independent results suggest that titanium(IV) and lithium enolates display opposing sense of stereoinduction, leading to all *syn*- or *syn*,*anti*-adducts, respectively. This conclusion has been supported by additional studies.[38]



Scheme 1.16: *Opposing induction for Ti(IV) and Li enolates **61**.*

When both aldol fragments are chiral one must consider the potential π-facial stereoselection of each. This is the essence of double stereodifferentiation in aldol reactions. Often it is difficult to predict which fragment will exhibit the dominant π-facial selectivity or what sense of stereoinduction will result, but generally it appears that enolates dominate the stereoselection of aldehydes in such reactions.

An additional form of enolate asymmetry can be achieved by incorporating a chiral auxiliary. While similar to substrate controlling chiral ketones in that the site of asymmetry is typically at the α-carbon, chiral auxiliaries are different because the chirality is removed at some stage after its stereoselective influence has been utilised. As such, the chirality of the auxiliary is not retained in the final product and in some instances the auxiliary can be retrieved and recycled after cleavage. Some early examples of chiral auxiliaries are the related ketones **64** and **65** developed by Masamune *et al.*[82,83] and Heathcock *et al.*,[84] respectively (Figure 1.4), which have been employed for *syn*-selective aldol reactions. These auxiliaries have been largely superseded by the *N*-acyl-2-oxazolidinones (*R*)-**66** and (*S*)-**66** developed by Evans *et al.*[71] and the lactate derived chiral ketones (*S*)-**67** and (*S*)-**68** introduced by Paterson *et al.*[85] (Figure 1.4).

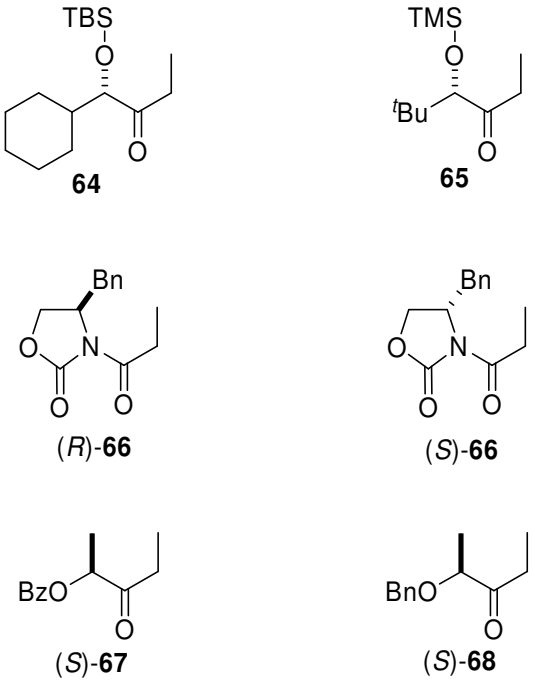
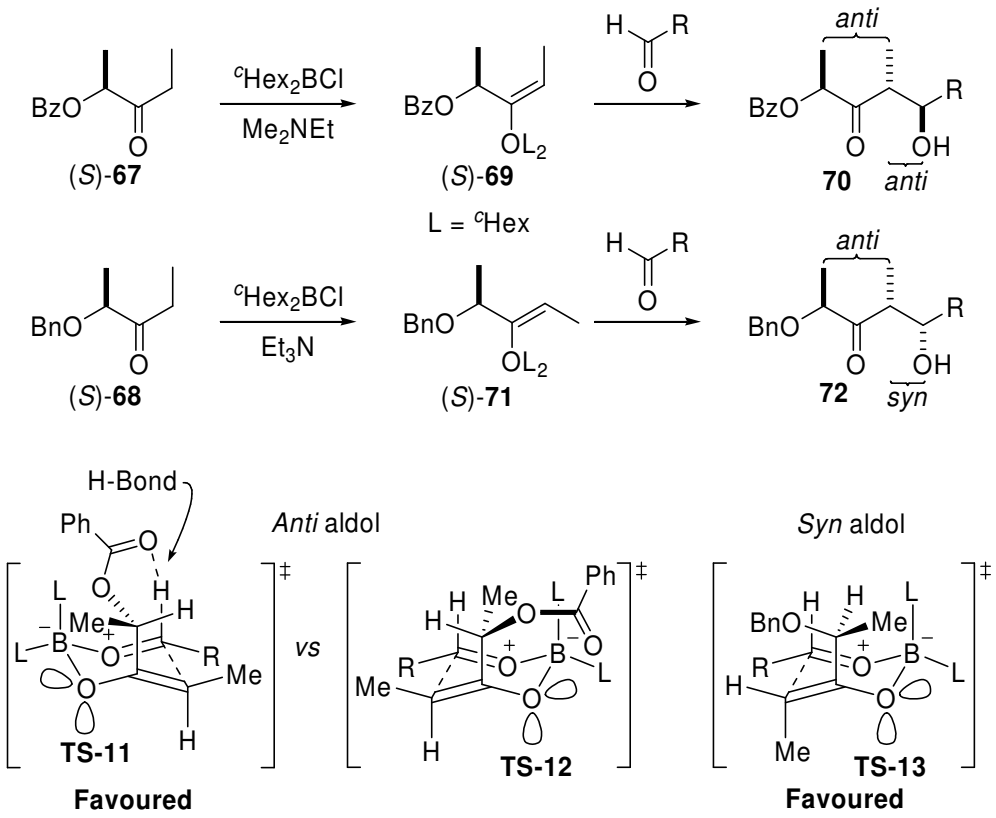


Figure 1.4: *Popular chiral auxiliaries used in asymmetric aldol reactions.*

Evans' *N*-acyloxazolidinones (*R*)-**66** and (*S*)-**66** are readily synthesised (2 steps) from commercially available D- and L-phenylalanine, respectively, [71] and have been used extensively for both diastereoselective C-alkylations and *syn*-aldol reactions (see Sections 2.3.1, 4.5.1 and 4.8.5 and references cited therein for examples). Indeed, a highly diastereoselective aldol reaction between compound (*R*)-**66** and propanal generates the precursor to β-ketoimide **53** discussed above.[72,73] The versatility of the Evans oxazolidinones derives from the ability to remove the auxiliary from elaborate congeners under a variety of conditions in a recyclable fashion. For instance, transamidation with Weinreb's salt leads to the corresponding *N*-methyl-*N*-methoxy amides,[86-89] which can inturn, be reacted with a multitude of nucleophiles (hydrides, Grignards etc.).[90] Also direct cleavage of the auxiliary with $LiBH_4$ affords the corresponding alcohol,[91] which can be similarly reacted (examples of both these transformations are given in Chapters 1 and 4).

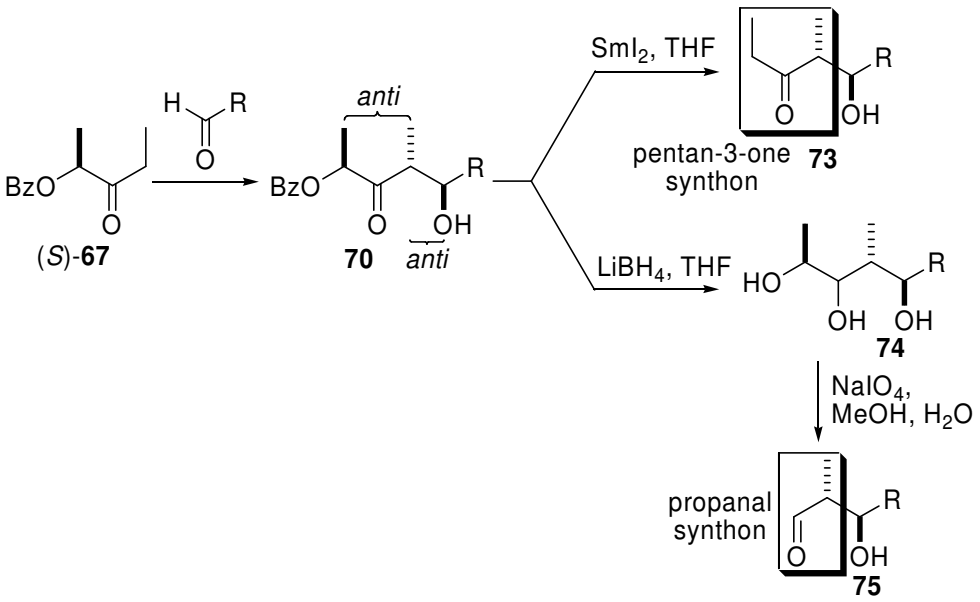
Paterson's lactate derived ketones (*S*)-**67** and (*S*)-**68** (and their respective enantiomers) are readily available (2 steps) from (*S*)-ethyl lactate (and (*R*)-isobutyl lactate).[85,92] While not auxiliaries in the sense that the chiral element can be recycled as a complete entity, the stereocentre that imparts asymmetry on the system can be removed from the congeners of these substrates. Intriguingly, ketones (*S*)-**67** and (*S*)-**68** can be transformed to the corresponding *E*-(*O*)- and *Z*-(*O*)-enolates (*S*)-**69** and (*S*)-**71**, respectively under almost identical enolising conditions (Scheme 1.17).[85] The respective enolates react with variously substituted aldehydes to give the *anti*,*anti*-adducts **70** and the *anti*,*syn*-adducts **72** with exceedingly high levels of diastereoselection.[85] Paterson has invoked the transition states depicted in Scheme 1.17 to explain the observed stereoselection.[85,92] In the reaction leading to *anti*,*anti*-adduct **70**, contra-steric transition state **TS-11** is favoured due to the conformation of the α-enolate rotamer, which permits a stabilising intramolecular hydrogen bond between the benzoyloxy carbonyl oxygen and the hydrogen of the aldehyde and minimisation of A(1,3) strain with the sterically undemanding hydrogen eclipsing of the enolate methyl. Competing transition state **TS-12** is seemingly destabilised by electrostatic repulsion of the lone-pairs on the enolate oxygen and the benzoyloxy carbonyl oxygen. The favoured transition state **TS-13**, leading to the *anti*,*syn*-adduct **72**, adopts a rotamer of the α-enolate bond where the sterically undemanding

hydrogen is directed toward the centre of the transition state. Again, dominating π-facial selectivity on the part of the enolate overrides any stereoinduction exhibited by chiral aldehydes, leading to faithful transfer of the depicted stereoselectivity regardless of the stereochemistry in the aldehyde.[92-94]



Scheme 1.17: *Interesting selectivity of Paterson's chiral ketones* (*S*)-**67** and (*S*)-**68**.

In a similar fashion to the Evans auxiliary, the versatility of Paterson's lactate derived ketones stems from the ease with which their congeners can be transformed to useful reaction intermediates.[85,92,93] Reactions of the benzoyloxy variant (*S*)-**67** are depicted in Scheme 1.18. After expressing diastereoselective control on the desired aldol process to afford adduct **70**, the controlling stereocentre can be removed in one of two ways (Scheme 1.18). Either the benzoate can be reductively cleaved with samarium(II) iodide to give the corresponding ethyl ketone **73**,[92,93] or a two step procedure of reduction with $LiBH_4$ and subsequent oxidation of the resultant diol **74** with $NaIO_4$ affords the corresponding aldehyde **75**.[92,93] As such, Paterson's lactate derived chiral ketones can be employed as both pentan-3-one and propanal synthons.



Scheme 1.18: *Versatility of Paterson's lactate derived chiral ketone (S)-**67**.*

1.5.4 Determining the Stereochemistry of Aldol Products

Having discussed the factors that control aldol selectivity, it seems prudent to identify how the selectivity of aldol reactions is determined. In most cases the relative *syn*- or *anti*-stereochemistry of aldol adducts can be distinguished by analysis of vicinal coupling constants in the ^{1}H NMR spectrum.[95] Due to the β-hydroxy ketone moiety that develops in aldol products, intramolecular hydrogen bonding often occurs between the hydroxyl group and the carbonyl to give a rigid, six-membered ring that can adopt a chair conformation (Figure 1.5).

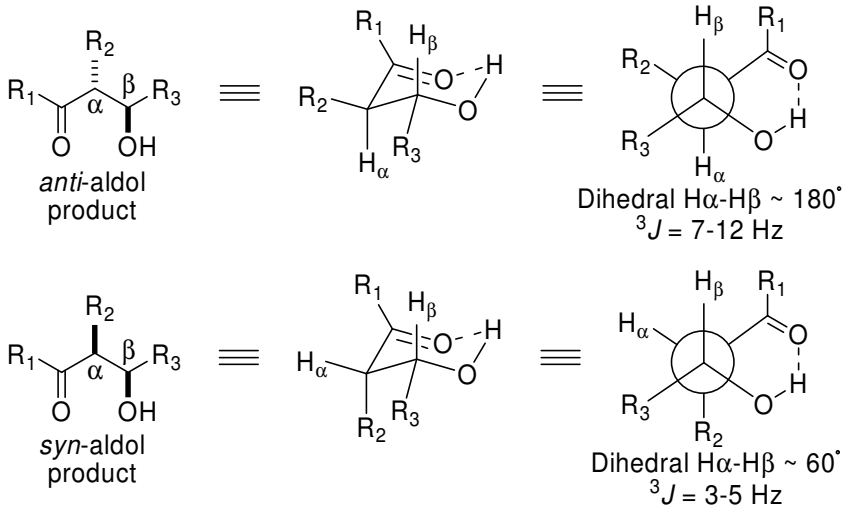
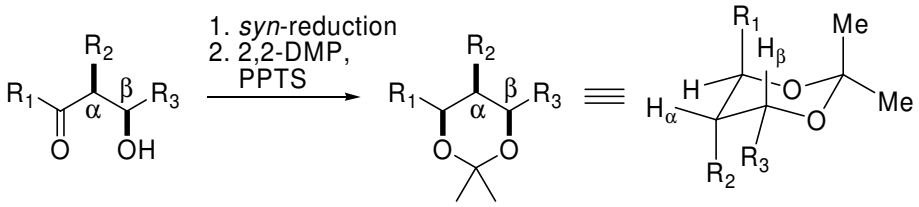


Figure 1.5: *Vicinal coupling constants for anti- and syn-aldol products.*

Figure 1.5 shows that the dihedral angle between the protons labelled α and β in *anti*-aldol products will be ~ 180°, which the Karplus relationship[96-98] predicts will result in a large vicinal coupling constant (^3J = 7-12 Hz). Conversely, in *syn*-aldol products the dihedral angle will be ~ 60°, resulting in a small vicinal coupling constant (^3J = 3-5 Hz). In situations where the vicinal coupling constants are not easily determined or where hydrogen bonding does not seem apparent, an alternative means to rigidify the product is available. To this end, selective *syn*-reduction of the aldol product, followed by reaction of the resultant diol with 2,2-dimethoxypropane (2,2-DMP) and catalytic pyridinium *para*-toluenesulfonate (PPTS), will give the corresponding acetonide as a rigid, six-membered, chair-like ring (Scheme 1.19).[73,99-101] This hydrogen bond mimic similarly allows the *syn*- or *anti*-stereochemistry of the aldol product to be determined.



Scheme 1.19: *Determining aldol selectivity using acetonide technology.*

1.6 Targets for Total Synthesis

The preceding sections have introduced marine natural products, in particular polypropionate derived secondary metabolites, and given an overview of the pivotal reaction in polypropionate assemblage; the aldol reaction. The innate structural complexity and propensity to display useful biological activity make polypropionate marine natural products particularly interesting synthetic targets. Studies in targeted natural product synthesis endeavour to probe three distinct objectives: 1) provide sufficient material for thorough biological testing, thus preserving the natural source; 2) use an asymmetric approach to present complete structural elucidation, particularly definitive relative and absolute stereochemical assignment; 3) devise and implement novel and efficient methodologies that advance the synthetic organic

arsenal. The following discussion and the concluding chapters of this thesis will elaborate three independent forays in targeted natural product synthesis.

Chapter 2 will elaborate an endeavour to synthesise hemiacetal **22** and ester **23** as well as their respective C4 epimers **76** and **77** (Figure 1.6) in an effort to establish the relative and absolute stereochemistry of two natural products isolated from marine pulmonate *Siphonaria australis* by Hochlowski *et al.* in 1984.[25] The uncertain stereochemistry of these compounds coupled with the possibility to probe the relationship between the hemiacetal and ester moieties makes these particularly interesting targets. While relatively simple structures, it was anticipated that the synthesis of hemiacetal **22** and ester **23** would provide an excellent foundation in asymmetric aldol homologation reactions and the manipulation of protecting groups for further studies.

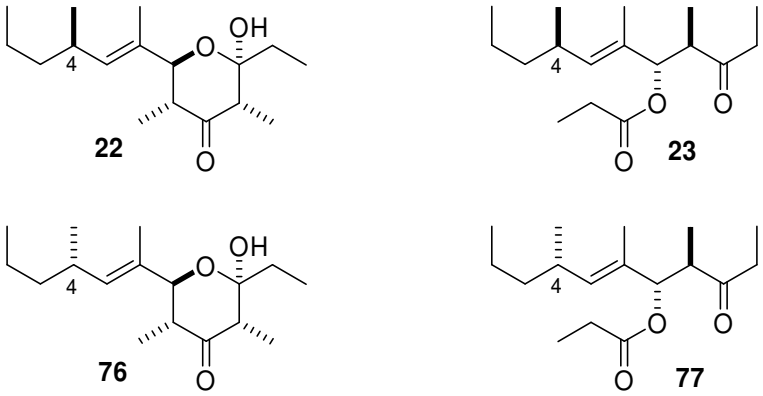


Figure 1.6: *Synthetic targets from Chapter 2 of this thesis.*

Dolabriferol (**30**) (Figure 1.7) is a complex polypropionate isolated in small quantities from specimens of *Dolabrifera dolabrifera* by Ciavatta *et al.* in 1996.[27] Given the suspected origins of this unusual natural product (see Section 1.4.3), it was hoped that a synthetic strategy could be implemented that would mimic the proposed 'biosynthetic' pathway. This would hopefully provide an insight in to the natural product status of dolabriferol (**30**).[28] It was anticipated that substrate control, employing Paterson's lactate derived ketone (*S*)-**67** (see Section 1.5.3 for discussions)[85,92] could be utilised to generate the two stereoclusters present in

dolabriferol (**30**), whose adjacent methyl and oxygen substituents are all *anti*-disposed. These endeavours are elaborated in Chapter 3.

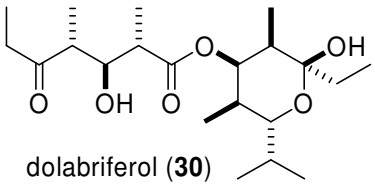


Figure 1.7: *Synthetic target dolabriferol (**30**).*

Chapter 4 will focus on the complex marine natural product auripyrone A (**78**) (Figure 1.8).[102] This elaborate, highly oxygenated compound possesses a central stereopentad, a unique spiroacetal-dihydropyrone moiety and a tethered γ-pyrone ring. These elaborate structural features alone would make auripyrone A (**78**) an admirable target for total synthesis. However, auripyrone A (**78**), which was isolated from the natural source (*Dolabella auricularia*) in 2.2 x 10^{-7}% yield, also displays potent cytotoxicity against HeLa S_3 cells ($IC_{50} = 0.26$ μg/mL). Additionally, the absolute stereochemistry of auripyrone A (**78**) remains unassigned. As such, an asymmetric total synthesis of this compound would provide more material for thorough biological testing and complete the elucidation of its structure. It is anticipated that multiple, complex aldol homologation reactions will be required to formulate the requisite stereochemical and structural features of auripyrone A (**78**).

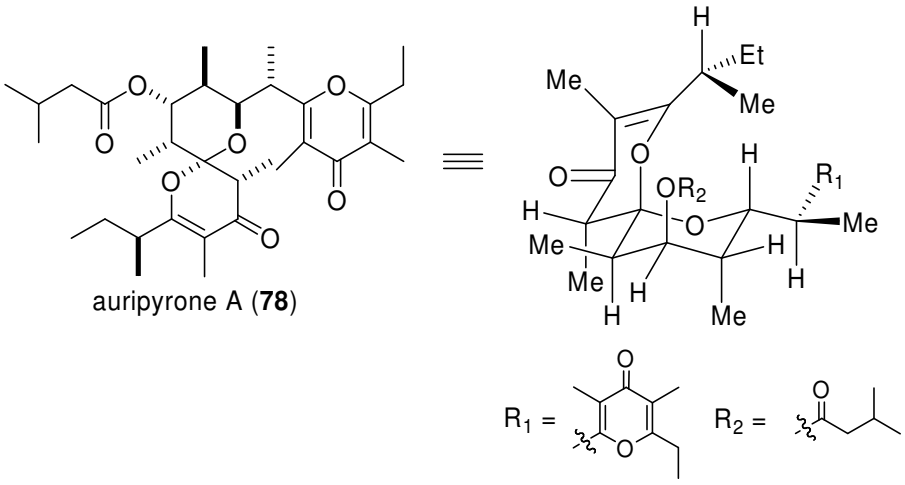


Figure 1.8: *Synthetic target auripyrone A (**78**).*

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Chapter Two

An Asymmetric Total Synthesis of the Marine Polypropionates Isolated from S. australis

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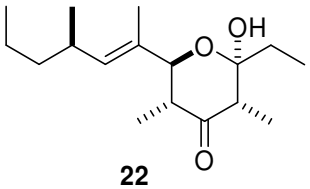
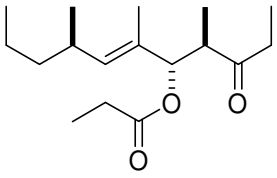
An Asymmetric Total Synthesis of the Marine Polypropionates Isolated from S. australis

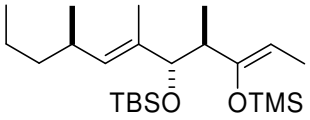
This chapter describes the first total synthesis of the marine polypropionate hemiacetal isolated from *S. australis* and thus defines the absolute stereochemistry of this natural product. The following sections detail the stereoselective synthesis of hemiacetal **22**, in which ketone (*S*)-**67** played a pivotal role in asymmetric control. Key steps include a mild and selective formation of silyl enol ether **109** and a base induced retro-Claisen fragmentation of **22**, giving **23**.



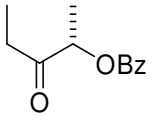
22



23



109



(*S*)-**67**

2.1 Introduction

2.1.1 *S. australis* and the Isolation of its Related Metabolites

Commonly known as false limpets, pulmonate molluscs of the genus *Siphonaria* are herbivorous, intertidal gastropods[1] that possess both gills and lungs and are thus amphibious. Siphonariids potentially represent an evolutionary link between marine and terrestrial gastropods[1] and are most commonly found either

firmly attached to depressions in rock surfaces at high tide, or foraging for encrusted algae and micro-organisms as the tide recedes.

The chemistry of Siphonariid secondary metabolites is dominated by polypropionate compounds[1,2] which frequently display either ketal, as exemplified by the denticulatins A (**12**) and B[3] (**13**), or pyrone functionality, as exhibited by the siphonarins A (**14**) and B[4] (**15**) (Figure 2.1). Although not a common attribute, several metabolites of the genus have exhibited antimicrobial activity. For example the diemenensins A (**16**) and B (**79**)[5] have shown inhibition of *Staphylococcus aureus* and *Bacillus subtilise*,[5] as has pectinatone (**80**),[6] which has also displayed activity against gram (+) bacteria, yeast *Candida albicans* and *Saccharomyces cerevisiae*.[6]

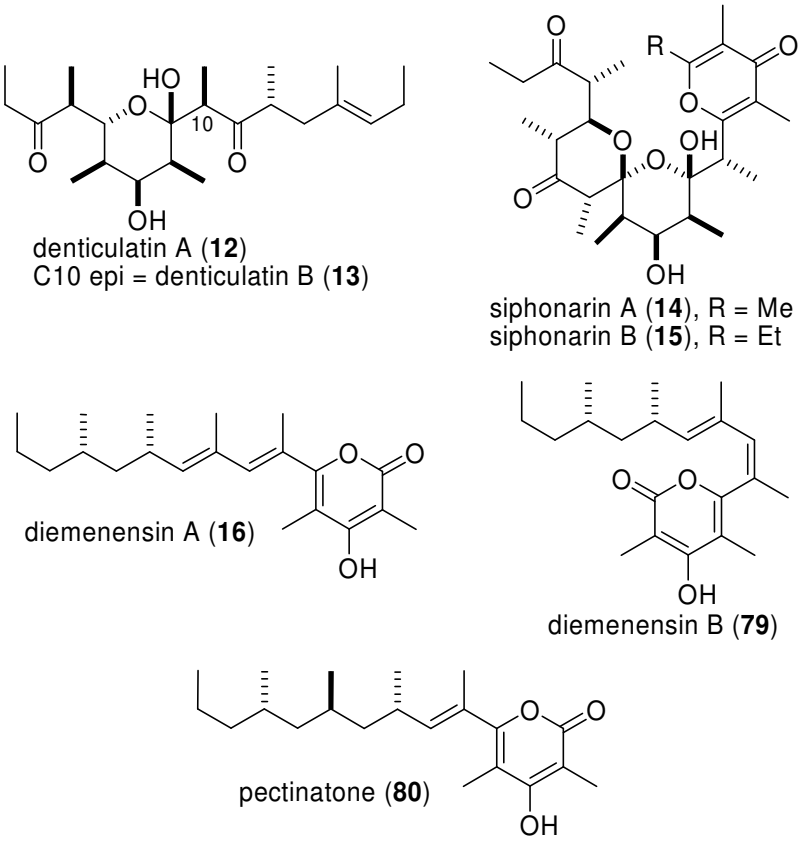


Figure 2.1: *Metabolites from pulmonates of the genus Siphonaria.*

In 1984, Hochlowski *et al.* reported[2] the isolation of two new polypropionate natural products **81** and **82** (Figure 2.3) from specimens of *Siphonaria australis* collected

near Auckland, New Zealand. *S. australis*, like other members of the genus, is a small (13-25 mm) mollusc that is found dwelling on rock formations in intertidal zones (Figure 2.2).

Figure 2.2: *Specimens of Siphonaria australis.*

2.1.2 Structural Elucidation

The structure of hemiacetal **81** and the associated ketol ester **82** (Figure 2.3) were established by NMR spectral analysis.[2] The secondary metabolites displayed a characteristic polypropionate structure, with compound **81** exhibiting a highly substituted hemiketal. The absolute configuration was not assigned, but NMR spectral data allowed Hochlowski *et al.* to determine the relative stereochemistry of the tetrahydro-γ-pyrone ring such that the C7 and C8 hydrogens were *anti*, all the alkyl substituents adopted equatorial positions and the ketal hydroxyl was in the anomerically favoured axial position. Furthermore, Hochlowski showed that base induced retro-Claisen fragmentation of hemiacetal **81** gave ester **82**, and thus established an analogous C7-C8 stereochemistry.[2] This association suggests that the ester **82** is an artefact, whereby its occurrence as an isolate was likely due to degradation of hemiacetal **81** upon extraction and purification and not independent extraction. The relative stereochemistry at C4 could not be assigned for either compound by Hochlowski.

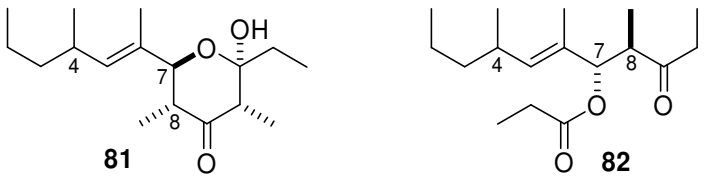
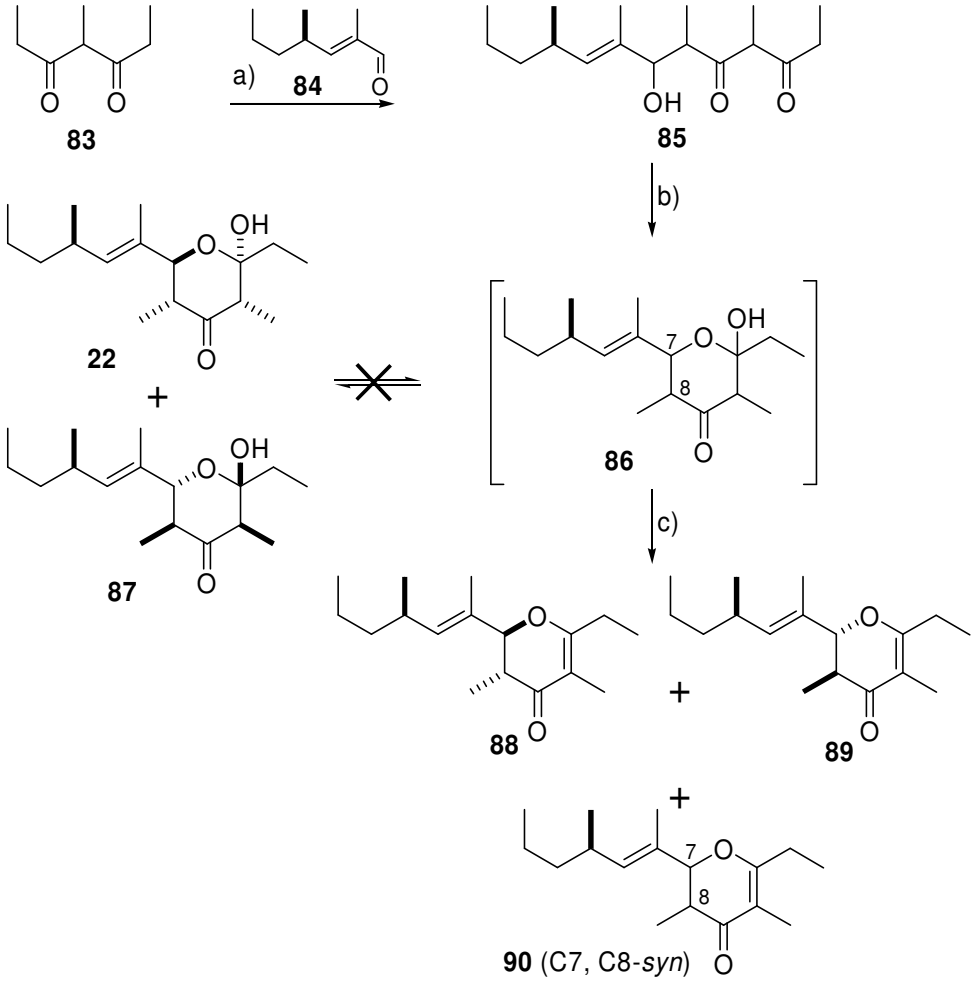


Figure 2.3: *Hemiacetal **81** and ester **82** isolated from S. australis.*

2.1.3 Previous Work

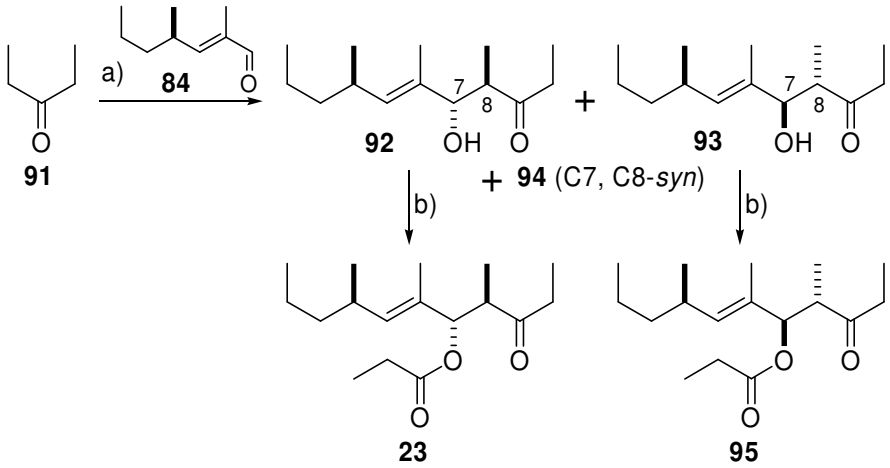
In 1992, Sundram *et al.* reported[7] an attempted synthesis of the natural products **81** and **82** employing the strategies shown in Schemes 2.1 and 2.2. An initial aldol coupling (Scheme 2.1) of the lithium dienolate of diketone **83** with chiral aldehyde **84** gave the stereochemically undefined product **85**. Sundram anticipated that thermodynamic equilibration of the C8 stereocentre (in compound **85** or **86**) would lead to the formation of thermodynamically favoured hemiacetals **22** and **87**. Unfortunately, equilibration was observed to be slower than acid catalysed dehydration leading to dihydropyrones **88**-**90**, whilst treatment of aldol adduct **85** with base gave only retro-Claisen products.



Reagents and conditions: a. i. LDA (2.2 eq), THF, –78 °C to 0 °C; ii. aldehyde **84**; **b.** H^+; **c.** *p*-TsOH (cat.), C_6H_6, 12 h.

Scheme 2.1: *Sundram's attempted synthesis of hemiacetal **22** and **87**.*

In a similar initial approach (Scheme 2.2), Sundram showed that reaction of the lithium enolate of diethylketone **91** with aldehyde **84** gave a mixture of separable C7-C8 *anti*-adducts **92** and **93**, along with a C7-C8 *syn*-adduct **94**. The stereochemistry of compounds **92** and **93** was assigned[7] using the derived *p*-bromobenzoates, utilising the excitation chirality method for the determination of the absolute configuration of acyclic allylic alcohols.[8] Acylation of alcohols **92** and **93** under standard conditions, afforded esters **23** and **95**, respectively. Compound **23** was reported[7] to have an identical ^{1}H NMR spectrum in C_6D_6 to **82** and was found to have a similar optical rotation. On this basis, Sundram assigned the relative and absolute configuration of **82** as that shown for synthetic ester **23**. Consequently, the stereochemistry of the natural hemiacetal **81** was assigned by Sundram[7] to be the same as shown for **22**, due to Hochlowski's earlier discovery[2] that hemiacetal **81** could be converted into ester **82**.



Reagents and conditions: a. i. LDA (1.1 eq), THF, −78 °C; ii. aldehyde **84**; **b.** EtOCl, pyridine, CH_2Cl_2.

Scheme 2.2: *Sundram's synthesis of ester **23** and **95**.*

2.1.4 A Stereocontrolled Approach

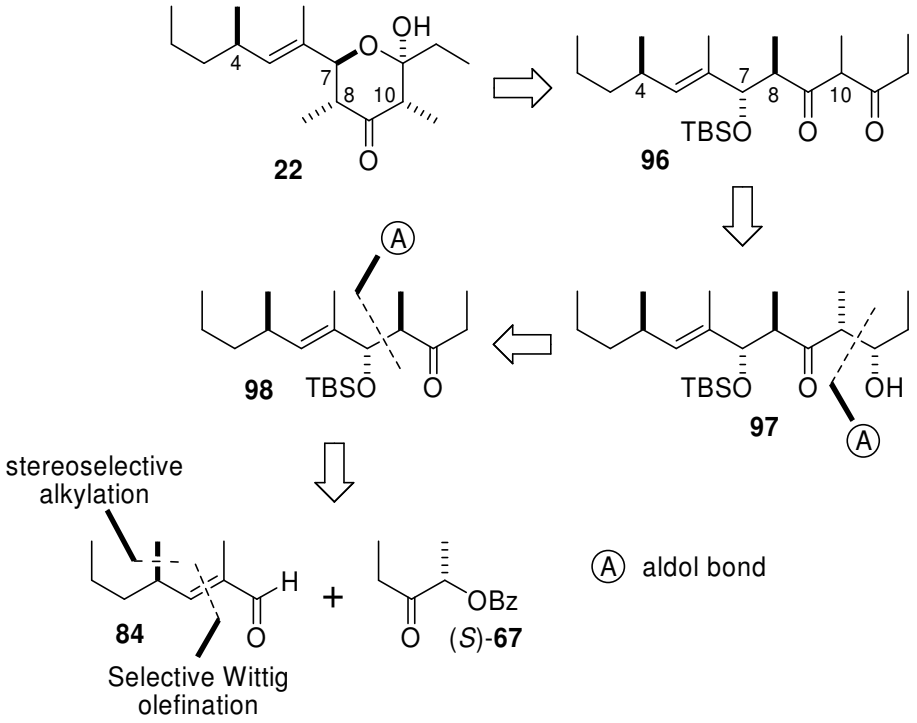
Whilst claiming "synthesis and absolute configuration of polypropionate metabolites from *Siphonaria australis*", Sundram only reports[7] the synthesis of ester **23** which, given its reported association to hemiacetal **22**, most likely represents a degradation product and not a true secondary metabolite. Additionally, although

utilising a reputed method, the assignment of absolute and relative configuration by Sundram for hemiacetal **81** and ester **82** was deduced from the non-empirical rules[8] relating to the positive Cotton effect exhibited in the circular dichroism spectra of ester **82**. Without an asymmetric synthesis of ester **82** to support these findings the configurational assignment made by Sundram was viewed with some trepidation.

It seemed clear that a stereocontrolled synthesis of both hemiacetal **22** and **87** was needed to provide an unambiguous solution to the absolute configuration of **81** and by extension **82**. The following sections detail the first such total synthesis.

2.2 Retro-Synthetic Analysis

The initial target for total synthesis was the structure shown for hemiacetal **22**, which was proposed by Sundram to be the natural product.[7] As shown retro-synthetically in Scheme 2.3, the final operation intended to yield hemiacetal **22** was cyclisation of linear precursor **96** upon liberation of the C7 alcohol. The desired configuration of C4, C7 and C8 stereocentres will be defined in precursor **96**. It was anticipated that the C10 stereocentre (based on its position between two carbonyl groups in the linear precursor) would undergo thermodynamic equilibration during the cyclisation and thus, the C10 methyl substituent would adopt the thermodynamically favoured equatorial position in hemiacetal **22**. Similarly, the hemiketal centre (C11), which possesses an anomerically favoured, axially disposed hydroxyl substituent, was expected to arise under thermodynamic control. Formation of β-diketone **96** was envisaged from an aldol-type propionate homologation of ketone **98** followed by oxidation of the resulting adduct **97**. Critical to the strategy would be the introduction of the C7 and C8 stereocentres in the correct absolute configuration. This was anticipated to be accomplished with a highly stereocontrolled *anti*-aldol reaction of lactate derived[9] ketone (*S*)-**67** with chiral aldehyde **84**. Fortunately, chiral aldehyde **84** was known,[10] although a slight modification to its synthesis was required.

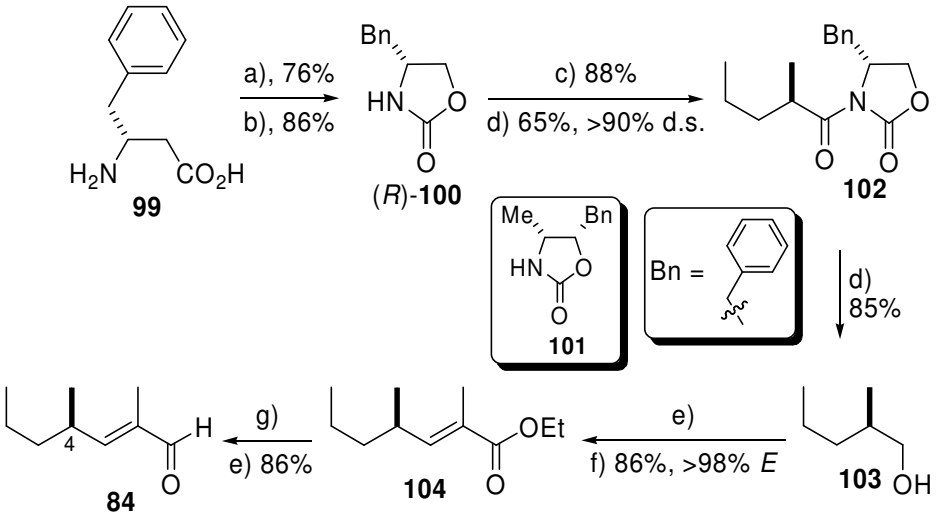


Scheme 2.3: *Retro-synthetic analysis for hemiacetal* ***22****.*

2.3 Total Synthesis of Hemiacetal 22 and Ester 23

2.3.1 Acquisition of Aldehyde 84

Although it was not anticipated that the configuration at the remote C4 stereocentre of aldehyde **84** would influence the asymmetric control of the initial substrate controlled aldol reaction, it was imperative to generate this fragment with high enantiopurity to avoid a diastereomeric mixture of aldol products and to ensure a diastereoselective synthesis of hemiacetal **22**. A highly enantioselective synthesis of aldehyde **84** has been previously reported.[10] However, a slight modification to this strategy was employed such that oxazolidinone (*R*)-**100** and not **101** was used (Scheme 2.4).



Reagents and conditions: a. i. $BF_3{\cdot}OEt_2$ (1.0 eq), THF, reflux, 2 h; ii. $BH_3{\cdot}SMe_2$ (1.15 eq), reflux, 6 h; **b.** $(EtO)_2CO$ (2.0 eq), K_2CO_3 (0.1 eq), 135 °C, 3 h; **c.** i. *n*-BuLi (1.02 eq), THF, −78 °C; ii. *n*-BuCl (1.1 eq), −78 °C, 30 min to rt, 1 h; **c.** i. LDA, THF, −78 °C, 45 min; ii. MeI (6.0 eq), −78 °C to −30 °C, o/n; **d.** $LiBH_4$ (2.4 eq), EtOH (2.4 eq), Et_2O, −10 °C, 2 h; **e.** i. DMSO (3.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (1.5 eq), −78 °C, 30 min; iii. alcohol **103**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (6.0 eq), −78 °C, 30 min to rt; **f.** $Ph_3P{=}C(CH_3)CO_2Et$ (1.2 eq), CH_2Cl_2, reflux, 6 days; **g.** $LiAlH_4$ (1.1 eq), THF, 0 °C to rt, 1.5 h.

Scheme 2.4: *Synthesis of chiral aldehyde* ***84*** *from (R)-phenylalanine* ***99****.*

In order to construct aldehyde **84**, chiral auxiliary (*R*)-**100** was synthesised by the procedure of Gage and Evans[11] as shown in Scheme 2.4. Commercially available (*R*)-phenylalanine **99** was converted to oxazolidinone (*R*)-**100** (65%) through initial boron trifluoride assisted borane reduction of the amino acid followed by reaction of the resultant amino alcohol with diethyl carbonate ($(EtO)_2CO$).[11] Acylation of the lithium anion (*n*-BuLi) of (*R*)-**100** with valeryl chloride and subsequent selective alkylation of the valeryloxazolidinone (LDA, MeI)[11] afforded **102** in greater than 90% diastereoselectivity, but as an inseparable mixture of diastereomers. Despite the inability to separate the small amount of unwanted diastereomeric product, the high degree of selectivity ensured that a high level of enantiomeric excess of aldehyde **84** would be achievable. Having served its function, the chiral auxiliary was reductively cleaved using $LiBH_4$[12] to afford primary alcohol **103** in good yield (85%) and pure

oxazolidinone (*R*)-**100**, which could be recycled. Swern oxidation[13] of alcohol **103** followed by *in situ* Wittig olefination,[14] with the commercially available stabilised ylide ($Ph_3P{=}C(CH_3)CO_2Et$), gave geometrically pure *E*-enoate **104** in 86 % yield over the two steps. Finally, reduction of ester **104** to the corresponding primary alcohol with lithium aluminium hydride[15] and subsequent Swern oxidation[13,15] furnished known volatile aldehyde **84** in good yield (86% from ester **104**, >80% e.e. based on the d.s. of compound **102**).

Despite reports suggesting that DIBAL-H is capable of reducing esters directly to the corresponding aldehydes, in practice it is often more convenient (and more pure) to effect complete reduction to the alcohol and oxidise back to the aldehyde. Due to the highly sensitive and volatile nature of aldehyde **84**, this compound was freshly prepared prior to use in the aldol reactions that follow.

The NMR spectroscopic data acquired for enal **84** were in accord with that reported by Danishefsky.[10] The ^{1}H NMR spectrum for this compound (Figure 2.4) shows the aldehydic proton as a singlet at δ 9.38 and the vinyl proton as a doublet of doublets at δ 6.25 (J = 9.9, 1.2 Hz). This significant downfield shift of the olefinic resonance is consistent with an α,β-unsaturated carbonyl system. The vinyl proton shows coupling to both the vinyl methyl doublet at δ 1.74. (J = 1.2 Hz) and the C4 methyl methine multiplet at δ 2.77-2.63 which in turn shows coupling to the methyl doublet at δ 1.05 (J = 6.6 Hz). The remaining 4H multiplet at δ 1.52-1.21 shows coupling to the methyl triplet at δ 0.89 (J = 7.1 Hz) and the C4 proton, and is consistent with the diastereotopic C2 and C3 methylene protons. The singlet at δ 5.29 corresponds to residual CH_2Cl_2 which could not be completely removed from the sample due to the volatility of aldehyde **84**.

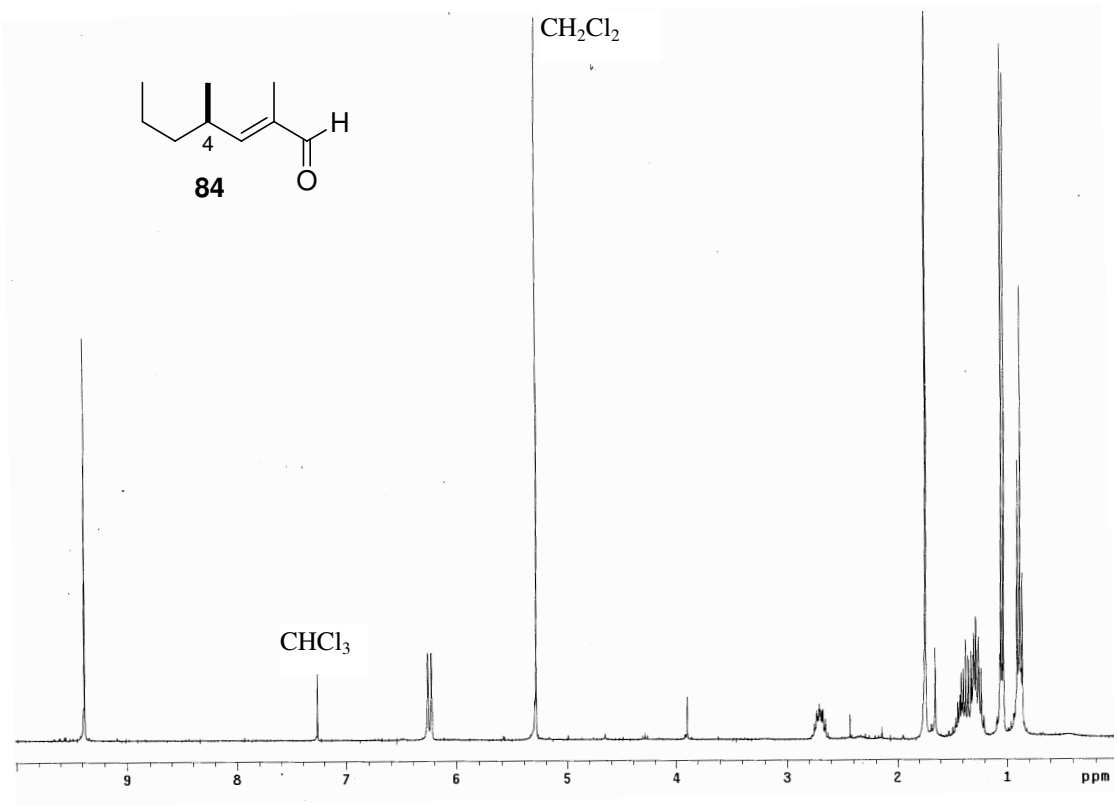
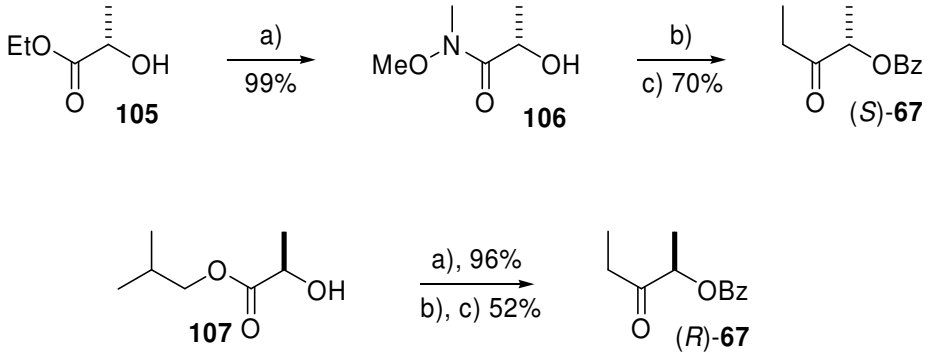


Figure 2.4: *300 MHz ^{1}H NMR spectrum of aldehyde* ***84*** *in $CDCl_3$.*

2.3.2 The Synthesis of Lactate Derived Ketones (*S*)-and (*R*)-67

Since their introduction in 1994 by Paterson and co-workers,[9] lactate derived ketones (*S*)-and (*R*)-**67**, have constituted the state-of-the-art in substrates for highly stereocontrolled *anti*-aldol reactions with both simple achiral and complex stereochemically rich aldehydes.[9,16-18] Scheme 2.5 shows the highly reliable synthesis of these chiral auxiliaries from their respective lactates.[18] Transformation of ethyl-(*S*)-lactate **105** to amide **106** was readily achieved under modified Weinreb conditions[19] (MeN(OMe)H·HCl and ^{i}PrMgCl). This initial transformation was essential to avoid over-addition in the forthcoming Grignard reaction. Treatment of **106** with EtMgBr followed by benzoylation of the free alcohol with benzoic anhydride (Bz_2O) gave (*S*)-**67** in good yield. The identical sequence, starting instead with isobutyl-(*R*)-lactate **107**, afforded (*R*)-**67** in similar overall yield.



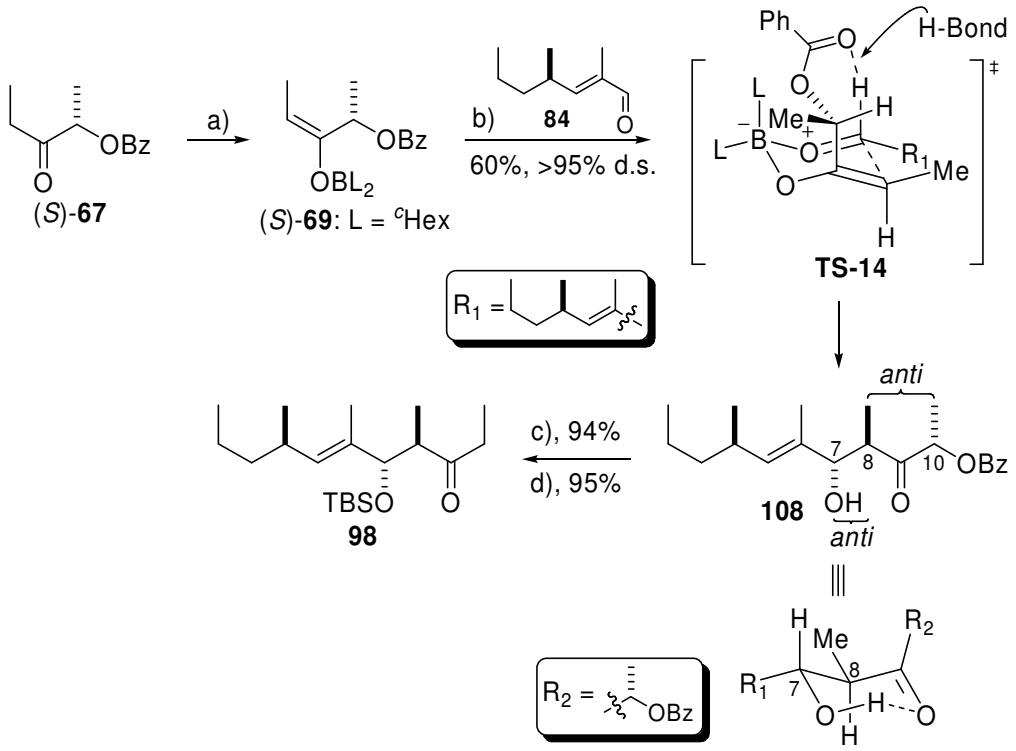
Reagents and conditions: a. MeN(OMe)H·HCl (2.5 eq), ^{i}PrMgCl (5.0 eq), 1:1 THF/Et_2O, −20 °C 1 h to 0 °C, 30 min; **b.** EtMgBr (3.2 eq), THF, 0 °C to rt, 1h; **c.** Bz_2O (1.5 eq), 4-DMAP (0.11 eq), $^{i}Pr_2EtN$ (1.91 eq), THF, rt, 14 h.

Scheme 2.5: *Synthesis of lactate derived ketones (S)- and (R)-**67**.*

2.3.3 Acquisition of Acyclic Precursor β-Diketone 96

With ketone (*S*)-**67** and aldehyde **84** in hand, attention was turned to their union as depicted in Scheme 2.6. The *E*-enol dicyclohexyborinate (*S*)-**69** was selectively forged[20,21] by treatment of (*S*)-**67** with dicyclohexylboron chloride ($^{c}Hex_2BCl$) (prepared from cyclohexene and monochloroborane-methylsulfide complex by the method of Brown[20,21]) and *N*,*N*-dimethylethylamine.[9,18] The *in situ* generated enolate was then reacted with a limiting amount (0.5 eq) of freshly prepared aldehyde **84** at −78 °C, followed by warming to −23 °C and stirring at this temperature overnight.[18] After standard oxidative work-up and purification by column chromatography, 7,8-*anti*-8,10-*anti*-adduct **108** was isolated as a single observable diastereomer in a moderate 60% yield (the low yield was due to volatility and sensitivity of the aldehyde). Notably, the diastereomeric product from the reaction between ketone (*S*)-**67** and the enantiomer of aldehyde **84** was not apparent, perhaps indicating kinetic diastereoselection on the behalf of the aldehyde, or more likely separation during chromatography. The high level of π-facial selectivity exhibited in this process can be explained by invoking chair transition state **TS-14**.[9,18] The facial stereoselection is a direct result of the steric and electronic contributions[22,23] of the H, Me and OBz substituents of the enolate. The inherent tendency of *E*-enol borinates to relieve A(1,3) allylic strain is satisfied by **TS-14**,

which adopts the rotamer where the hydrogen is eclipsing the enolate double bond. Whilst contrary to steric demand, directing the bulky benzoate into the transition state is compensated for by a hydrogen bond like interaction[24,25] between the benzoyl carbonyl and the hydrogen of the aldehyde.



Reagents and conditions: a. $^{c}Hex_2BCl$ (1.5 eq), Me_2NEt (1.8 eq), Et_2O, 0 °C, 2 h; **b.** aldehyde **84** (0.5 eq), Et_2O, −78 °C, 2 h to −23 °C, o/n; **c.** i. 2,6-lutidine (2.0 eq), CH_2Cl_2, −78 °C; ii. TBSOTf, (1.5 eq), −78 °C, 30 min; **d.** SmI_2 (~4.0 eq), THF, 0 °C.

Scheme 2.6: *Installation of the C7 and C8 stereocentres and synthesis of ketone* ***98****.*

The ^{1}H and ^{13}C NMR spectra (Figure 2.5 and 2.6) of aldol adduct **108** displayed the appropriate resonances as single peaks, indicative of high diastereomeric purity. In particular, the oxymethine proton (C7-H) appears as a broad doublet at δ 4.17 (J = 9.3 Hz) and shows coupling to both the hydroxyl proton and the C8 methyl methine proton, which resonate as a broad singlet at δ 1.98 and a doublet of quartets at δ 3.03 (J = 9.3, 6.9 Hz), respectively. The large coupling (J= 9.3 Hz) between the C7 and C8 protons is indicative of an *anti*-relationship and results from restricted rotation

about the new C-C bond due to intramolecular hydrogen bonding between the hydroxyl moiety and the neighbouring carbonyl (see Scheme 2.6 and related discussion in Section 1.5.4). The acyloxymethine proton appears as a quartet at δ 5.45 (J = 6.9 Hz) and couples to the methyl at δ 1.57 (J = 6.9 Hz). This distinctive quartet and downfield doublet are characteristic of the lactate derived ketones and all their respective aldol congeners. The remaining signals were consistent with those already reported for the aldehyde portion of the structure.

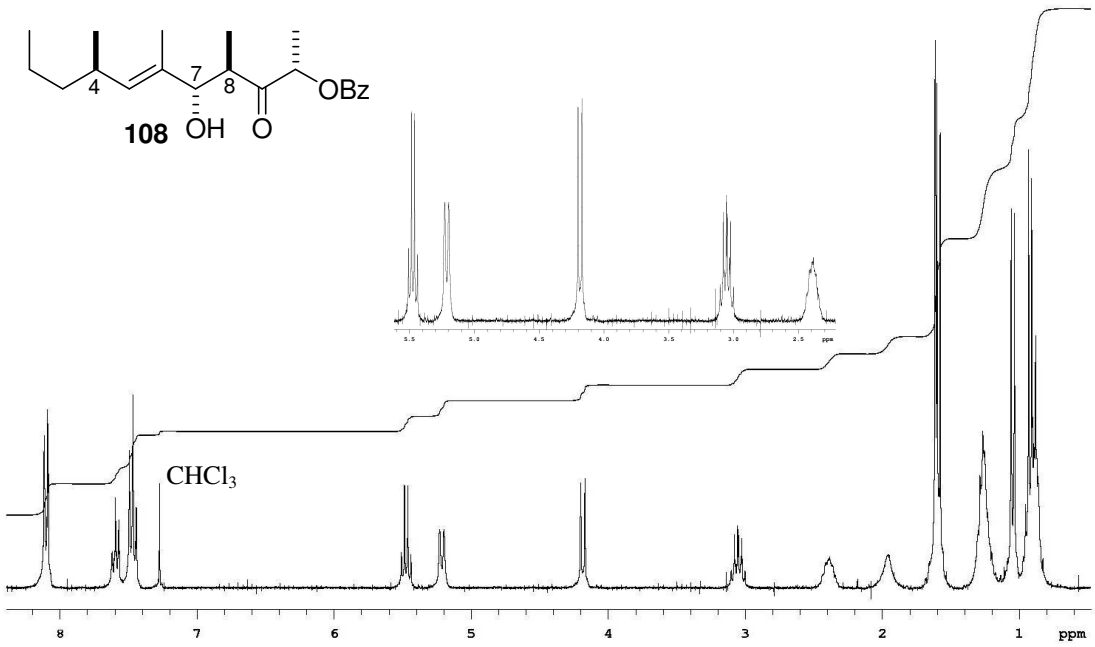


Figure 2.5: *300 MHz ^{1}H NMR spectrum of aldol adduct* ***108*** *in $CDCl_3$.*

The ^{13}C NMR spectrum showed a ketone carbonyl resonance at δ 211.1 and an ester carbonyl signal at δ 165.8. Peaks corresponding to the two oxymethine carbons appeared at δ 80.2 and 75.1, while the remaining resonances were consistent with the assigned structure. A broad absorption band at 3514 cm^{-1} and a strong absorption at 1721 cm^{-1} in the infrared spectrum are indicative of the alcohol and carbonyl groups, respectively and an accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{30}O_4$.

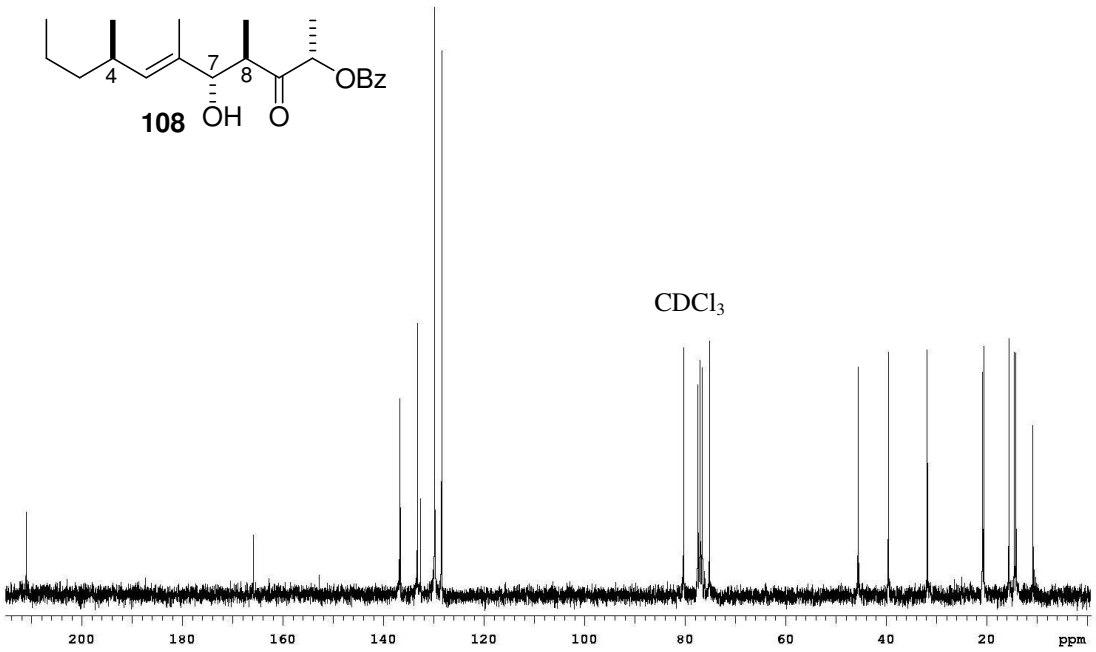


Figure 2.6: *75.5 MHz ^{13}C NMR spectrum of aldol adduct* ***108*** *in $CDCl_3$.*

The generated C7 hydroxyl was protected as a *tert*-butyldimethylsilyl (TBS) ether under standard conditions (TBSOTf, 2,6-lutidine)[26] and subsequent removal of the benzoate, under reductive conditions with samarium diiodide (SmI_2),[16,18,27] gave ethyl ketone **98** in excellent overall yield (89%) as shown in Scheme 2.6. Despite not being a recoverable and ultimately recyclable chiral auxiliary, the utility of the α-stereocentre for asymmetric control in the initial aldol reaction and then subsequent removal of this pivotal stereocentre makes the lactate derived ketones powerful chiral pentan-3-one synthons. Notably, it is imperative that hydroxyl protection precedes benzoate cleavage, as significant decomposition prevails if the reaction is carried out in the presence of the free alcohol. Disappearance of a broad absorption band above 3500 cm^{-1} and significant sharpening of the carbonyl stretch at 1721 cm^{-1} in the infrared spectrum of compound **98** was indicative of successful masking of the C7 alcohol and cleavage of the benzoate.

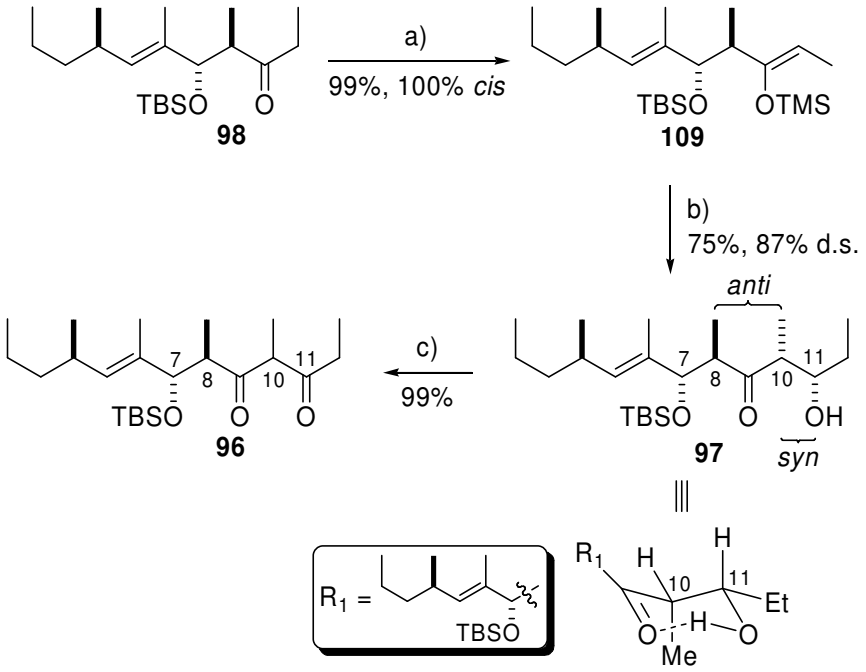
In accordance with a previous study,[28] which indicated the susceptibility of simple ethyl ketones to undergo enolisation and subsequent capture as enolsilanes under very mild conditions, Scheme 2.7 shows that trimethylsilyl enol ether **109** was formed from ketone **98**. To that end, exposure of **98** to conditions that normally

constitute standard silyl protection of alcohols,[26] namely trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine at −78 °C, followed by warming to ambient temperature and stirring overnight, afforded enolsilane **109** in near quantitative yield and as a single geometric isomer (100% *Z*). The ^{1}H NMR spectrum for compound **109** (not shown) displayed a vinyl proton as a quartet at δ 4.49 (*J* = 6.6 Hz) which coupled to a vinyl methyl doublet at δ 1.48 (*J* = 6.6 Hz). These features in addition to a 9H singlet at δ 0.21 and a medium absorption band at 1678 cm^{-1} in the infrared spectrum are characteristic of a trimethylsilyl enol ether.

Whilst selective enolate generation and capture as the TMS enol ether is well presented in the literature,[29,30] the typical procedure involves the use of strong, sterically demanding amides in conjunction with trimethylsilyl chloride (TMSCl).[29,30] Indeed, the general procedure for the synthesis of geometrically pure *cis*-TMS enol ethers from simple ethyl ketones requires the use of 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (LiTMDPS) followed by the addition of TMSCl.[30] The use of TMSOTf presumably resulted in greater polarisation of the carbonyl, enhancing α-proton acidity, thus enabling the utility of a very mild base (2,6-lutidine). This appears to constitute the mildest form of this reaction to be reported.

Enol silanes find use primarily as substrates for Lewis acid catalysed Mukaiyama aldol homologation reactions.[31-33] With this in mind and with a highly efficient and novel method to convert ethyl ketone **98** into enolsilane **109** at hand, a Mukaiyama aldol process seemed perfectly suited to the final C-C bond forming reaction of the synthesis. This conjecture proved correct, as a solution of (*Z*)-TMS enol ether **109** and propanal in CH_2Cl_2 at −78 °C when treated with $BF_3{\cdot}OEt_2$,[34,35] successfully reacted to afford aldol adduct **97** in good yield (75%) and high diastereoselectivity (87% d.s., Scheme 2.7). Purification by column chromatography led to the isolation of **97** as a single diastereomer, whose stereochemical assignment is based on literature precedent.[35] The stereochemical outcome of Mukaiyama aldol additions is more difficult to predict and rationalise than metal enolate variants due to a variety of competing, open transition states.[32,36] Despite this, systematic studies have shown[35] that Mukaiyama aldol reactions show reliable *syn*-selectivity with respect to the developing stereocentres and excellent levels of asymmetric induction, regardless of

the enolsilane geometry. In particular, (*Z*)-enolsilane substrates display a persistent facial bias towards 1,3-*anti*-dimethyl selectivity across the developing carbonyl.[35]



Reagents and conditions: a. i. 2,6-lutidine (4.0 eq), CH_2Cl_2, −78 °C; ii. TMSOTf, (3.0 eq), −78 °C, 5 min to rt, o/n; **b.** i. propanal, CH_2Cl_2, −78 °C, 2 h; ii. $BF_3{\cdot}OEt_2$, −78 °C, 1.5 h; **c.** i. DMSO (3.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (1.5 eq), −78 °C, 30 min; iii. alcohol **97**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (6.0 eq), −78 °C, 30 min to rt.

Scheme 2.7: *Completion of the carbon framework and synthesis of precursor* ***96****.*

The ^{1}H NMR spectrum of compound **97** (Figure 2.7) displays a small coupling constant (J = 2.6 Hz) between the C10 methyl methine proton (δ 2.60) and the C11 oxymethine (δ 3.90-3.84) which substantiates the *syn*-selectivity of the reaction. As before, restricted rotation due to strong intramolecular hydrogen bonding allowed this stereochemical relationship to be deduced. The new oxymethine resonance appears as a multiplet at δ 3.90-3.84 and shows additional coupling to the broad hydroxyl singlet at δ 2.98 and the two methylene multiplets at δ 1.62-1.47 and δ 1.44-1.32. These multiplets in turn couple to the methyl triplet at δ 0.95 (J = 7.5 Hz).

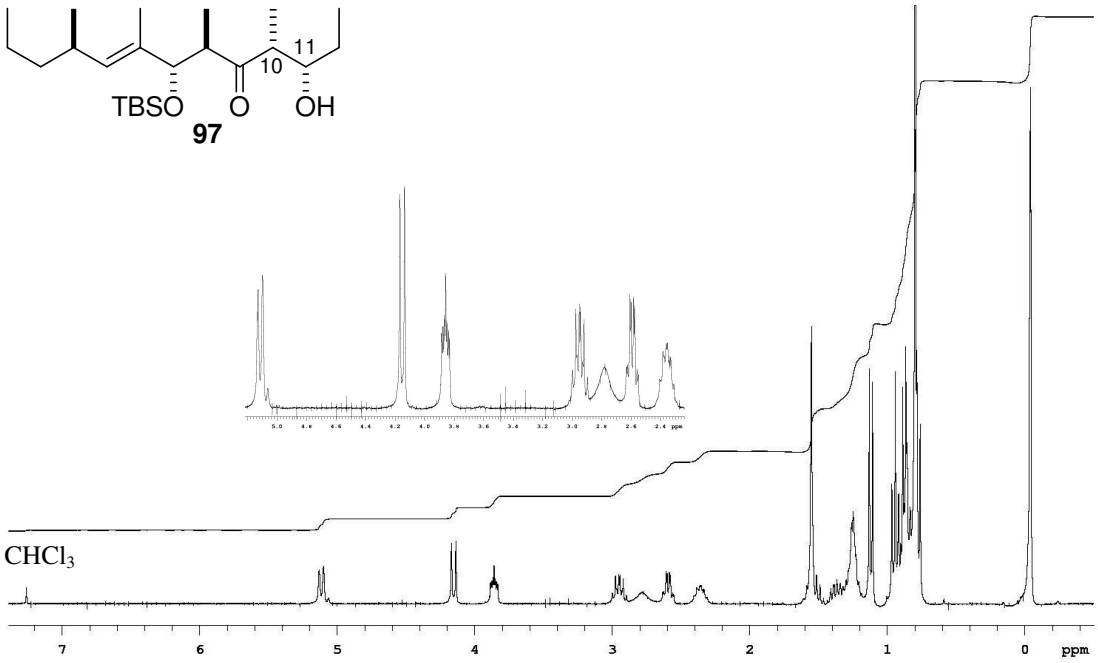


Figure 2.7: *300 MHz ^{1}H NMR spectrum of aldol adduct* ***97*** *in $CDCl_3$.*

The C11 oxymethine resonates at δ 72.5 in the ^{13}C NMR spectrum (Figure 2.8) which, in addition to a new methylene (δ 27.0) and methyl signal (δ 8.0), confirms propionate homologation.

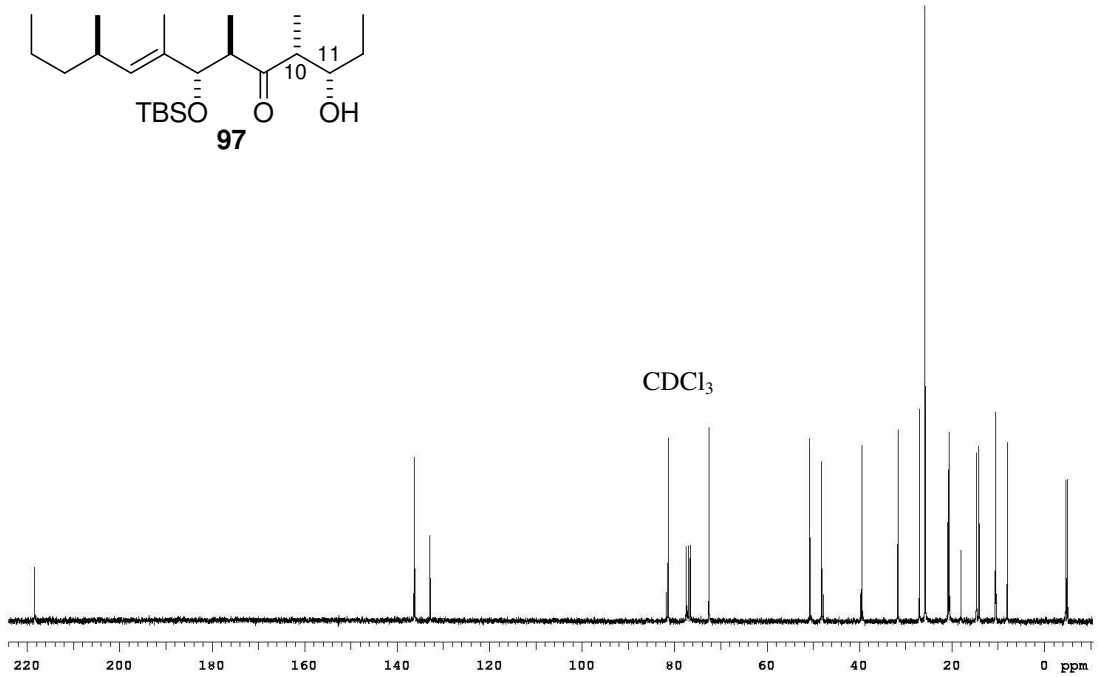


Figure 2.8: *75.5 MHz ^{13}C NMR spectrum of aldol adduct* ***97*** *in $CDCl_3$.*

Ultimately, the selectivity and stereochemical assignment was of little consequence as the impending oxidation would remove the C11 stereocentre and place the C10 substituent between a β-dicarbonyl system, thus exposing it to certain epimerisation. In this regard, Swern oxidation[13,15] of aldol adduct **97** smoothly afforded β-diketone **96** in near quantitative yield as a mixture of dione and enol forms (Scheme 2.7). As suspected, the C10 methyl substituent was readily epimerised under the acidic conditions of column chromatography (silica gel). This epimerisation was crucial as the methyl group was initially in the wrong configuration for thermodynamic cyclisation to occur.

2.3.4 Completion of the Synthesis of Hemiacetal 22

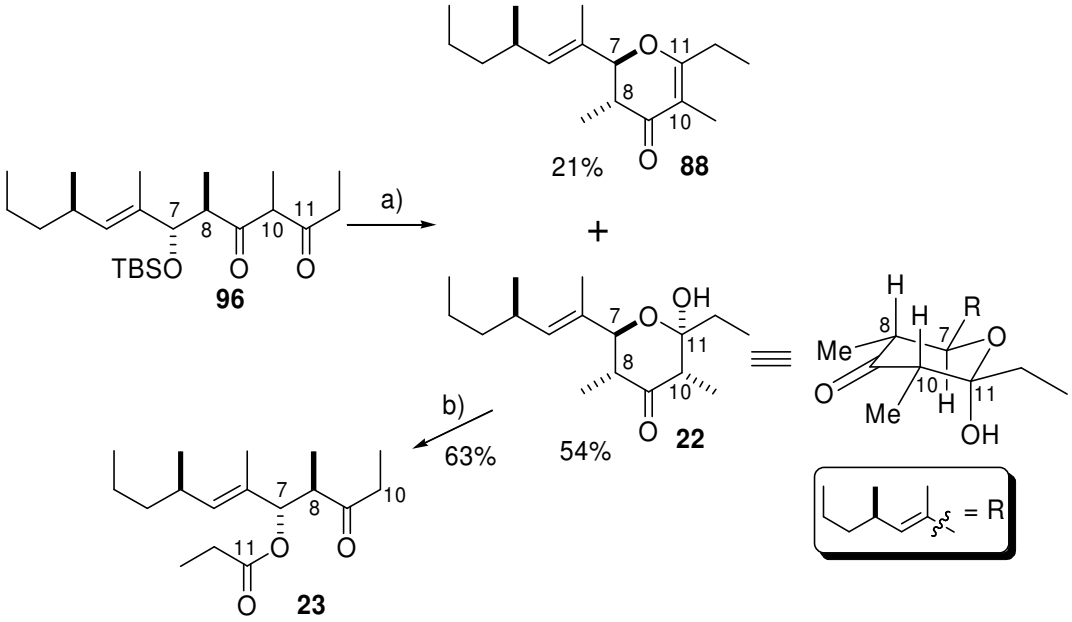
With the final synthetic operation at hand, namely liberation of the C7 alcohol, a suitable method was sought for the removal of the TBS protecting group. As delineated in Scheme 2.8, exhaustive deprotection was facilitated by the method developed by Hoffman for the cleavage of TBS ethers from precursors to acetal functionalities.[37] In practice, compound **96** was treated with buffered[38,39] pyridinium hydrofluoride[ϕ] and a catalytic amount of water[37] for six days at room temperature to give, after purification by flash chromatography on buffered[π] silica, hemiacetal **22** as a single isomer in satisfactory yield (54%). A small amount of material was lost to dehydration (compound **88**, 21%). The ^{13}C NMR (C_6D_6) spectral shifts for hemiacetal **22** showed excellent agreement with those reported[2] for the natural product **81**, but apparent and considerable inconsistencies in the ^{1}H NMR spectra ($CDCl_3$) led to an initial concern that the structural assignment of **81** was not the same as shown for **22**.

Replicating the finding of Hochlowski[2], hemiacetal **22** was almost completely converted to ester **23** under the action of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). Unfortunately, the resultant mixture of starting material and product could not be

[ϕ] A stock solution was prepared from dry THF (10 mL), pyridine (5 mL) and pyridinium hydrofluoride 2.1 g, 30%) and kept in the freezer.

[π] Silica gel was buffered by spinning silica gel 60 (mesh size 0.040-0.063 mm, 100 g) with pH 7 phosphate buffer (10 mL) on a rotary evaporator overnight at atmospheric pressure. This was employed to minimize acid catalysed (silica gel) dehydration of hemiacetal **22**.

separated, but the spectroscopic data for ester **23** could be deduced by subtraction of the minor peaks due to hemiacetal **22**.



Reagents and conditions: a. HF·pyridine/pyridine in THF (excess), H_2O (cat.), rt, 6 days; **b.** DBU (cat.), C_6H_6, rt 30 min.

Scheme 2.8: *Completion of the synthesis of hemiacetal* ***22*** *and conversion to ester* ***23****.*

High field ^{1}H NMR spectral analysis (Figure 2.9) of hemiacetal **22** revealed an oxymethine doublet at δ 4.15 (J = 10.2 Hz) which showed coupling to a doublet of quartets of doublets at δ 2.18 (J = 10.2, 6.6, 1.2 Hz). This is consistent with the C7 and C8 protons, where the large coupling constant (J = 10.2 Hz) confirms their *anti*-periplanar relationship (see Scheme 2.8). The signal at δ 2.18 also shows coupling to the methyl doublet at δ 1.01 (J = 6.6 Hz) and a very small cross coupling to the methyl methine broad quartet at δ 2.26 (J = 6.6 Hz). The signal at δ 2.26 is consistent with the C10 proton which shows reciprocal coupling to the C8 proton (δ 2.18) in addition to small W-coupling to the hydroxyl proton (δ 1.39, J = 1.2 Hz) and to the methyl doublet at δ 1.13 (J = 6.6 Hz). The diastereotopic C12 methylene protons appear as multiplets at δ 1.54-1.45 and δ 1.34-1.27 and show reciprocal coupling in addition to coupling to the methyl triplet at δ 0.79 (J = 7.5 Hz).

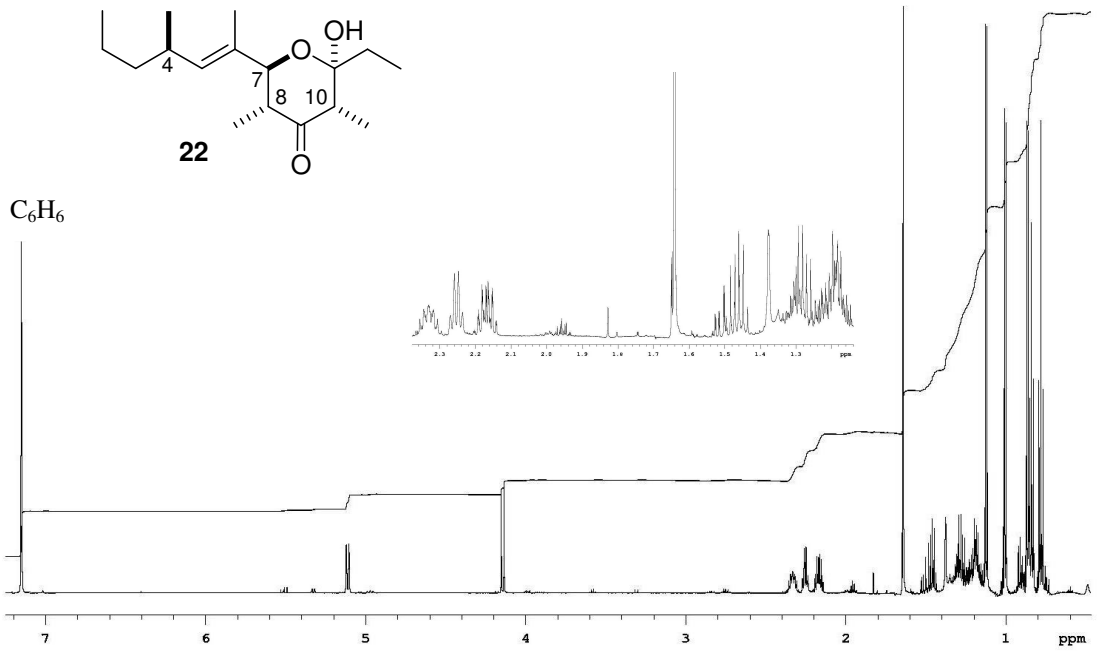


Figure 2.9: *600 MHz ^{1}H NMR spectrum of hemiacetal* ***22*** *in C_6D_6.*

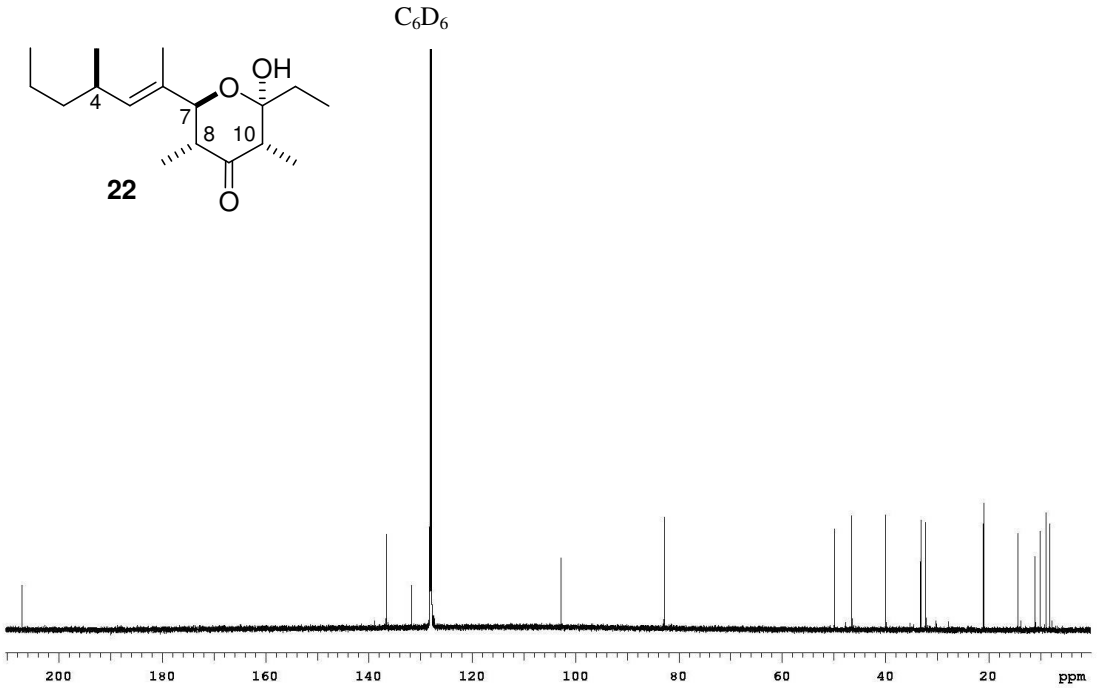


Figure 2.10: *151 MHz ^{13}C NMR spectrum of hemiacetal* ***22*** *in C_6D_6.*

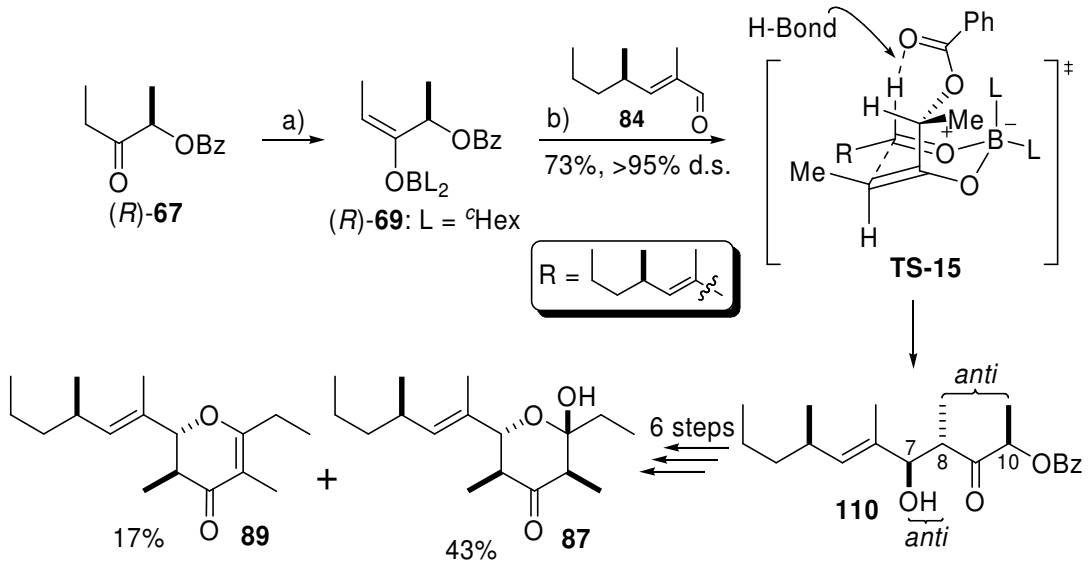
The ^{13}C NMR spectrum displays the characteristic quaternary hemiacetal signal at δ 103.5 as well as carbonyl and oxymethine resonances at δ 207.2 and 82.8, respectively. Infrared spectral analysis showed a broad hydroxyl stretch at 3468 cm^{-1}

and a sharp carbonyl absorption band at 1719 cm^{-1}, and high resolution mass spectrometry confirmed a molecular formula of $C_{17}H_{30}O_3$.

2.3.5 The Synthesis of Hemiacetal 87 for Spectral Comparison

To confirm the stereochemical assignment of the natural product hemiacetal, it was necessary to determine what effect the configuration of the remote C4 stereocentre would have on the ^1H NMR and ^{13}C NMR spectroscopic data. Accomplishing this would require the synthesis of the C4 epimer of hemiacetal **22**. However, for convenience, aldehyde **84** would be coupled with (*R*)-**67**, which is the enantiomer of the previously used (*S*)-**67**; this would ultimately furnish hemiacetal **87**, which is the enantiomer of (and thus has the same physical data as) the C4 epimer of hemiacetal **22**.

As shown in Scheme 2.9, the initial aldol coupling between (*R*)-**67** (shown in Scheme 2.5) and aldehyde **84** (containing a small amount of *ent*-**84**) proceeded under identical conditions[9,18] to those previously stated to afford aldol adduct **110** in good yield and excellent selectivity. Notably, the diastereomeric product from reaction of the enantiomer of aldehyde **84** with (*R*)-**67** was detected in slightly higher quantities than in the previous case (Section 2.3.3). This would be expected if, as previously suggested, aldehyde **84** displayed a small kinetic diastereoselection for ketone (*S*)-**67**. Small differences in the ^{13}C NMR spectrum between compound **110** and **108** enabled identification of this minor isomer (as it is the enantiomer of **108**) in the crude reaction products. Fortunately, the quantity of the minor diastereomer decreased after each purification as compound **110** was taken through the remaining sequence to the point where it was undetectable by the end of the synthesis. To this end, adduct **110** was submitted to the same six step sequence previously described to furnish hemiacetal **87** as a single isomer in 6.9 % overall yield, in 13 steps from oxazolidinone (*R*)-**100**.



Reagents and conditions: a. $^{c}Hex_2BCl$ (1.5 eq), Me_2NEt (1.8 eq), Et_2O, 0 °C, 2 h; **b.** aldehyde **84**, Et_2O, −78 °C 2 h to −23 °C, o/n.

Scheme 2.9: *Synthesis of isomeric hemiacetal **87**.*

The ^{1}H and ^{13}C NMR spectra (Figures 2.11 and 2.12) of hemiacetal **87** displayed all the expected resonances for its structure and was similar but not identical to the spectra acquired for diastereomeric hemiacetal **22**.

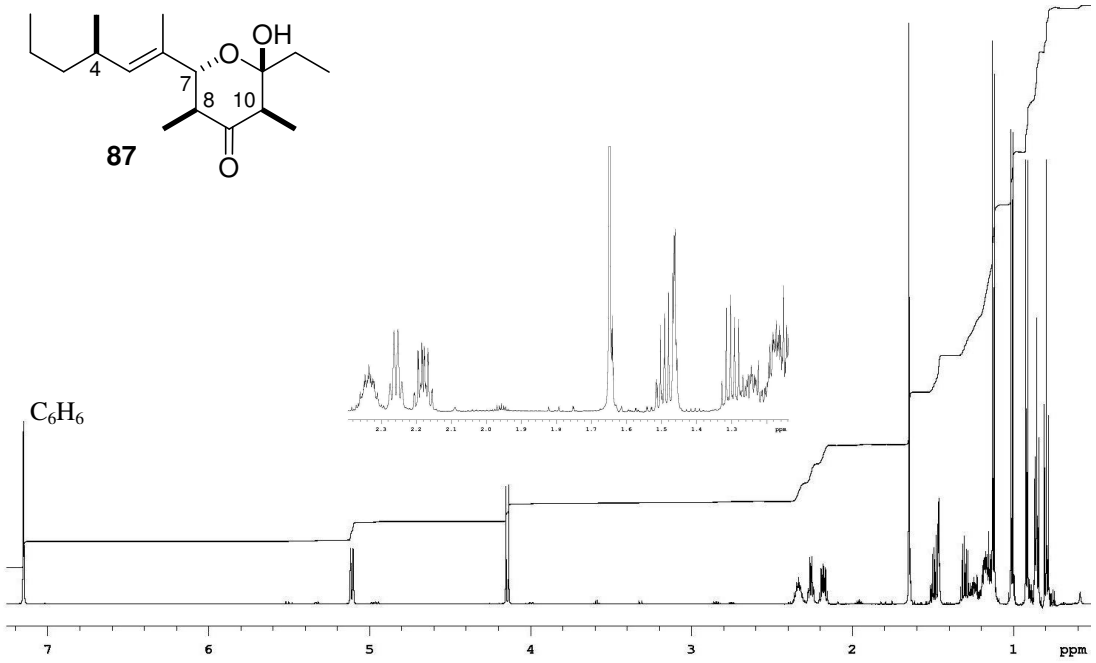


Figure 2.11: *600 MHz ^{1}H NMR spectrum of hemiacetal **87** in C_6D_6.*

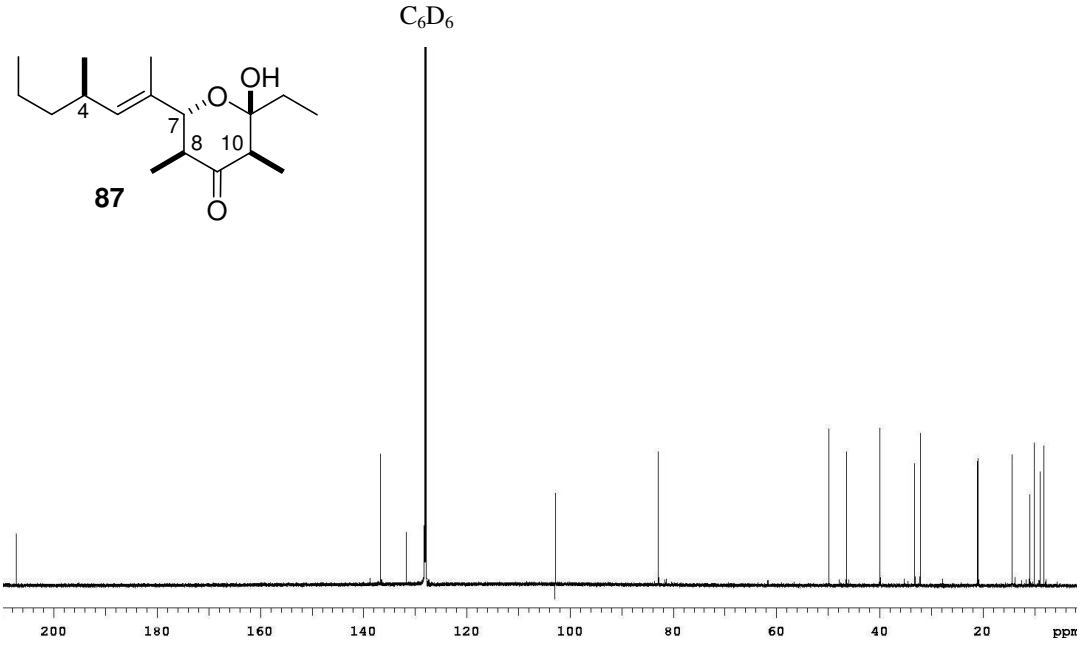
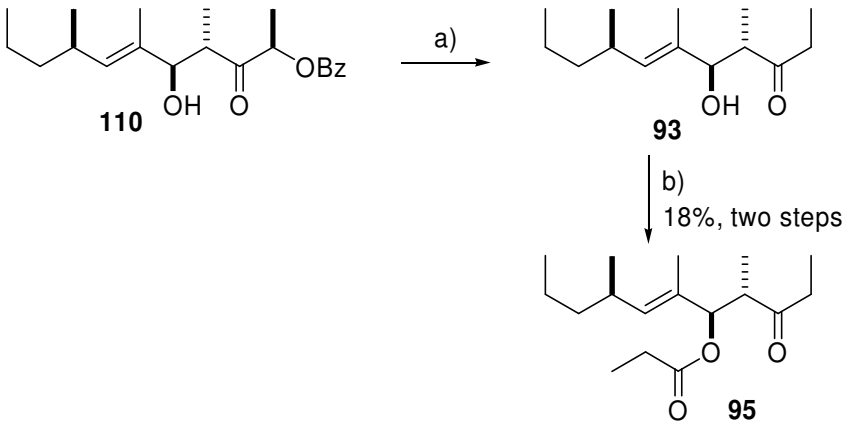


Figure 2.12: *151 MHz ^{13}C NMR spectrum of hemiacetal **87** in C_6D_6.*

In an attempt to obtain ester **95** in a higher state of purity than was accomplished for its diastereomer **23**, the unprotected aldol adduct **110** was treated directly with SmI_2[16,18] to give the free alcohol **93** albeit in poor yield. Subsequent acylation with propionyl chloride gave pure ester **95**. The extremely poor yield for the reductive cleavage of the benzoate exemplifies the need to protect such adducts before exposure to SmI_2. However, for the purposes of obtaining ester **95** this was deemed an acceptable sacrifice.



Reagents and conditions: a. SmI_2 (~4.0 eq), THF, 0 °C; **b.** propionyl chloride (5.0 eq), pyridine (5.3 eq), CH_2Cl_2, rt, 2 h.

Scheme 2.10: *Synthesis of ester **95** from adduct **110**.*

2.3.6 Identifying the Stereochemistry of the Natural Products

The ^{13}C NMR spectral data for isomers **22** (Figure 2.10) and **87** (Figure 2.12) in C_6D_6 were virtually identical and consistent with that reported[2] for hemiacetal **81**. While the isomers could not be distinguished by ^{13}C NMR spectral analysis, the ^{1}H NMR spectra (C_6D_6) showed small but significant differences. Notably, the C17 methyl group in hemiacetal **22** resonates at δ 0.87, while in hemiacetal **87** this same group resonates at δ 0.93. After acquiring[θ] copies of the original ^{1}H NMR spectra for hemiacetal **81** and ester **82**, it became clear that the spectra were recorded in CCl_4 and not $CDCl_3$ as was reported in the isolation paper. This explained the notable inconsistencies between the ^{1}H NMR spectral data acquired for hemiacetal **22** in $CDCl_3$ with that reported for the natural product. Copies of the authentic data also included a ^{1}H NMR spectrum of the natural product in C_6D_6. Ultimately, ^{1}H NMR spectra of hemiacetal **22** recorded in both CCl_4 and C_6D_6 were found to be identical to that of the natural product, but different to hemiacetal **87** (^{1}H NMR spectrum recorded in CCl_4 for synthetic **22** and authentic **81** are shown in Figure 2.13 and 2.14, respectively). Unfortunately, copies of the original ^{13}C NMR spectra were not available for direct comparison, but the data recorded for hemiacetal **22** was identical to that reported for the authentic material. Additionally, the optical rotation found for hemiacetal **22** was $[\alpha]^{20}_{D}$ = + 27.1 (*c* 0.6, $CHCl_3$), which is in excellent agreement with that reported[2] for the natural product **81** ($[\alpha]^{20}_{D}$ = +22.3 (*c* 0.84, $CHCl_3$)) and allowed the absolute configuration of the natural product **81** to be assigned as that shown for compound **22**.

[θ] Copies of the original ^{1}H NMR spectra recorded in CCl_4 and C_6D_6 for hemiacetal **81** and ester **82** were kindly provided by Ms. Catherin M. Sinich, Professor William Fenical and the late Professor D. John Faulkner, Centre for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography.

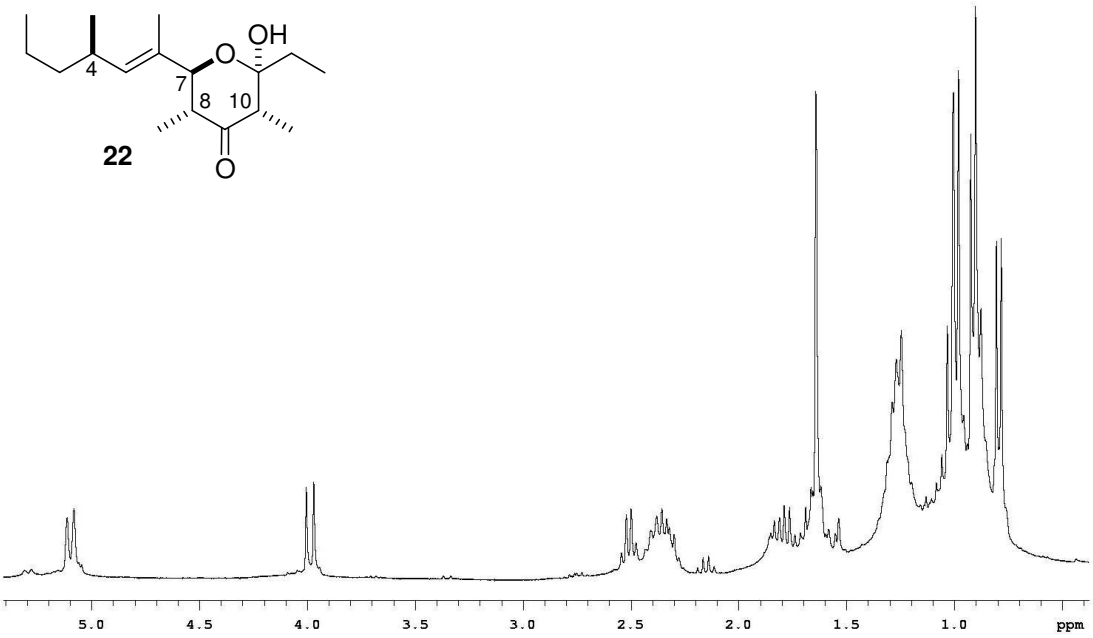


Figure 2.13: *300 MHz ^{1}H NMR spectrum of synthetic hemiacetal* ***22*** *in CCl_4.*

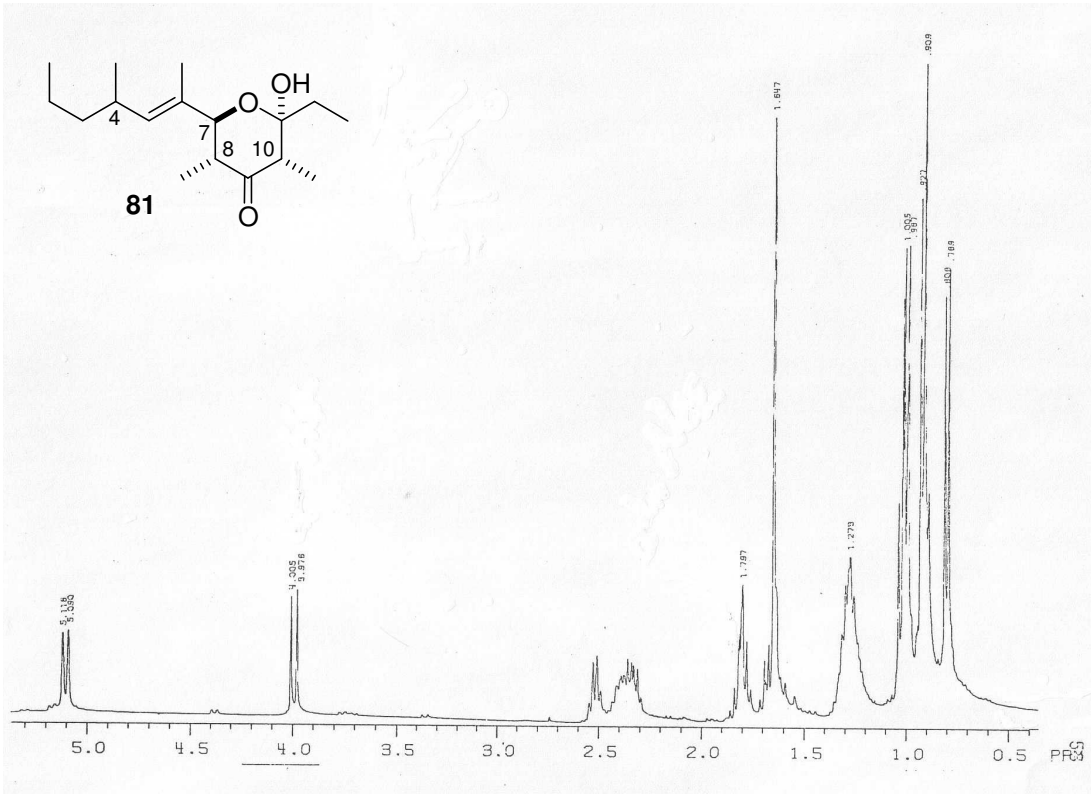


Figure 2.14: *300 MHz ^{1}H NMR spectrum of authentic hemiacetal* ***81*** *in CCl_4.*

Inspection of the authentic ^{1}H NMR (C_6D_6) spectrum of ester **82** clearly indicated that it was identical to that of synthetic ester **23**, but different to ester **95**.

Additionally, the optical rotation for ester **23** $[\alpha]^{20}_{D} = -6.0$ (*c* 0.5, $CHCl_3$) was consistent with that reported[2] for ester **82** ($[\alpha]^{20}_{D} = -7.1$ (*c* 0.5, $CHCl_3$)).

The detailed spectral data confirm that Sundram's original configurational assignment[7] of hemiacetal **81** and ester **82** was indeed correct.

2.4 Conclusion

The previous sections detail a highly stereocontrolled synthesis of hemiacetal **22** and the associated ester **23** in 7.6% and 4.8% yield respectively, from (*R*)-4-benzyl-2-oxazolidinone [(*R*)-**100**].[11] It was subsequently shown that the NMR spectroscopic data and optical rotations of these synthetic compounds are identical to those reported[2] for hemiacetal **81** and ester **82** isolated from *Siphonaria australis*. As such, the first total synthesis and unambiguous configurational assignment of the natural product hemiacetal **81** had been achieved. The strategy employed for this synthesis utilised Paterson's lactate derived[9] ketone (*S*)-**67** in a substrate controlled *anti*-aldol reaction to generate the C7 and C8 stereocentres and a stereoselective alkylation to install the remote C4 stereocentre. The methodology also employed a novel, highly efficient, and selective strategy to synthesize trimethylsilyl enol ether **109**, which was used as a substrate for a Lewis acid catalysed Mukaiyama aldol homologation.[31]

The base induced retro-Claisen synthesis of ester **23** has confirmed its potential formation as a degradation artefact of hemiacetal **22**. This particular approach to ester synthesis in non-contiguous polypropionates will be pursued and elaborated upon in the following Chapter in which marine natural product dolabriferol (**30**) will be targeted.

2.5 References

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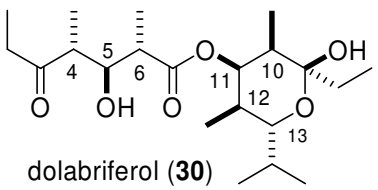
Chapter Three

A Retro-Claisen Approach to the Marine Polypropionate Dolabriferol

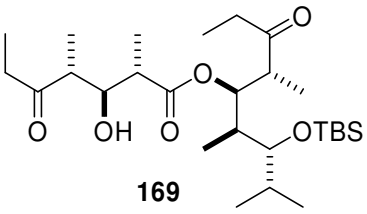
Chapter Three

A Retro-Claisen Approach to the Marine Polypropionate Dolabriferol

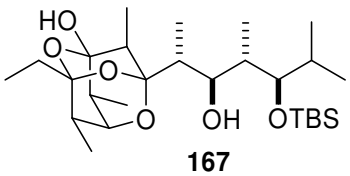
This chapter describes progress made towards a total synthesis of the unusual marine natural product dolabriferol (**30**). The following sections will elaborate a highly efficient asymmetric synthesis of direct precursor **169** to dolabriferol (**30**), using lactate derived ketone (*S*)-**67** to develop the requisite C4-C6 and C10-C13 stereoarrays. Key events include the synthesis of trioxaadamantane **167** and its fragmentation, *via* a retro-Claisen pathway, to give precursor **169**.



dolabriferol (**30**)



169



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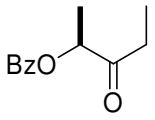


(*S*)-**67**

3.1 Introduction

3.1.1 *Dolabrifera dolabrifera* and the isolation of dolabriferol (30)

Dolabrifera dolabrifera is a small (<40 mm) opisthobranch belonging to the Dolabriferidae family of marine gastropods, which is typically found circum-globally in warm tropical and sub-tropical waters.[1] This sea hare differs from members of the *aplysia* genus by the presence of small asymmetric parapodia, a calcified internal shell and a flattened body[2] that is usually mottled green or brown, but can range from

pink to dark brown (Figure 3.1). Sometimes termed the 'warty seacat', the species is covered in projections that resemble tubercles, which bear retractile single or compound papillae, and crawls with a very characteristic leech-like movement.[1]

Figure 3.1: *Specimen of Dolabrifera dolabrifera.*

Despite being the most common species of the genus *Dolabrifera*,[2] *D. dolabrifera* has received very little attention from the chemical community. In fact, when Ciavatta and co-workers reported[2] the isolation of dolabriferol (**30**) in 1996, it constituted the first chemical study to be conducted on an opisthobranch belonging to the Dolabriferidae family.[2,3] Specimens collected off the coast of Cuba (11 individuals), yielded 7.5 mg of dolabriferol (**30**) as the main metabolite from the diethyl ether soluble fraction of the acetone extracts (0.7 mg/animal).[2] Interestingly, the metabolite was shown to be present (tlc) in the acetone extracts of the dissected parapodia and hepatopancreas of a single specimen, but absent in the digestive glands.[2] This suggests that dolabriferol (**30**) is produced for some ecological advantage and not simply acquired through algal grazing or symbiotic production. Unfortunately, Ciavatta *et al.* made no mention of any biological activity associated with dolabriferol (**30**), or indeed if a biological assay was performed.

3.1.2 Structural Elucidation of Dolabriferol

The structure of dolabriferol (**30**) was elucidated by Ciavatta *et al.* using extensive NMR studies and the complete relative stereochemistry of the compound was confirmed by single crystal X-ray analysis.[2] While the absolute configuration

remains unassigned, a comparison to the seemingly related baconipyrones A-D (**111**-**114**, Figure 3.2)[4] suggested the structure drawn for **30** as the candidate for synthesis. Dolabriferol (**30**) comprises polypropionate architecture, featuring a highly substituted hemiketal, tethered to a β-hydroxyketone *via* an unusual ester linkage. The presence of a non-contiguous carbon backbone assigns dolabriferol to group of similarly episodic marine polypropionates[5] that includes the baconipyrones (**111**-**114**),[4] siserrone A (**115**),[5] and ester **23** (isolated from *S. australis*)[6] (Figure 3.2).

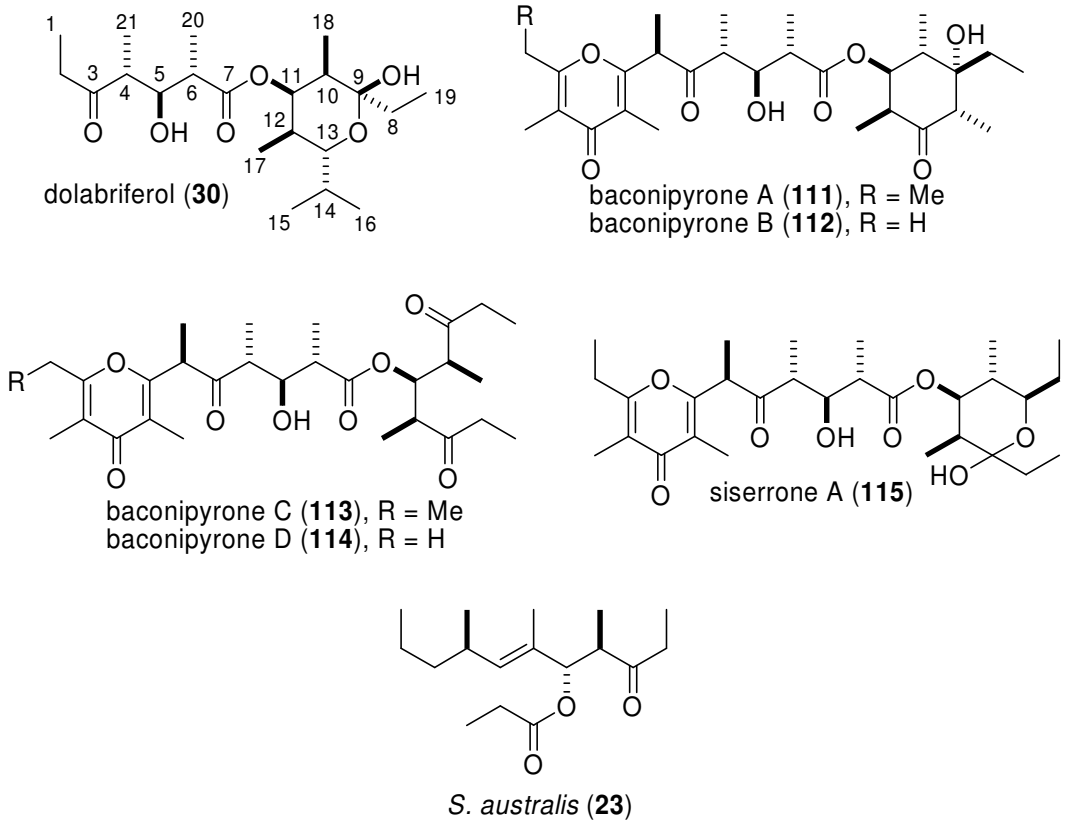
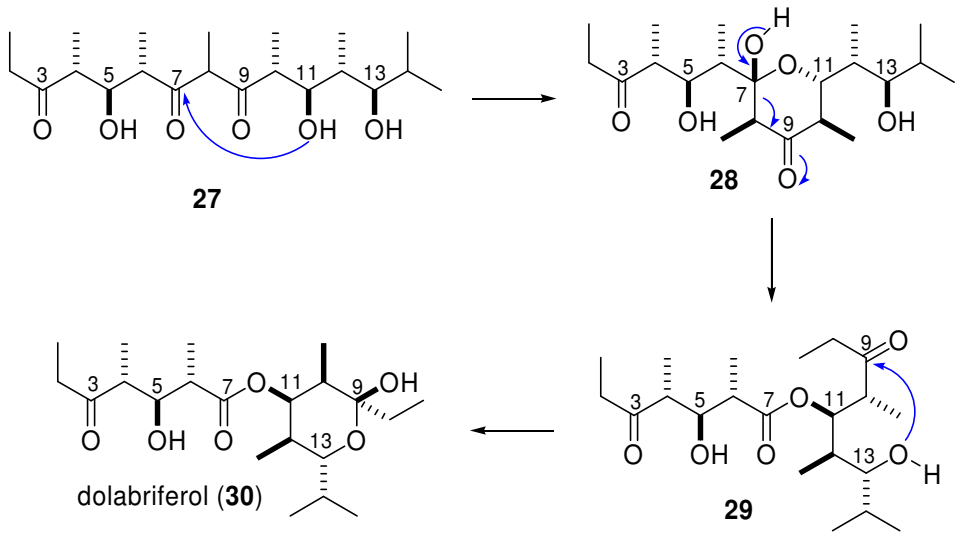


Figure 3.2: *Dolabriferol and other non-contiguous polypropionates.*

Despite the findings of Ciavatta *et al.*,[2] which showed that dolabriferol (**30**) was present in extracts of the parapodia and hepatopancreas, but not the digestive glands (Section 3.1.1), it has been suggested[5] that the hetero-atom motif present in dolabriferol (**30**), and common to compounds **23** and **111**-**115,** is not the result of rich biodiversity, but rather is formulated from a putative acyclic precursor upon extraction. Consequentially, these seemingly unique natural products may be artefacts. The proposed[2,5] formation of dolabriferol (**30**) is shown in Scheme 3.1,

where thermodynamic cyclisation of putative acyclic precursor **27**, followed by opening of intermediate hemiacetal **28** *via* a retro-Claisen type fragmentation, leads to ester **29**. Subsequent hemiketalisation of ester **29** affords dolabriferol (**30**). A similar mechanism can be invoked to explain the presence of the ester functionality in compounds **23** and **111-115** (Figure 3.2). As such the natural product status of dolabriferol (**30**), and the related compounds, has been questioned.[5]



Scheme 3.1: *Proposed synthesis of dolabriferol (**30**) form acyclic precursor **27**.*

3.2 Previous Work

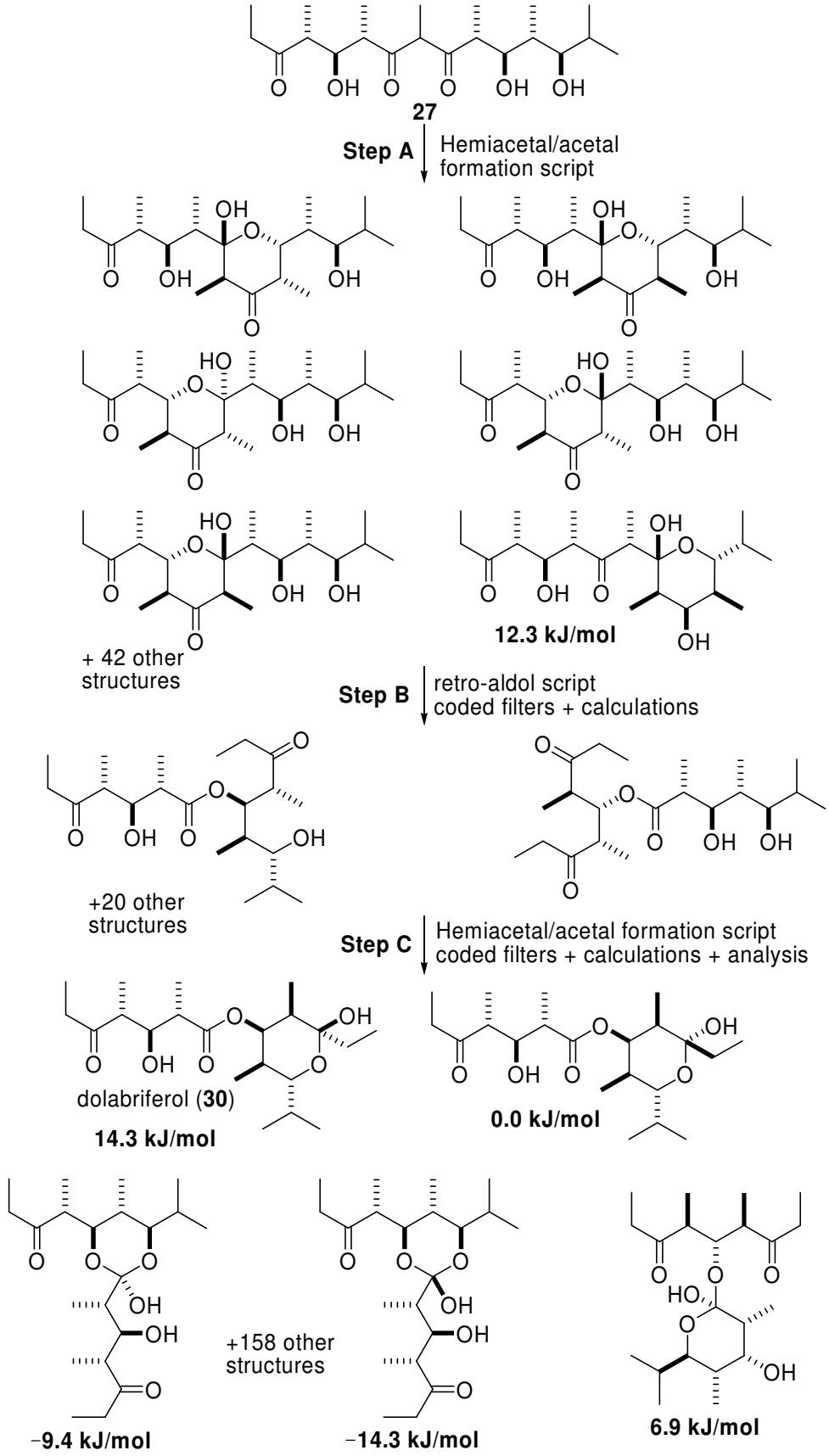
3.2.1 Overview

Since the isolation of dolabriferol (**30**) in 1996,[2] there have been efforts made by several research groups worldwide to complete a total synthesis of this interesting natural product. Despite the limited number of publications concerning these efforts, it was clear that each group, whilst investigating their own unique strategies, had opted to attempt to access dolabriferol (**30**) *via* union of an appropriate acid and alcohol fragment in a direct esterification reaction. The following sections present an overview of the current progress these groups have made towards a total synthesis of dolabriferol (**30**).

3.2.2 Goodman's Computational Studies

In conjunction with yet unpublished synthetic efforts, Jonathan Goodman of Cambridge University in England has recently detailed[7] a computational study of the reaction pathway leading to dolabriferol (**30**) starting from the proposed acyclic precursor **27**. ROBIA[7] is a reaction prediction program developed by Goodman *et al.* to aid organic chemists by generating possible reaction pathways and automatically assessing the most favourable route. The program is rule based, using coded reaction knowledge to make decisions on the primary aspects of organic reactivity, such as the location of reactive sites and which bonds are to be broken or made. The program utilises integrated molecular modelling to perform energy minimisations and conformational searching on input and output structures. The sequence takes the reactant through a series of intermediate steps in which all possible structures are formed and then filtered and selected according to the coded rules and reaction conditions. ROBIA is also capable of generating and considering all possible stereocentres in instances where there are stereocentres of unknown configuration, or where new stereocentres are formed.

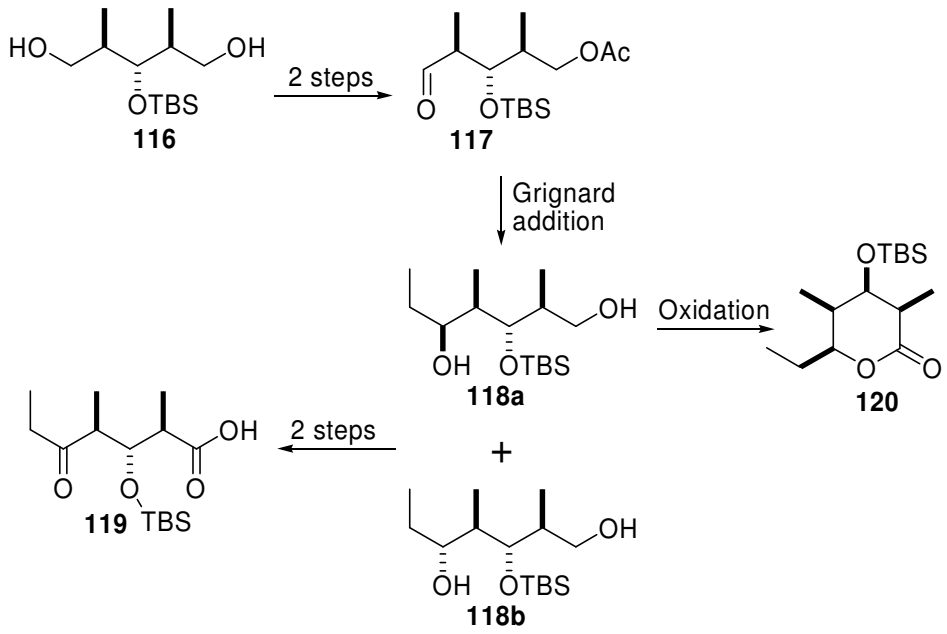
ROBIA was used to predict the low energy structures resulting from linear precursor **27** after a three step sequence of hemiketalisation, retro-aldol and hemiketalisation.[7] Scheme 3.2 shows a summary of the structures generated by the program and indicates the single point *ab initio* energy calculated for the final products. It was clear that the program, whilst capable of predicting dolabriferol (**30**) as a potential product, also predicted 162 other possible products, several of which have a lower predicted energy than dolabriferol (**30**). While Goodman conjectured that these lower energy structures could be omitted based on experimental evidence, thus leaving dolabriferol (**30**) as the lowest energy product, it was apparent that an immense number of compounds can be formed from putative acyclic precursor **27**.



Scheme 3.2: *Results of Goodman's ROBIA calculation.*

3.2.3 Chênevert's Synthesis of Ketoacid Fragment 119

Chênevert's group at Université Laval in Canada have recently reported[8] an enantioselective synthesis of acid **119** which corresponds to the carboxylate portion of dolabriferol (**30**). Their convergent strategy took advantage of the structural symmetry present in dolabriferol, such that precursor **116** could be used to formulate both the acid and alcohol fragments. Given the ambiguity surrounding the absolute stereochemistry of dolabriferol (**30**), Chênevert *et al.* drew on their own previous work[9] to obtain **116**, which would ultimately lead to the enantiomer of the structure depicted by Ciavatta[2] for dolabriferol (**30**).



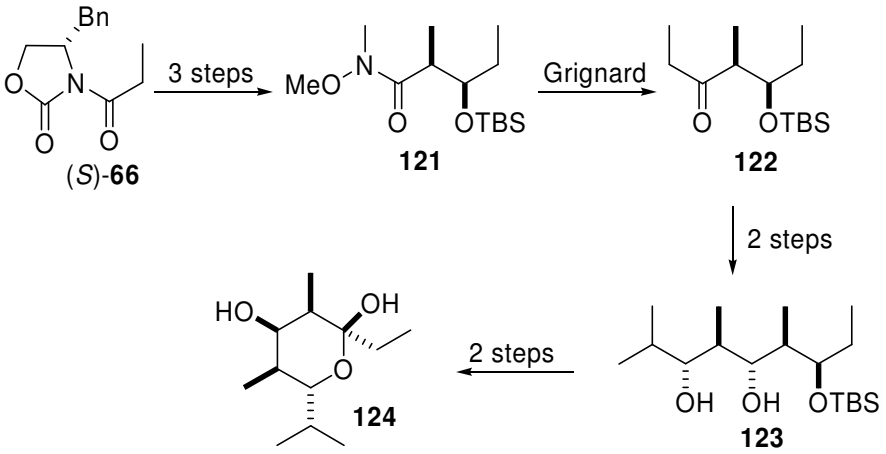
Scheme 3.3: *Chênevert's synthesis of the ketoacid fragment **119** of dolabriferol (**30**).*

The synthesis commenced[8] with desymmetrisation of **116** through the action of *Candida rugosa* lipase in conjunction with vinyl acetate, which proceeded with excellent enantiomeric excess (94% e.e.). Dess-Martin oxidation furnished aldehyde **117**, which in turn underwent a highly selective ethyl Grignard addition (with concomitant acetate cleavage) to give a 6:1 ratio of separable alcohols **118a** and **118b**, respectively. Finally, double Swern oxidation afforded an intermediate keto aldehyde (not shown), which was further oxidised with $RuCl_3$ to give the target ketoacid **119** in excellent overall yield (58%, for 5 steps). The stereochemistry of **118a** was confirmed by treatment with PDC, which resulted in fast chemoselective

oxidation of the primary alcohol to give the corresponding acid, which subsequently cyclised to give known[10] lactone **120**.

3.2.4 Dias's Studies on Direct Esterification

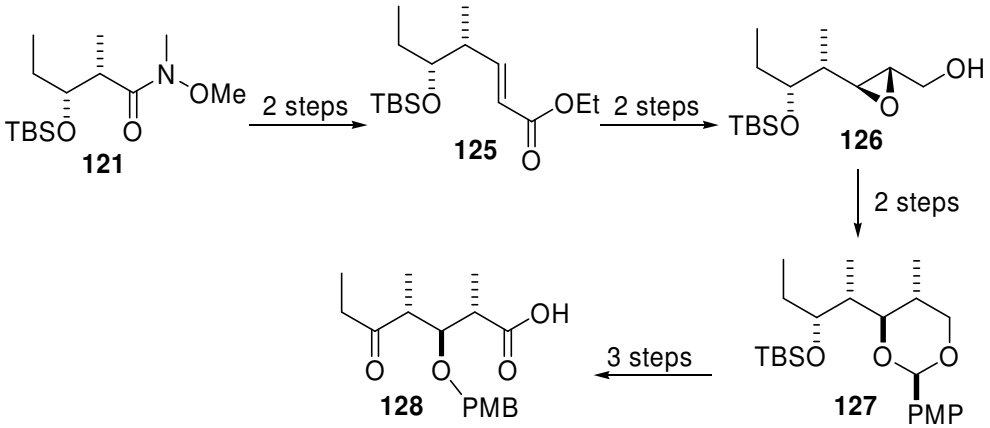
In 2003, Luiz Dias and co-workers at the Instituto de Química in Brazil published[11] their substantial efforts towards a synthesis of dolabriferol (**30**). Their strategy also exploited the inherent symmetry of dolabriferol (**30**) by employing intermediate **121** to access both the acid and alcohol fragments required for esterification. Amide **121** was synthesised from known[12] *N*-acyloxazolidinone (*S*)-**66** *via* a standard three step sequence of aldol addition, protection and transamidation, as shown in Scheme 3.4 (both enantiomers of **121** are readily available, hence Dias *et al.* decided to target the structure of dolabriferol (**30**) as arbitrarily depicted by Ciavatta *et al.*). Subsequent ethyl Grignard addition gave ketone **122**, which underwent a highly selective *anti*-aldol addition and subsequent *syn*-reduction ($Zn(BH_4)_2$) to give diol **123**. Desilylation of **123** was followed by chemoselective Swern oxidation, which afforded the desired lactol **124** in a modest 40% yield.[11] This ambitious oxidation strategy was representative of the challenges posed by the alternating oxidation states of the oxygen substituents in dolabriferol (**30**).



Scheme 3.4: *Dias's synthesis of lactol **124**.*

As depicted in Scheme 3.5, reduction and *E*-selective olefination of common fragment **121** afforded enoate **125**. Subsequent DIBAL-H reduction and epoxidation of the olefin gave epoxide **126** in good yield (78%, for 4 steps) and high

diastereoselectivity (>95:5). Alkylation with methylcupurate and protection of the resultant diol gave benzylidene **127**, from which the target ketoacid **128** was formulated, through a series of standard functional group manipulations.[11] Recent discussions with the Dias group[13] have revealed that despite their extensive efforts, advanced intermediates **124** and **128** do not participate in the desired esterification reaction, giving instead only decomposition products.



Scheme 3.5: *Dias's synthesis of acid **128**.*

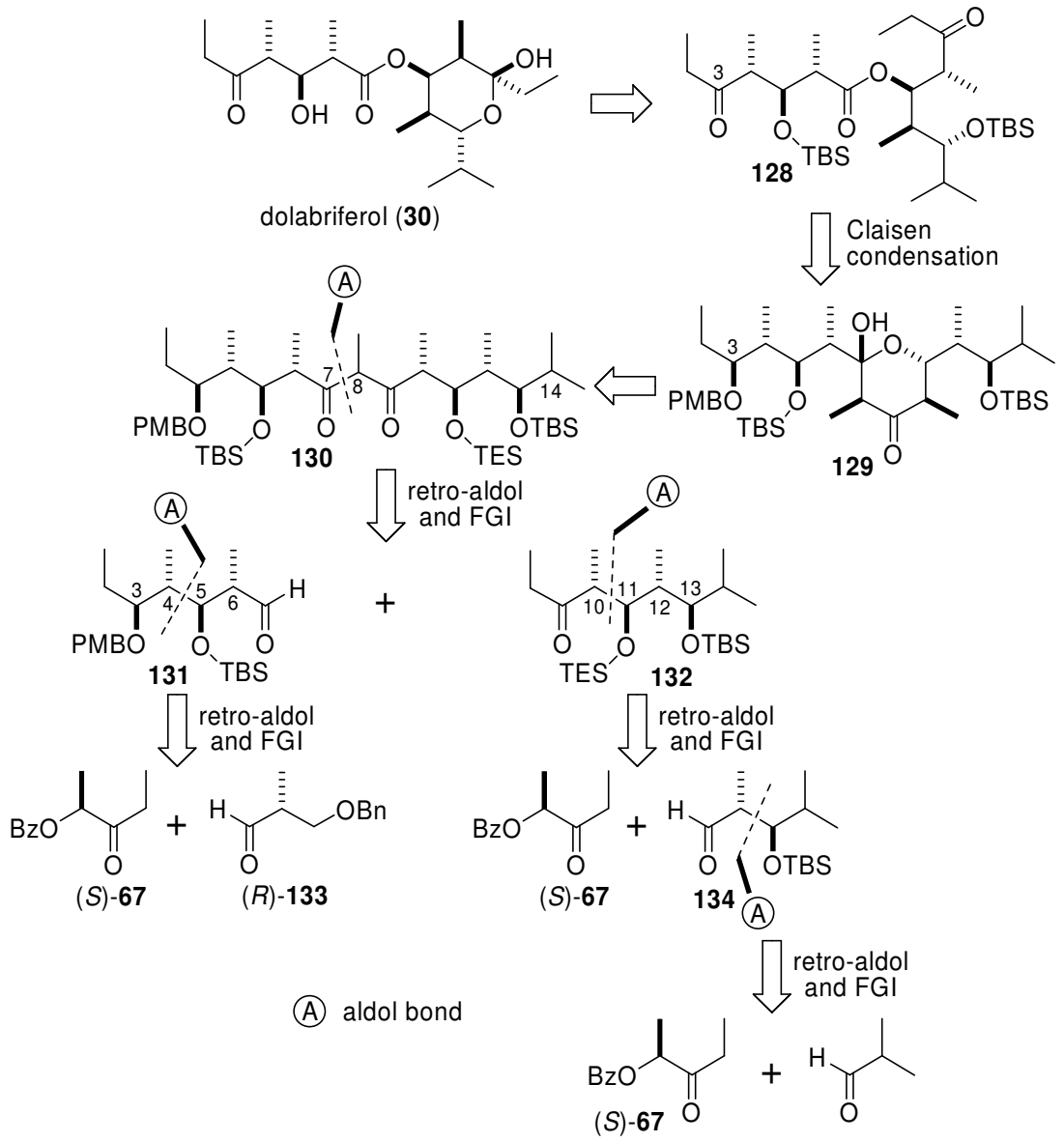
3.3 Synthetic Strategy and Retro-Synthetic Analysis

Since its isolation in 1996,[2] dolabriferol (**30**) has remained an elusive target for total synthesis. The strategies[8,11] discussed in the preceding section are directed towards reaction between an acid and alcohol fragment to install the ester moiety of dolabriferol (**30**), which despite being an obvious retro-synthetic disconnection, has proven difficult to implement.[13] The approach to dolabriferol (**30**) presented herein avoids direct esterification, while providing an insight to the compounds biological origin.

The chosen strategy adopts a 'pseudo biomimetic' approach, such that the ester moiety of dolabriferol (**30**) would be accessed from a linear precursor by-way of retro-Claisen fragmentation of an intermediate hemiketal. As shown retro-synthetically in Scheme 3.6, opening of the hemiacetal ring in dolabriferol (**30**) reveals acyclic ester **128**, whose synthesis was anticipated to result from retro-

Claisen fragmentation of hemiacetal **129**, followed by correction of the C3 oxidation state. This latter compound represented a key intermediate in the synthesis, as only hemiacetal **129** would give the desired ester upon retro-Claisen fragmentation. Selective deprotection and subsequent thermodynamic cyclisation of β-diketone **130** should afford hemiacetal **129**. The backbone of linear precursor **130** displays *pseudo* C2 symmetry, which is only broken by the additional methyl group at C14 (the protecting groups depicted in **130** were chosen to permit controlled cyclisation). Also evident is the continuous *anti*-relationship between oxygen bearing and methyl bearing stereocentres along the carbon backbone. This results in all the methyl substituents pointing 'down' as depicted for compound **130**. A retro-aldol bond disconnection (C7-C8) of β-dicarbonyl **130** leads to β-silyloxy-δ-alkoxyaldehyde **131** and bis-silyloxy ethyl ketone **132**, which are of almost equal size, thus affording a highly convergent strategy. Aldehyde **131** was anticipated to be available, after several steps, from an initial substrate controlled *anti*-aldol coupling of lactate derived[14] ketone (*S*)-**67** with known[15] aldehyde (*R*)-**133**. This union would be responsible for generating the C4-C6 stereotriad. Notably, it was foreshadowed that manipulation of the C3 oxidation state would be critical to avoid potential hemiketalisation at various points in the synthesis. Acquisition of bis-silyloxyketone **132** would rely on an iterative *anti*-aldol homologation sequence starting from ketone (*S*)-**67**.

Significantly, the strategy employed lactate derived[14] ketone (*S*)-**67** to install all but the C6 stereocentre (introduced from the chiral pool *via* (*R*)-**133**). Additionally, it was anticipated that the retro-Claisen approach to ester **128** would closely mimic the strategy employed[16] to synthesise ester **23** from hemiacetal **22** (Scheme 2.8, Chapter 2).



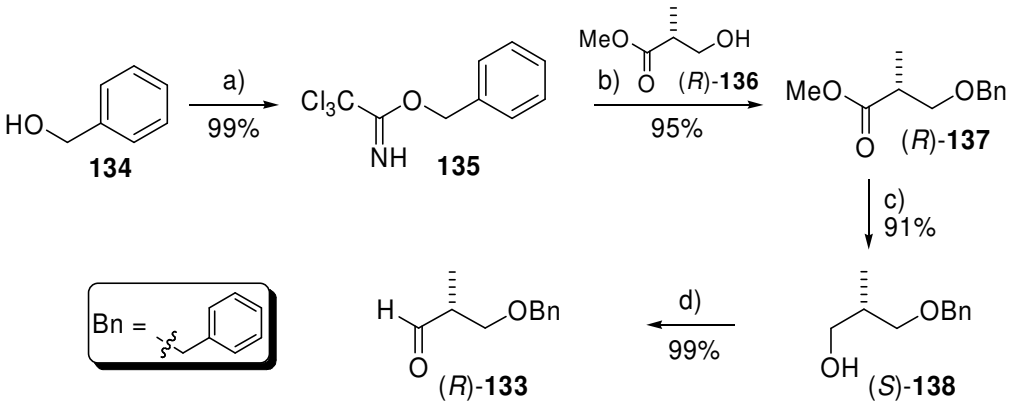
Scheme 3.6: *Retro-synthetic analysis of dolabriferol (**30**).*

3.4 Synthesis of Pivotal Acyclic Precursor 130

3.4.1 Acquisition of Aldehyde 131

With lactate derived ketone (*S*)-**67** in hand (Scheme 2.5, Chapter 2),[14,17] the early stages of the synthesis of aldehyde **131** focussed on acquiring aldehyde (*R*)-**133**, which was accomplished through well established chemistry[15,18-20] (Scheme 3.7). To that end, hydroxyl ester (*R*)-**136** was protected as the known[20] benzyl ether (*R*)-**137**, by reaction with benzyl-acetimidate **135** and a catalytic amount of triflic acid (TfOH) in CH_2Cl_2 at room temperature.[21,22] Acetimidate **135** was readily

available from benzyl alcohol **134**, NaH and trichloroacetonitrile.[21,22] Known aldehyde (*R*)-**133** was then smoothly obtained by complete reduction of ester (*R*)-**137** with $LiAlH_4$ and subsequent Swern oxidation[23,24] of the resultant primary alcohol (*S*)-**138**. Aldehyde (*R*)-**133** was prepared and purified (column chromatography, buffered silica) just prior to use.

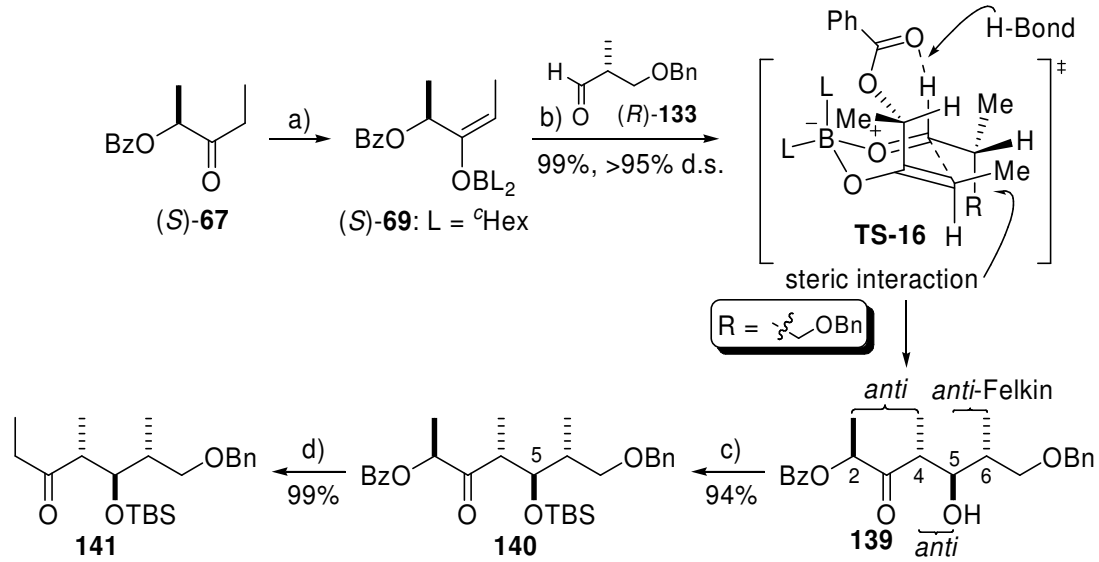


Reagents and conditions: a. i. NaH (0.1 eq), Et_2O, rt, then alcohol **33**; ii. Cl_3CCN, (1.0 eq), 0 °C to rt, 1 h; **b.** ester (*R*)-**136** (0.67 eq), CH_2Cl_2, rt, then TfOH (10 mol%), rt, 18 h; **c.** $LiAlH_4$ (1.1 eq), 0 °C to rt, 30 min; **d.** i. DMSO (3.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (1.5 eq), −78 °C, 30 min; iii. alcohol (*S*)-**138**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (6.0 eq), −78 °C, 30 min to rt.

Scheme 3.7: *Synthesis of known aldehyde (R)-**133**.*

Addition of freshly prepared aldehyde (*R*)-**133** (1.5 eq)[25] to a solution of pre-formed[26,27] *E*-enol dicyclohexylborinate (*S*)-**69** in Et_2O at −78 °C followed by stirring at −23 °C overnight[17] gave known[17,28] 2,4-*anti*-4,5-*anti*-5,6-*anti*-Felkin aldol adduct **139** as a single observable stereoisomer in near quantitative yield (Scheme 3.8). This addition reaction, giving the *anti*-Felkin adduct, is mismatched with respect to the aldehyde, given the persistent Felkin preference (see Section 1.1.5.3 for discussion)[29-31] displayed by aldehydes in aldol reactions with *E*-(O)-enolates (see Section 1.5.3 for related discussion). Transition state[14,17] **TS-16** depicts the steric interaction between the methyl substituent of the enolate and the side chain of the aldehyde that causes the reaction to be mismatched. The observed selectivity of this reaction is testament to the π-facial control exerted by the enolate and indicates that

the selectivity of enolate (*S*)-**69** overrides Felkin-Ahn induction[29-31] from the aldehyde. Protection of the free C5 alcohol as the TBS ether proceeded under standard conditions (TBSOTf and 2,6-lutidine)[32] to give silyloxane **140**. Subsequently, the benzoate was removed by treatment[17,33] with an excess of SmI_2, to furnish ethyl ketone **141** in excellent yield (93% from **139**).



Reagents and conditions: a. $^{c}Hex_2BCl$ (1.5 eq), Me_2NEt (1.8 eq), Et_2O, 0 °C, 2 h; **b.** aldehyde (*R*)-**133** (1.5 eq), Et_2O, −78 °C, 2 h to −23 °C, o/n; **c.** i. 2,6-lutidine (2.0 eq), CH_2Cl_2, −78 °C; ii. TBSOTf, (1.5 eq), −78 °C, 30 min; **d.** SmI_2 (~4.0 eq), THF, 0 °C.

Scheme 3.8: *Construction of the C4-C6 stereotriad and synthesis of ketone* ***141****.*

The ^1H NMR spectrum of TBS protected aldol adduct **140** was consistent with that reported by Paterson *et al.*[17] and is displayed in Figure 3.3. The characteristic acyloxymethine proton appears as a quartet at δ 5.46 (*J* = 7.0 Hz) and shows coupling to the methyl doublet at δ 1.51 (*J* = 7.0 Hz). The remaining TBS oxymethine proton resonates at a doublet of doublets at δ 4.06 (*J* = 9.0, 2.4 Hz) and couples to the methyl methine protons at δ 3.23 (dq, *J* = 9.0, 6.9 Hz) and δ 2.01 (sex d, *J* = 6.9, 2.4 Hz). The methyl methine protons at δ 3.23 and δ 2.01 show coupling to the respective methyl doublets at δ 1.13 (*J* = 6.9 Hz) and δ 1.00 (*J* = 7.2 Hz), while the multiplet at δ 2.01 shows additional coupling to the oxymethylene doublet

of doublets at δ 3.60 (*J* = 9.6, 6.9 Hz) and δ 3.27 (*J* = 9.6, 6.9 Hz). The peaks due to the TBS protecting group are clearly visible as singlets at δ 0.82 (9H), δ 0.06 (3H) and δ –0.06 (3H), while the peaks in the aromatic region (δ 7.2-8.2) and the singlet at δ 4.46 can be attributed to the benzyl protecting group and the phenyl ring of the benzoate. An infrared spectrum of compound **140** showed a broad signal at 1723 cm^{-1}, consistent with overlapping ester and ketone carbonyl bands and high resolution mass spectrometry confirmed the expected molecular composition of $C_{29}H_{42}O_5Si$.

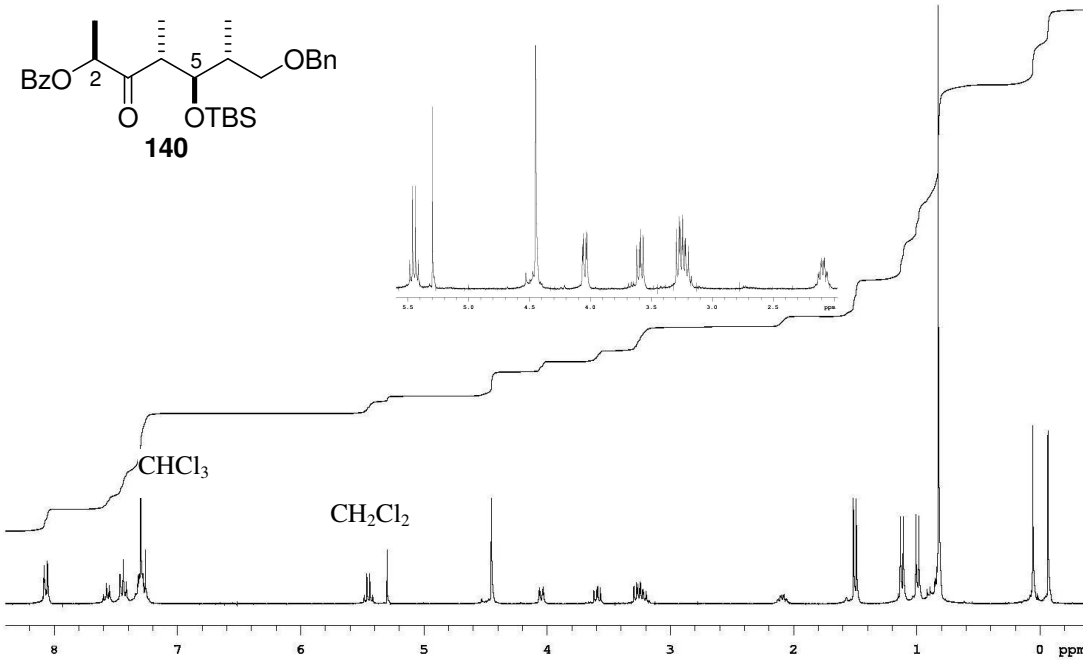
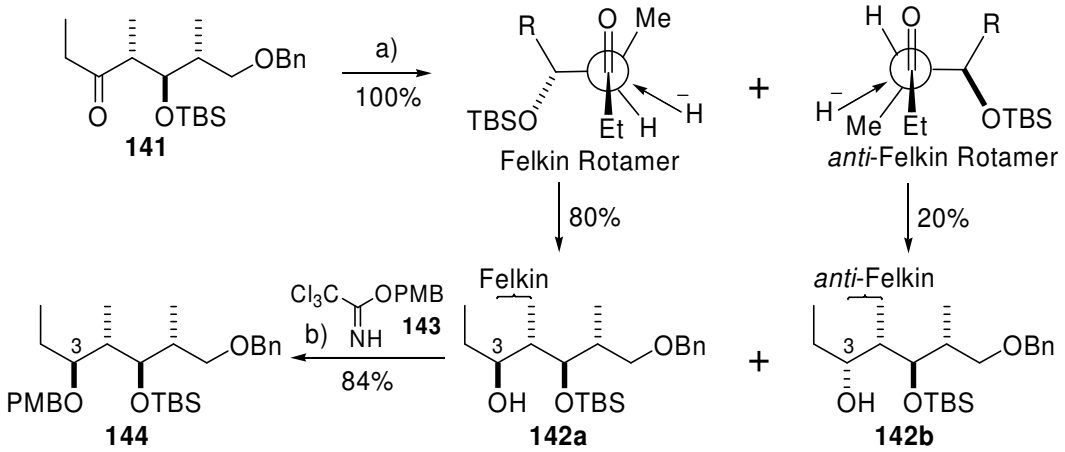


Figure 3.3: *300 MHz ^{1}H NMR spectrum of TBS protected aldol adduct* ***140*** *in $CDCl_3$*

As alluded to in the retro-synthetic analysis, reduction of the C3-carbonyl was anticipated to be crucial to avoid cyclisation at various stages of the synthesis, namely upon liberation of the primary benzyl ether as a prelude to acquiring aldehyde **131**. In this respect, ketone **141** was treated with $NaBH_4$ in EtOH to give alcohols **142a** and **142b** as separable stereoisomers in a 4:1 ratio (Scheme 3.9). The major isomer was tentatively assigned as alcohol **142a** based on well established Felkin delivery[29-31] of the hydride to the C3 carbonyl. No attempt was made to improve the selectivity of the reduction by sourcing a more hindered hydride reagent, as an impending oxidation to correct the C3 oxidation state would negate any

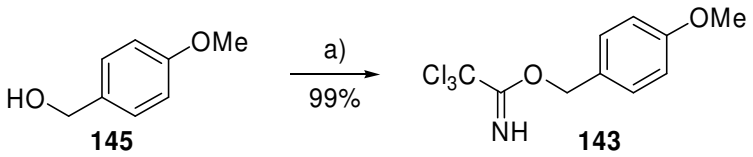
enhancement. Furthermore, given the ready separation of isomers **142a** and **142b** and thus the ability to take each isomer independently through the remaining sequence of steps before recombining prior to oxidation, made scouting for a more selective protocol unnecessary. For simplicity, the remaining steps are elaborated for the major isomer only. As such, protection of the secondary C3 alcohol as the PMB ether with PMB-acetimidate **143** (Scheme 3.10) and triflic acid[34,35] afforded bis-benzyl ether **144** in 84% yield.



Reagents and conditions: a. $NaBH_4$ (2.2 eq), EtOH, 0 °C to rt, 5 h; **b.** PMB-imidate **143** (2.0 eq), Et_2O, 0 °C, then TfOH (0.1 mol%), 0 °C, to rt, 1 h.

Scheme 3.9: *Reduction of the C3 carbonyl and synthesis of bis-benzyl ether* ***144****.*

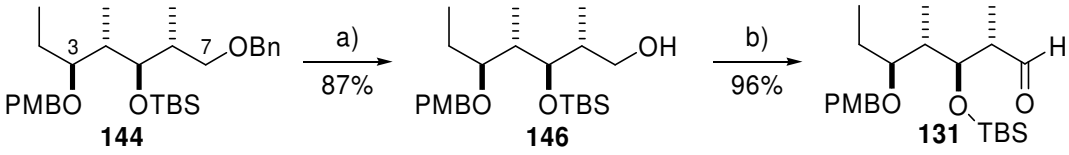
The synthesis of PMB-imidate **143** (Scheme 3.10) followed the protocol outlined by Patil,[36] and was a significant advancement over the original reference,[21,22] which was utilised in the synthesis of benzyl imidate **135** (Scheme 3.7). As shown in Scheme 3.10, treatment of *p*-methoxybenzyl alcohol **145** with aqueous KOH and catalytic tetrabutylammonium hydrogen sulphate followed by addition of trichloroacetonitrile afforded imidate **143** quantitatively, with no need for purification.[36] This methodology is applicable to a broad spectrum of benzyl alcohols and avoids the cumbersome washing and handling of NaH that is required of the traditional method.



Reagents and conditions: a. i. KOH (50% aq), *n*-$Bu_4NH_4{\cdot}HSO_4$ (cat.), CH_2Cl_2, −15 °C, 5 min; ii. Cl_3CCN (1.2 eq), −15 °C, 30 min to rt, 30 min.

Scheme 3.10: *Improved procedure for the synthesis of benzyl-acetimidates (**143**).*

The decision to install a PMB-ether at C3 was made with the anticipation that the C7 primary benzyl ether would be selectively cleaved in the presence of the secondary PMB-ether.[35,37] In practice this conjecture proved correct, as treatment of bis-benzyl ether **144** with W2-Raney nickel (synthesized from nickel aluminium and NaOH according to the procedure of Mozingo)[38] under an atmosphere of hydrogen resulted in liberation of primary alcohol **146** in 87% yield after purification (Scheme 3.11). The use of W2-Raney Ni was considered critical, as standard hydrogenation conditions (Pd/C, H_2) would likely prove non-selective,[37] and lead to a mixture of products. Finally, Dess-Martin oxidation[39,40] furnished the target aldehyde **131** as a single stereoisomer, in excellent yield (96%).



Reagents and conditions: a. W2-Raney nickel (excess), EtOH, H_2, rt, 6 h; **b.** DMP (1.5 eq), CH_2Cl_2, rt, 1 h.

Scheme 3.11: *Completion of the synthesis of aldehyde **131**.*

The ^{1}H NMR spectrum for aldehyde **131** (Figure 3.4) shows the expected aldehydic proton resonanating as a doublet at δ 9.81 (J = 2.7 Hz), which displays coupling to the methyl methine multiplet at δ 2.52 (qdd, J = 6.9, 5.4, 2.7 Hz). The multiplicity of the resonance at δ 2.52 is due to additional coupling to the methyl doublet at δ 1.11 (J = 6.9 Hz) and the TBS oxymethine which appears as a doublet of doublets at δ 4.14 (J = 5.4, 2.7 Hz). The PMB oxymethine resonance at δ 3.42 (apt sextet, J = 3.6

Hz) couples to the methyl methine signal at δ 2.07 (qdd, *J* = 6.9, 3.6, 2.7 Hz) and the diastereotopic methylene resonances at δ 1.70 (dqd, *J* = 14.7, 7.2, 3.6 Hz) and δ 1.49 (apt dqn, *J* = 14.7, 7.2 Hz). The signal at δ 2.07 shows expected coupling to the methyl doublet at δ 0.84 (*J* = 6.9 Hz), while the diastereotopic methylenes show coupling to the methyl triplet at δ 0.96 (*J* = 7.2 Hz) in addition to reciprocal coupling. The peaks at δ 7.28 (d, *J* = 8.7 Hz), δ 6.90 (d, *J* = 8.7 Hz), δ 4.49 (d, *J* = 11.1 Hz), δ 4.36 (d, *J* = 11.1 Hz) and δ 3.83 (s) are consistent with the *para*-disubstituted PMB protecting group.

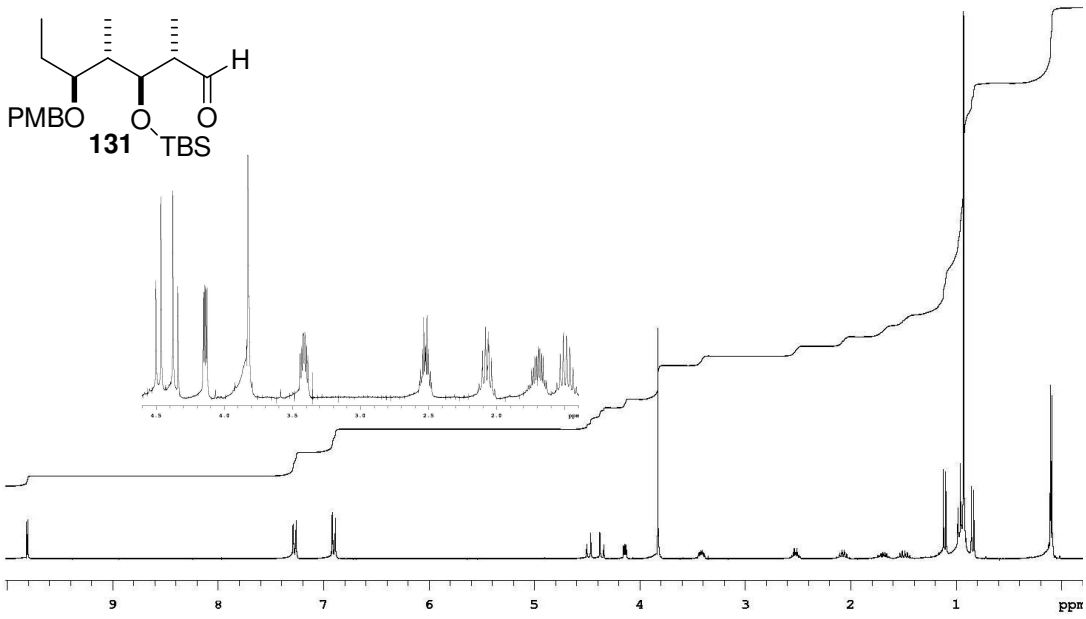


Figure 3.4: *300 MHz ^{1}H NMR spectrum of aldehyde* ***131*** *in $CDCl_3$*

The ^{13}C NMR spectrum for compound **131** (Figure 3.5) displays the correct number of peaks in the expected regions. In particular, the aldehyde carbonyl resonates at δ 205.3, the four signals for the *para*-disubstituted aromatic group appear at δ 159.0, δ 130.9, δ 129.1 and δ 113.7 and the four oxygen bearing carbons resonate at δ 80.2, δ 75.2, δ 70.5 and δ 55.2. The EI mass spectrum indicated a base peak at *m/z* 121 which corresponds to the *p*-methoxybenxyl radical and high resolution mass spectrometry confirmed the expected molecular formula of $C_{23}H_{40}O_4Si$.

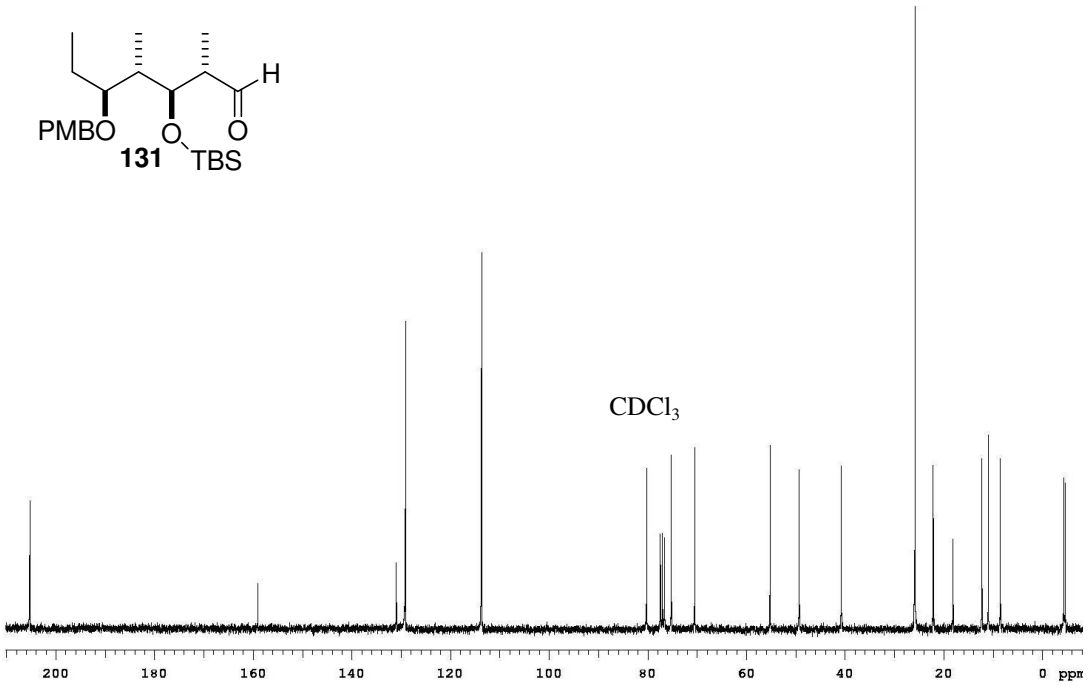
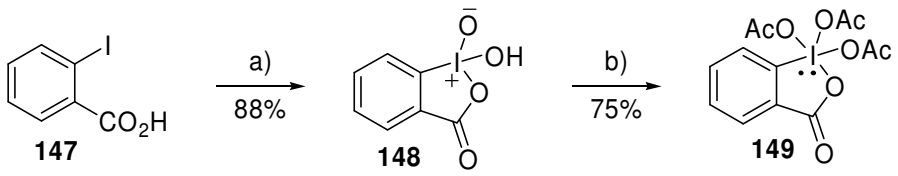


Figure 3.5: *75.5 MHz ^{13}C NMR spectrum of aldehyde **131** in $CDCl_3$*

Dess-Martin periodinane **149** was synthesised according to the procedure depicted in Scheme 3.12. The intermediate iodoxybenzoic acid (**148**) was generated by treatment of iodobenzoic acid (**147**) with potassium bromate and sulphuric acid in accordance with Dess and Martin's original procedure.[39,40] Acetylation of **148** with catalytic *p*-toluenesulphonic acid and acetic anhydride[41] gave the active reagent **149** in good yield on 50-gram scale. The latter procedure was introduced by Ireland[41] to combat the often sporadic behaviour of the Dess-Martin acetylation.[40,42,43]

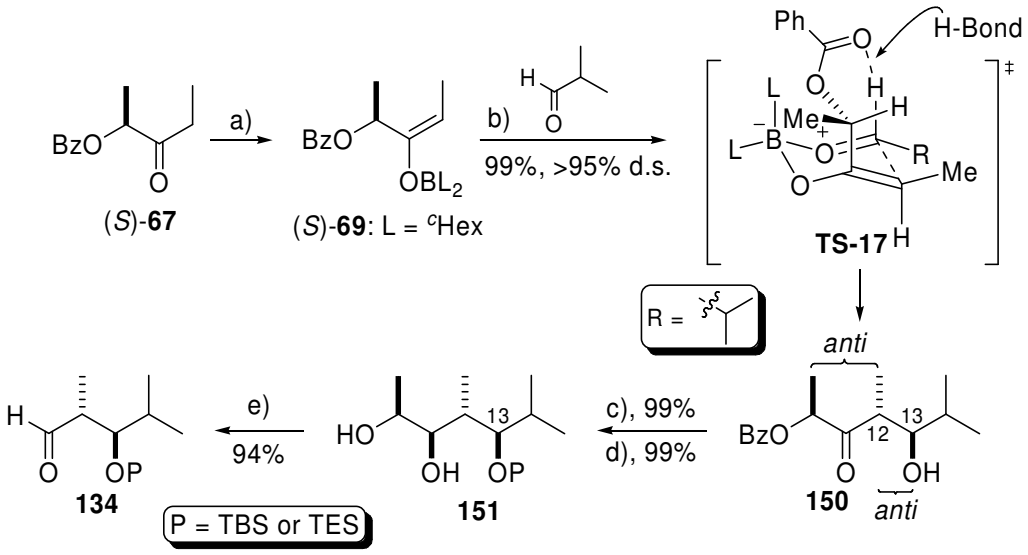


Reagents and conditions: a. $KBrO_3$ (1.3 eq), H_2SO_4 (0.7 M, 1.57 eq), 68 °C, 3.6 h; **b.** *p*-TsOH (cat.), Ac_2O, 80 °C, 2 h.

Scheme 3.12: *Synthesis of Dess-Martin periodinane **149**.*

3.4.2 The Synthesis of Ketone Fragment 132

In planning the synthesis of ethyl ketone **132** it was recognised that β-silyloxy aldehyde **134**, containing the requisite C12 and C13 stereocentres, could be acquired from lactate derived ketone (*S*)-**67** *via* a known protocol.[17,33] Thus, *E*-(O)-borinate (*S*)-**69** was prepared under standard conditions (^{c}Hex$_2$BCl/Me$_2$NEt)[17] and reacted with freshly distilled isobutyraldehyde to give 11,12-*anti*-12,13-*anti*-aldol adduct **150** as a single observable stereoisomer, in virtually quantitative yield. The stereoinduction for this aldol addition again comes from the strong diastereofacial preference exhibited by the enolate (resulting from the stabilising H-bond depicted in **TS-17**), leading to the common *anti*,*anti*-selectivity.[14,17]



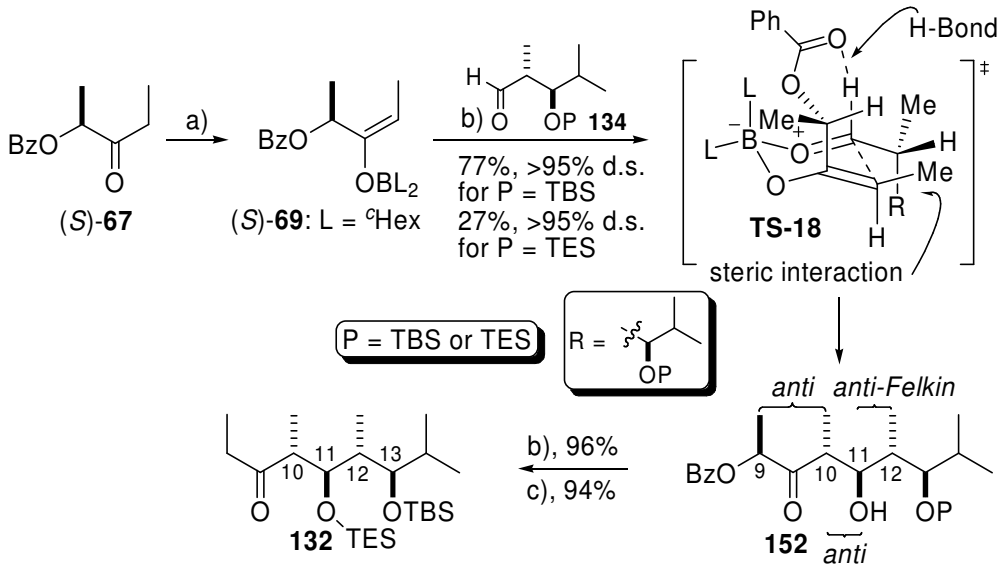
Reagents and conditions: a. ^{c}Hex$_2$BCl (1.5 eq), Me$_2$NEt (1.8 eq), Et$_2$O, 0 °C, 2 h; **b.** isobutyraldehyde (4.0 eq), Et$_2$O, −78 °C, 2 h to −23 °C, o/n; **c.** i. 2,6-lutidine (2.0 eq), CH$_2$Cl$_2$, −78 °C; ii. TBSOTf or TESOTf, (1.5 eq), −78 °C, 30 min; **d.** LiBH$_4$ (20.0 eq), THF, −78 °C to rt, o/n; **e.** NaIO$_4$ (6.0 eq), MeOH, H$_2$O, rt, 10 min.

Scheme 3.13: *Synthesis of both TES and TBS analogues of β-silyloxy aldehyde* ***134****.*

With adduct **150** in hand a decision concerning the most suitable protecting group for the generated C13 alcohol was required. Keeping all options open, it was decided to employ both triethylsilyl (TES) and *t*-butyldimethylsilyl (TBS) protecting groups in anticipation of one ultimately proving more compatible with the remaining synthetic

operations. Remarkably, identical product yields were obtained in the remaining three steps of the synthesis of the TES and TBS analogues of aldehyde **134** (Scheme 3.13). In practise, TES and known[17,33] TBS protected β-silyloxy aldehydes **134** were obtained[32,44] after silylation of adduct **150**, followed by $LiBH_4$ mediated reduction of the benzoate to give diol **151** and oxidative cleavage of the diol with sodium periodate ($NaIO_4$).[17,33]

As shown in Scheme 3.14, the reactivity of the TES and TBS analogues significantly departed from equality in the first step towards the synthesis of ketone **132**. Reaction[14,17,25] of the differently protected β-silyloxy aldehydes **134** with the *E*-(O)-enolate (*S*)-**39** gave adduct **152** in very poor yield (27%) for the TES analogue and good yield (77%) for the TBS analogue. The yield of **152** in both cases was lower than the preceding *anti*-aldol reactions (Schemes 3.8 and 3.13) due to the sensitivity of β-silyloxy aldehyde **134** to the reaction conditions (material was lost to β-elimination).



Reagents and conditions: a. $^cHex_2BCl$ (1.5 eq), Me_2NEt (1.8 eq), Et_2O, 0 °C, 2 h; **b.** aldehyde **134** (1.5 eq), Et_2O, −78 °C, 2 h to −23 °C, o/n; **c.** i. 2,6-lutidine (2.0 eq), CH_2Cl_2, −78 °C; ii. TESOTf, (1.5 eq), −78 °C, 30 min; **d.** SmI_2 (~4.0 eq), THF, 0 °C.

Scheme 3.14: *Completion of the synthesis of bis-silylketone **132**.*

Configurational assignment of the generated stereocentres in this mismatched aldol reaction was based on the overriding π-facial selectivity exhibited by enolate (*S*)-**69** for the 9,10-*anti*-10,11-*anti*-adduct (see **TS-18**).[14,17] With the TBS protecting group proving far more robust, this analogue of adduct **152** was protected[44] at C11 as the TES ether and subsequent reductive removal of the benzoate (SmI_2)[17,33] afforded ethyl ketone **132** in excellent overall yield (90% from **152**).

This relatively short sequence afforded ketone **132** as a single stereoisomer in 63% yield over 7 steps and completed construction of the requisite C10-C13 stereoarray. Additionally, ketone (*S*)-**67** was employed as both a chiral pentan-3-one and propanal synthon, thus displaying the true power of Paterson's lactate derived ketone aldol technology.

The ^{1}H NMR spectrum for ketone **132** (Figure 3.6) shows single resonances for all peaks indicating excellent diastereomeric purity. The TES and TBS oxymethine protons resonate as doublets of doublets at δ 4.19 (*J* = 6.2, 5.3 Hz) and δ 3.66 (*J* = 6.8, 2.6 Hz), respectively. The signal at δ 4.19 shows coupling to the methyl methine resonance at δ 2.73 (apt qn, *J* = 6.8 Hz), which in turn couples to the methyl doublet at δ 1.07 (*J* = 7.2 Hz), and the 2H multiplet at δ 1.92-1.77. The multiplet at δ 1.92-1.77 shows additional coupling to the TBS oxymethine at δ 3.66 and the methyl doublets at δ 0.90, δ 0.86 and δ 0.80 and thus comprises the C12 and C14 methyl methine protons. The C8 methyl methylene protons are diastereotopic and appear as doublets of quartets at δ 2.56 (*J* = 18.5, 7.2 Hz) and δ 2.47 (*J* = 18.5, 7.2 Hz) and show coupling to the methyl triplet at δ 1.02 (*J* = 7.2 Hz) in addition to reciprocal coupling. The peaks due to the TES and TBS protecting groups resonate at δ 0.94 (9H, t, *J* = 8.0 Hz), δ 0.59 (6H, q, 8.0 Hz) and δ 0.91 (9H, s), 0.11 (3H, s), 0.05 (3H, s), respectively.

The ^{13}C NMR spectrum (Figure 3.7) of compound **132** also shows singular resonances. The ketone carbonyl appears at δ 214.0 and the two silyloxymethine carbons resonate at δ 76.9 and δ 75.1. Additionally, the TBS protecting group has resonances for the *tert*-butyl methyls at δ 26.2 and the quaternary carbon centre at δ 18.5 and the two methyl groups at δ −3.4 and δ −4.4, whilst the carbons of the TES

ether resonate at δ 7.5 and δ 7.0. A band at 1721 cm^{-1} in the infrared spectrum of ketone **132** confirmed the presence of the ketone carbonyl group and high resolution mass spectrometry identified the expected molecular formula of $C_{24}H_{52}O_3Si_2$.

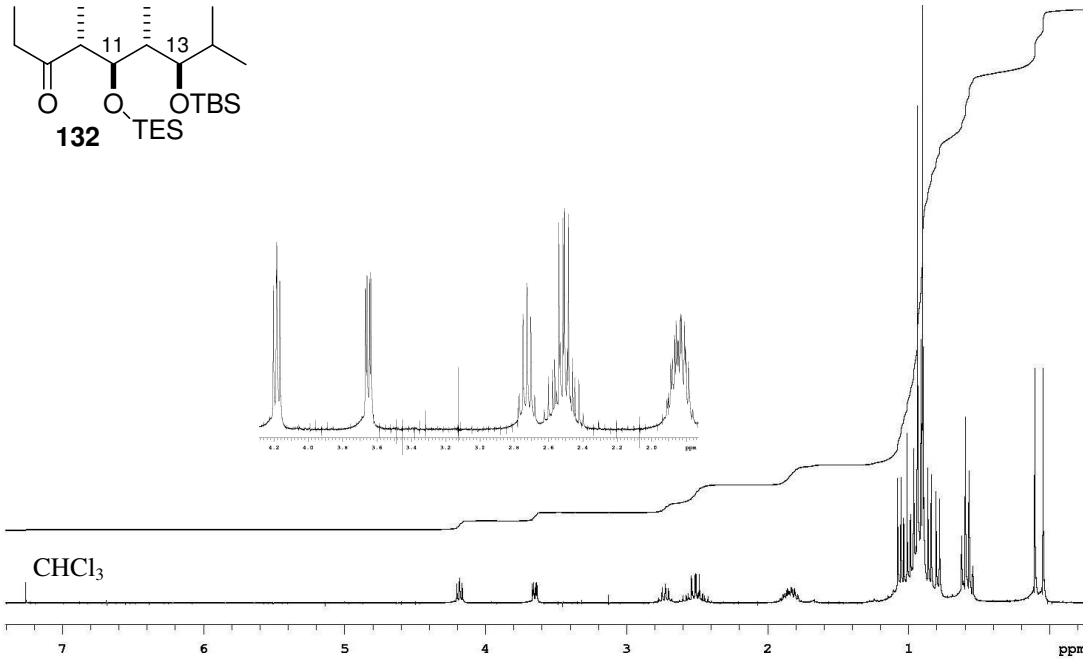


Figure 3.6: *300 MHz ^{1}H NMR spectrum of ketone **132** in $CDCl_3$*

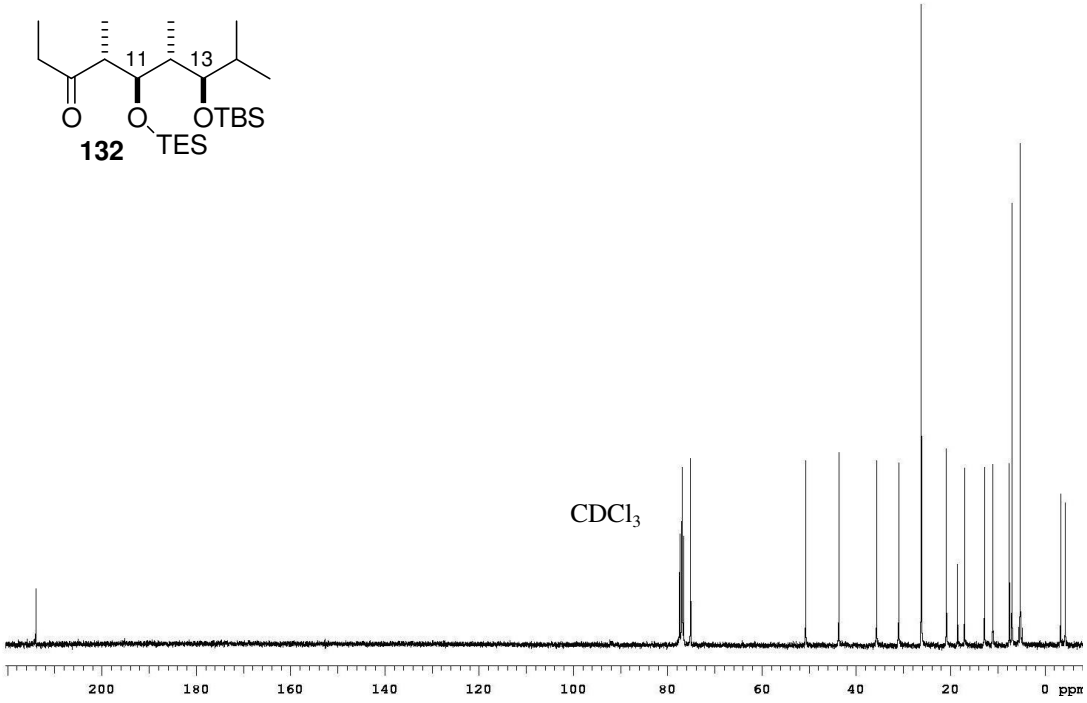


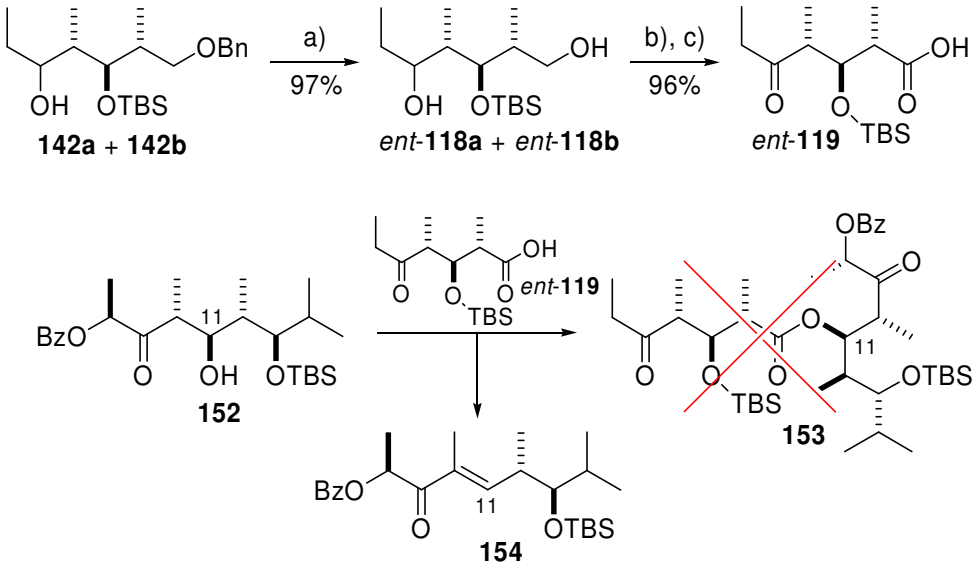
Figure 3.7: *75.5 MHz ^{13}C NMR spectrum of ketone **132** in $CDCl_3$*

With the key aldol fragments (aldehyde **131** and ketone **132**) in hand, the task of forging the requisite stereocentres for dolabriferol (**30**) was complete. However, prior to performing the coupling of these critical intermediates (Section 3.4.4), a brief digression to a direct esterification approach to dolabriferol (**30**) was investigated.

3.4.3 A Direct Approach to Esterification

It was anticipated that suitable acid and alcohol fragments, whose coupling would fashion the ester linkage of dolabriferol (**30**), could be derived from intermediates in the synthesis of aldehyde **131** and ketone **132**. Given this, the decision was taken to simultaneously pursue a direct esterification approach in the hope of probing the applicability of such a strategy to the synthesis of dolabriferol (**30**).

To this end, the requisite C5 TBS protected ketoacid *ent*-**119** was secured beginning from alcohols **142a** and **142b** (Scheme 3.9) as shown in Scheme 3.15. In practice, the mixed alcohols were subjected to debenzylation under hydrogenation conditions (Pd/C, H_2)[45] to afford diols *ent*-**118a** and *ent*-**118b** in excellent yield (97%). Subsequent double Swern oxidation[23,24] of the mixed diols, followed by further oxidation of the intermediate ketoaldehyde with $NaClO_2$,[46,47] afforded carboxylic acid *ent*-**119** in 96% yield over the two steps.



Scheme 3.15: *Attempted esterification of acid ent-**119** and alcohol **152**.*

Under the assumptions that the benzoate would not affect reactivity in the intended esterification reaction and could be efficiently removed if the coupling was successful, aldol adduct **152** (Scheme 3.14) was used, without modification, as the alcohol fragment.

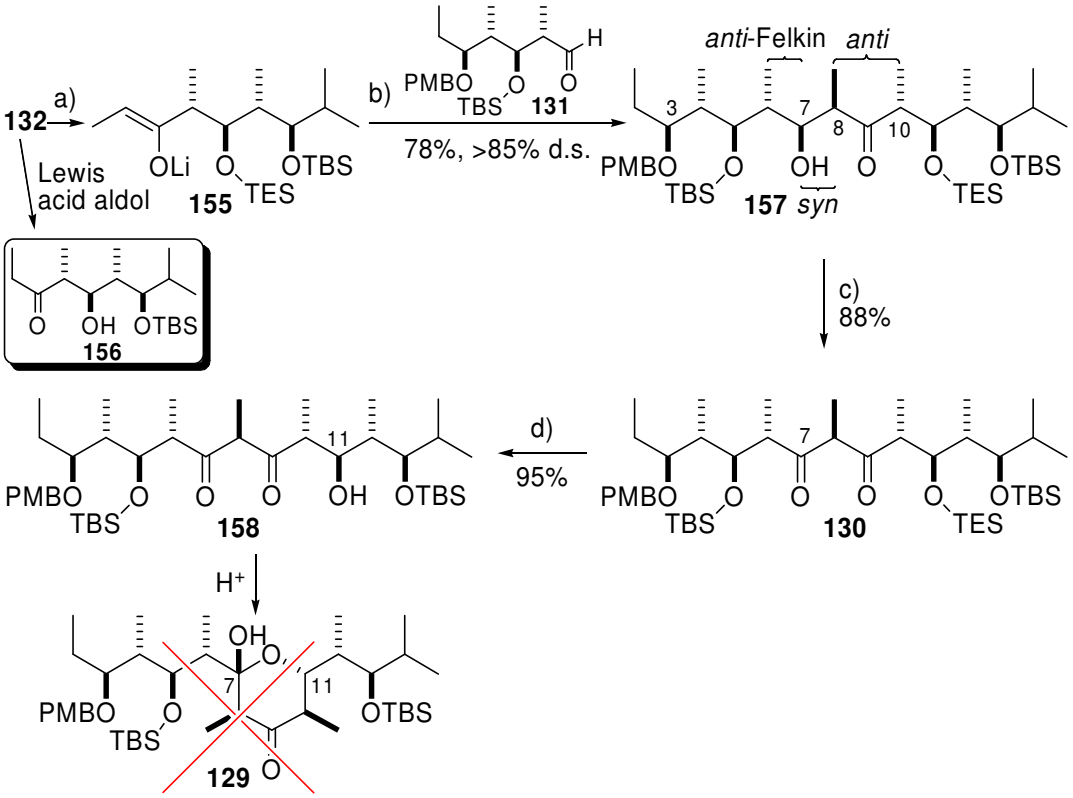
Unfortunately, investigations using Keck's modification[48] of the Steglich protocol[49] (DCC, DMAP, DMAP·HCl), Yonemitsu's variation[50] of the Yamaguchi method[51] (DMAP, Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$) and Paterson's adjustment[47] of the Yonemitsu-Yamaguchi technique (same reagents, lower temperatures) all failed to induce coupling to give the desired ester **153**. The Yamaguchi protocols gave enone **154** exclusively, while Keck's protocol gave a complex mixture that included the enone. It was apparent that the C11 alcohol of **152** was prone to dehydration under basic conditions (a fact that will be highlighted in forthcoming discussions) and that a sterically demanding reaction origin prohibited the desired coupling reaction.
These studies, in conjunction with the findings of Diaz,[13] indicated that a direct esterification approach to dolabriferol (**30**) was not a viable approach.

3.4.4 Merger of the Aldol Fragments and Synthesis of Dione 130

It was hoped that the merger of aldehyde **131** and ketone **132** could be achieved under Mukaiyama aldol conditions,[52-54] thus mimicking the successful propionate homologation of enol silane **109** encountered in Chapter 2 (Section 2.3.3, Scheme 2.7). Unfortunately, enolisation of ketone **132** and capture as the trimethylsilyl enol ether[16] proved more sluggish and less selective than the previous example (Section 2.3.3, Scheme 2.7) and all subsequent attempts to couple the enolsilane with various aldehydes under Lewis acid conditions[55,56] failed to yield the desired products. Furthermore, experiments to affect this union under more traditional aldol reaction conditions, namely Lewis acid ($TiCl_4$)/amine base (DIPEA) enolisation of ketone **132**,[57] proved equally disappointing, with maximum yields not exceeding 20%. It was clear from these two results (and confirmed by tlc and chromatographic isolation of **156**) that the Lewis acid ($BF_3·OEt_2$ or $TiCl_4$) was causing facile cleavage of the labile C11 TES ether in ketone **132**, leading to the recovery of β-hydroxy ketone **156** (Scheme 3.16). This presumably resulted in poor levels of enolisation and hence, poor reactivity.

To combat this, enolisation of ketone **132** was performed using a strong, sterically demanding amide base as delineated in Scheme 3.16. To that end, a solution of ketone **132** in THF at −78 °C was treated with lithium hexamethyldisilylazide (LiHMDS)[35,58,59] and stirred for 30 minutes before being warmed to −50 °C and stirred for a further 30 minutes to ensure complete enolisation. The *Z*-(O)-enolate **155** was then re-cooled to −78 °C and aldehyde **131** was added. After 2 hours at −78 °C, the reaction was quenched, and the crude product purified by column chromatography, to afford two separable isomeric adducts in good yield (78%) and excellent diastereoselectivity (>85% d.s.). Significantly, the extent of conversion in this reaction was greatly dependent of the concentration of the enolate in THF. Optimum yields were obtained at a concentration of 0.5 M, with anything less than this resulting in drastically lower isolated yields. The major diastereomer was tentatively assigned the configuration depicted for **157**, which corresponded to 6,7-*anti*-Felkin-7,8-*syn*-8,10-*anti*-selectivity, and was consistent with similar double stereodifferentiating lithium aldol reactions.[58]

The high level of selectivity can be attributed to the fact that both the inherent *anti*-Felkin preference[29-31] typically exhibited by α-methyl aldehydes in aldol reactions with *Z*-(O)-enolates (see Section 1.5.3 for related discussion) and 8,10-*anti* selectivity across the developing carbonyl, which is the preferred sense of induction for lithium enolates,[59] were satisfied. Notably, the minor diastereomer from this reaction corresponded to the major isomer isolated from the titanium(IV) mediated process. This observation helped confirm the tentative assignment of **157**, as evidence suggests that titanium(IV) enolates display the opposite sense of stereoinduction compared to their lithium enolate counterparts;[57,59] namely *syn*-selectivity across the developing carbonyl (see Section 1.5.3 for related discussion). In any case, the configuration of these new stereocentres was inconsequential as they are either lost on oxidation or were expected to become epimerisable in subsequent steps, but the formation of one major isomer allowed the progression of stereochemically pure material.



Reagents and conditions: a. LiHMDS (1.1 eq), THF −78 °C, 30 min to −50 °C 30 min; **b.** aldehyde **131** (1.5 eq), THF, −78 °C, 2 h; **c.** i. DMSO (10.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (5.0 eq), −78 °C, 30 min; iii. alcohol **157**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (20.0 eq), −78 °C, 30 min to rt; **d.** *p*-TsOH, 1:1 MeOH/CH_2Cl_2, 0 °C, 1 h or HF·pyr/pyr, THF, 0 °C, 5 h.

Scheme 3.16: *Aldol union of aldehyde* ***131*** *and ketone* ***132*** *and synthesis of dione* ***130****.*

Adduct **157** justifies the necessity of the preinstalled C3-PMB ether, as hemiketalisation arising from attack of the generated C7 alcohol upon a C3-carbonyl could have proven problematic. Furthermore, maintaining this oxidation state at C3 was considered critical to avoid potential spirocyclisation upon oxidation at C7 and subsequent liberation of the C11 alcohol as the prelude to hemiacetal synthesis (for reference see related transformation leading to compound **163** in Scheme 3.17).

The ^{1}H NMR and ^{13}C NMR spectra for aldol adduct **157** (Figures 3.8 and 3.9, respectively) show the complexity of this heavily protected compound. The data contained in these spectra essentially comprises a combination of the data presented

for aldehyde **131** and ketone **132**, which helps confirm the successful union. Particularly notable is the new hydroxymethine resonance which appears as a 2H multiplet with the C5 TBS oxymethine signal at δ 4.08-4.04. This multiplet shows coupling to the new methyl methine resonance at δ 2.71 (qd, J = 6.9, 2.1 Hz) which in turn couples to the 45H multiplet at δ 0.96-0.85, which contains the majority of the methyl signals. Also readily apparent are the four 3H methyl singlets between δ 0.19 and δ 0.06 accounting for the methyl groups attached to silicon for two TBS residues, the methylene quartet of the TES protecting group at δ 0.55 (J = 7.9 Hz) and the peaks in the aromatic and oxygen substituted regions, corresponding to the PMB protecting group.

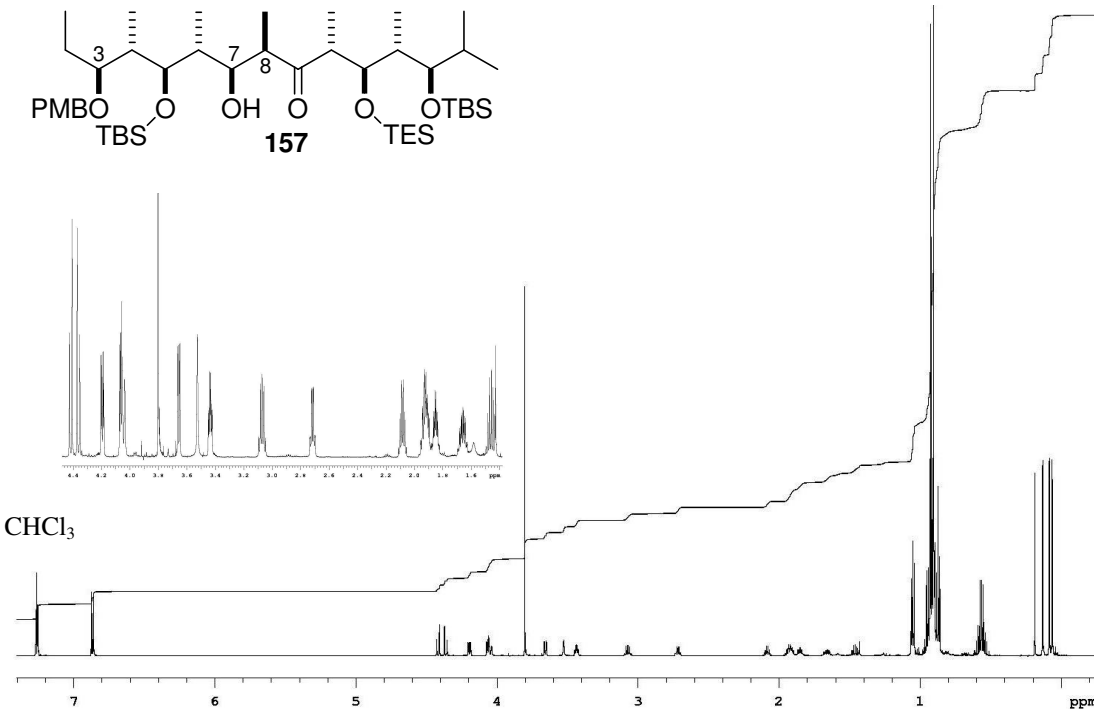


Figure 3.8: *600 MHz ^{1}H NMR spectrum of aldol adduct **157** in $CDCl_3$*

The ^{13}C NMR spectrum shows the correct number of resonances in the expected regions, with the ketone carbonyl resonance at δ 216.2 being of particular interest. Analysis of the infrared spectrum of compound **157** identified bands at 3505 cm^{-1} and 1717 cm^{-1}, indicative of hydroxyl and carbonyl groups, respectively and high resolution mass spectrometry confirmed the expected molecular formula [$C_{47}H_{92}O_7Si_3$] for compound **157**.

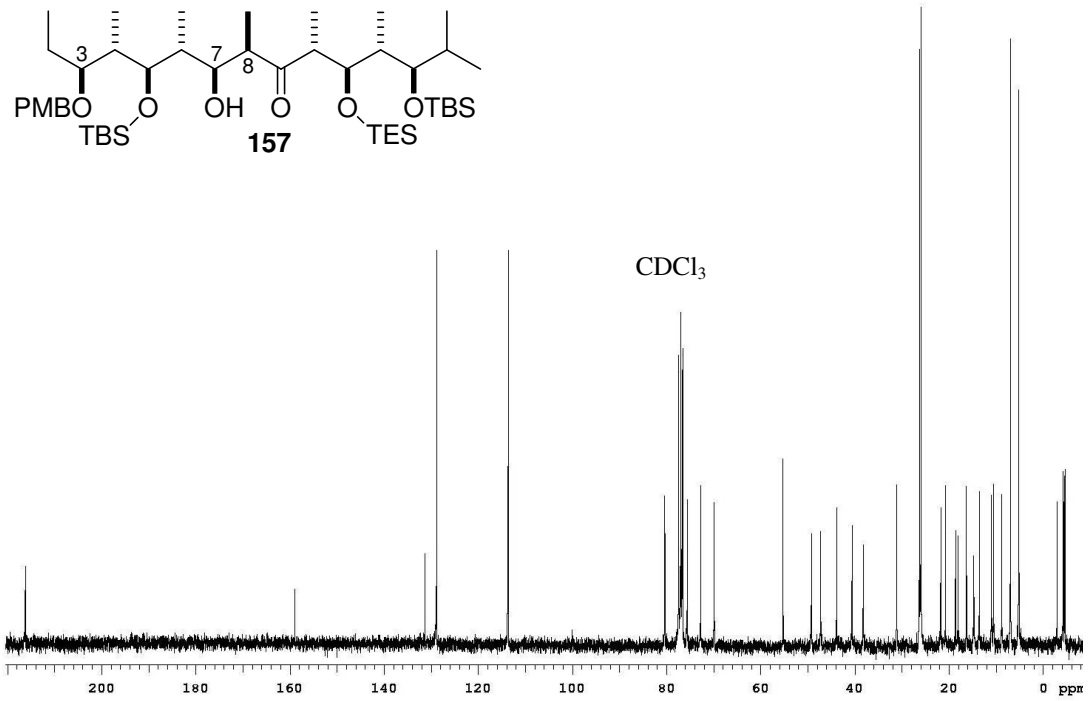
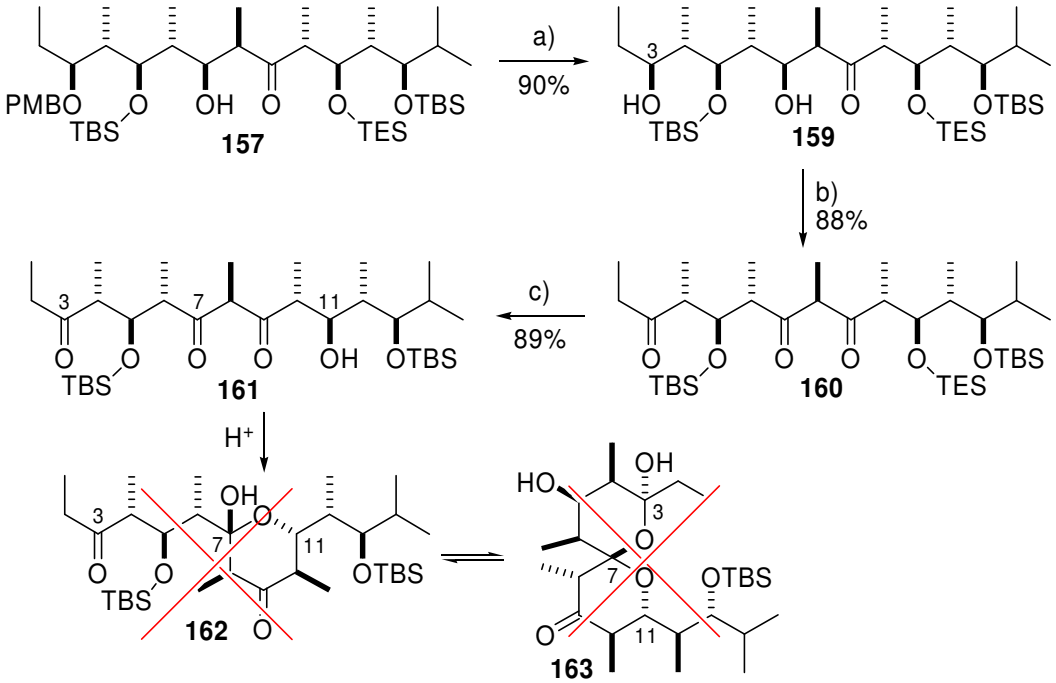


Figure 3.9: *75.5 MHz ^{13}C NMR spectrum of aldol adduct **157** in $CDCl_3$*

Swern oxidation[23] of major aldol adduct **157** smoothly afforded dione **130** (Scheme 3.16), which surprisingly, after chromatographic purification (silica gel), existed as a single epimer of the β-diketone (i.e. no enol or epimeric forms were apparent). Given the non-epimerisable nature of dione **130** it was presumed that the C8 methyl substituent would retain the configuration formulated by the aldol union, as depicted in Scheme 3.16. Selective desilylation of the TES ether proceeded under either acidic conditions (*p*-TsOH) or the action of fluoride ion (HF·pyr/pyr)[42,60] to give the deprotected acyclic dione **158** in excellent yield (95%). This compound also proved stable to epimerisation and unfortunately, failed to cyclise under acidic conditions to give the desired hemiacetal **129**. Given this failure to cyclise, the decision was taken to abandon the fully protected approach.

Assuming that steric hindrance was prohibiting cyclisation, the oxidation state at C3 was corrected to that of dolabriferol (**30**) by cleavage of the PMB ether from aldol adduct **157**, as depicted in Scheme 3.17. To that end, exposure of compound **157** to DDQ[37] in aqueous pH 7 phosphate buffer/CH_2Cl_2 for 30 minutes at 0 °C[25] gave diol **159** in 90% isolated yield. Subsequent double Swern oxidation[23] afforded triketone **160**, which also proved stable to epimerisation. Removal of the TES ether with *p*-

TsOH gave compound **161**, which again failed to cyclise to give the desired hemiacetal **162**, indicating that the bulky TBS ethers were responsible for the inhibition of cyclisation. As such, the earlier proclaimed fears (Section 3.3) of uncontrollable spirocyclisation upon liberation of the C11 alcohol in the presence of a carbonyl at C3 were unfounded (see compound **163** for reference).



Reagents and conditions: a. DDQ (1.5 eq), pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 30 min; **b.** i. DMSO (12.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (6.0 eq), −78 °C, 30 min; iii. alcohol **159**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (24.0 eq), −78 °C, 30 min to rt; **c.** *p*-TsOH (cat.), 1:1 MeOH/CH_2Cl_2, 0 °C, 1 h.

Scheme 3.17: *Correction of the C3 oxidation state to aid in hemiacetal formation.*

The stability of triketone **160** as a single epimer (no epimeric or enol forms) is readily evident from inspection of the ^{1}H NMR and ^{13}C NMR spectra depicted in Figures 3.10 and 3.11, respectively. Both spectra were acquired in $CDCl_3$ which typically contains enough residual HCl to cause enolisation of β-dicarbonyl moieties. In particular, the ^{1}H NMR spectrum displays a methyl methine resonance at δ 3.93 (q, J = 6.9 Hz) which shows coupling to the methyl doublet at δ 1.23 (J = 6.9 Hz)

and is indicative of a proton situated between two carbonyl groups. This quartet is flanked on either side by the silyloxymethine resonances, which appear as doublets of doublets at δ 4.48 (*J* = 7.2, 4.5 Hz, C5), δ 4.19 (*J* = 8.7, 3.3 Hz, C11) and δ 3.59 (*J* = 8.4, 2.1 Hz, C13). The three methyl methine protons that are adjacent to a carbonyl group resonate in close proximity at δ 2.88 (apt qn, *J* = 7.2 Hz, C6), δ 2.78 (dq, *J* = 8.7, 7.2 Hz, C10) and δ 2.72 (qd, *J* = 6.9, 4.5 Hz) and each shows coupling to the respective methyl doublets. The methyl methylene protons adjacent to the C3 carbonyl are diastereotopic and resonate as doublets of quartets at δ 2.59 (*J* = 18.0, 7.2 Hz) and δ 2.49 (*J* = 18.0, 7.2 Hz) and couple to the methyl triplet at δ 1.04 (*J* = 7.2 Hz). The remaining peaks are consistent with the assigned structure.

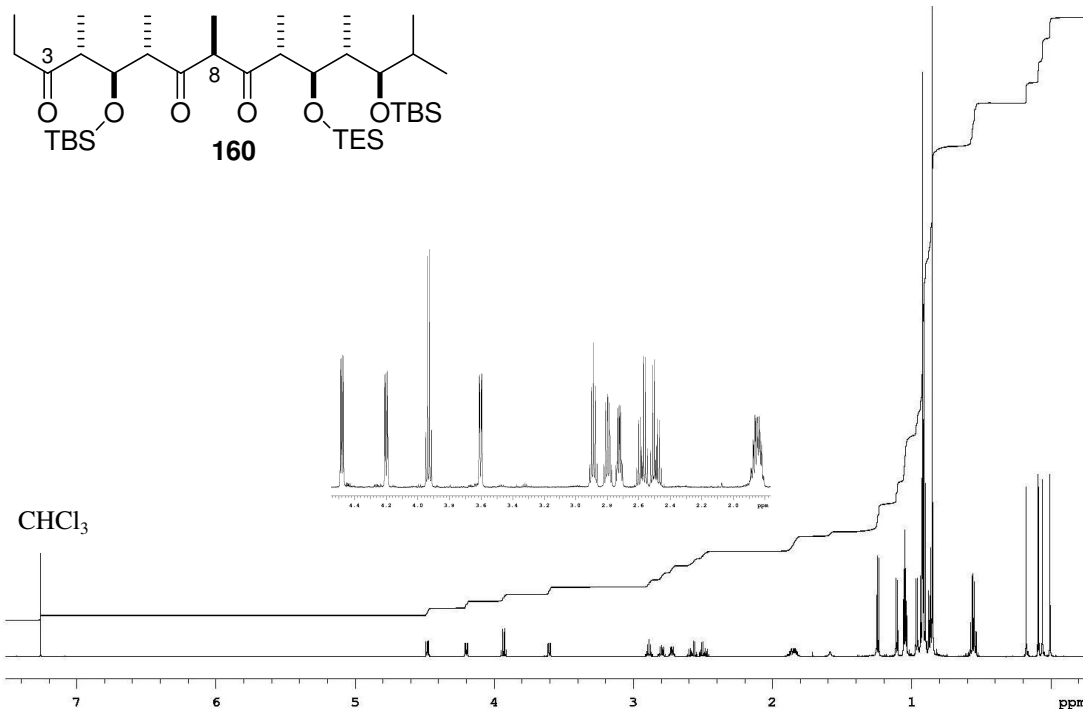


Figure 3.10: *600 MHz ^{1}H NMR spectrum of triketone* ***160*** *in $CDCl_3$*

The ^{13}C NMR spectrum of compound **160** confirms the presence of three carbonyl groups with peaks at δ 211.8, δ 209.8 and δ 209.7. Additionally, a broad stretch at 1716 cm^{-1} indicates multiple carbonyl bands. The EI mass spectrum shows a strong molecular ion at *m/z* 752 [M+Na] and an accurate mass measurement on this species established the molecular formula $C_{39}H_{80}O_6Si_3$.

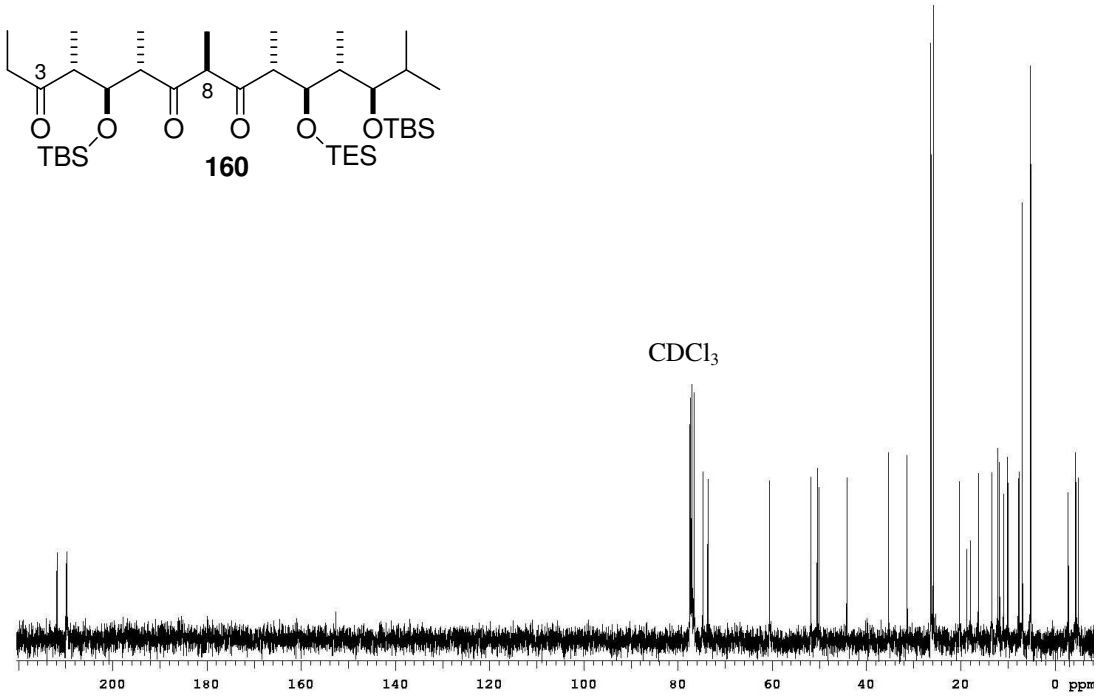
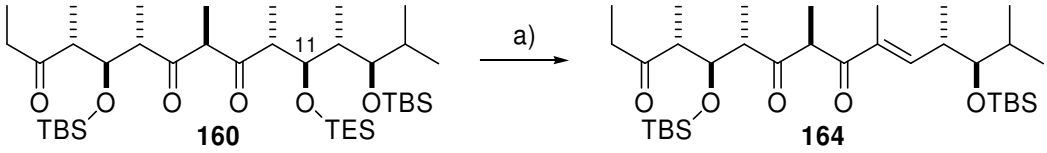


Figure 3.11: *75.5 MHz ^{13}C NMR spectrum of triketone* ***160*** *in $CDCl_3$*

3.5 Acquisition of Ester 169

Clearly, removal of one or both of the TBS protecting groups in compound **160** was required to gain access to the desired hemiacetal. However, this proposition introduced a potential myriad of competing cyclisation modes, but with little other recourse available, it seemed a viable path forward.

The base sensitivity of the C11 oxygen bearing stereocentre was highlighted when deprotection of trione **160** was attempted using tetrabutylammonium fluoride (TBAF).[61] This reaction led to exclusive formation of enone **164**, as depicted in Scheme 3.18 (interestingly the TBS groups were unaffected). Anhydrous TBAF (F^-) is known to be strongly basic[62] and is often neutralised by the addition of acetic acid to the reaction mixture.[63] In this instance however, a more promising reagent was sourced.



Reagents and conditions: a. TBAF (7.5 eq), THF, 0 °C, 1 h.

Scheme 3.18: *Attempted global deprotection of trione* ***160*** *with TBAF.*

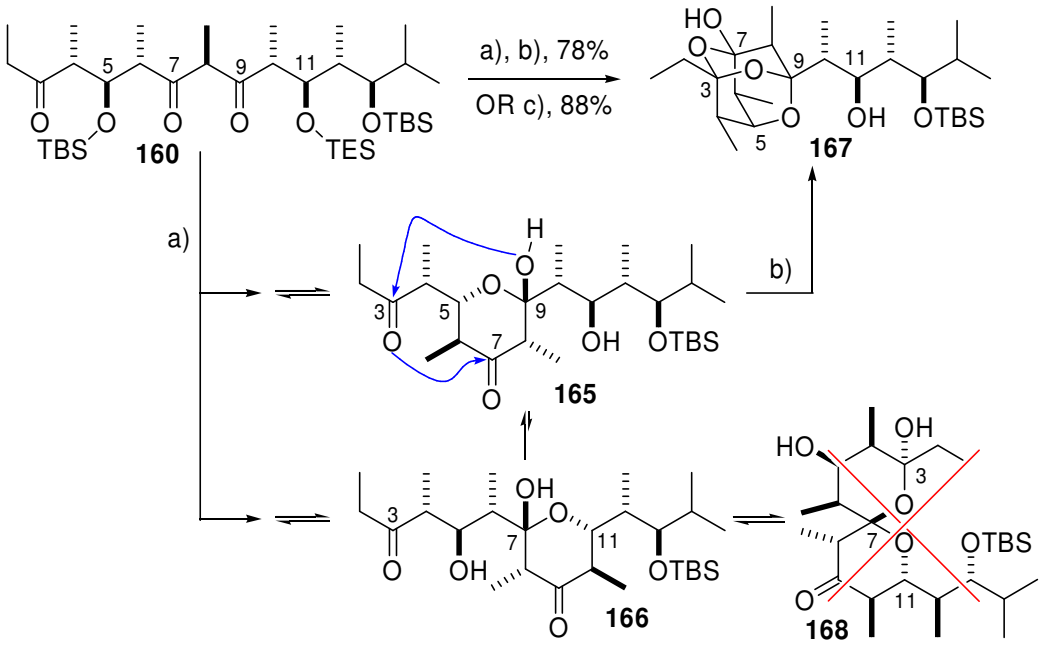
In 1998 the Roush group from the University of Michigan in the U.S.A. introduced tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) as a mild reagent for use in the deprotection of silyl ethers in base sensitive compounds.[64] The need for a sensitive reagent by the group developed from persistent, undesired β-elimination that they were experiencing when using TBAF in their endeavours towards a synthesis of natural product (−)-bafilomycin A_1.[65] Ultimately, the use of TAS-F in a final step global deprotection enabled Roush and co-workers to complete the total synthesis of this complex macrolide.[65]

Given this, triketone **160** was treated with an excess of TAS-F (10-17 eq) in DMF and H_2O for periods ranging from 5 hours to overnight, in accordance with the protocol developed by Roush.[64,65] Despite solving the problem of β-elimination, this approach gave vastly inconsistent results with various fully and incompletely deprotected products being obtained. Exposure of the product mixtures to DBU,[16] to facilitate retro-Claisen rearrangement of any desired hemiacetal that may have formed, failed to afford an ester containing product.

After considerable experimentation it was discovered that controlled desilylation could be achieved when triketone **160** was reacted with 5 equivalents of TAS-F at room temperature for 2 hours (Scheme 3.19). This protocol resulted in cleavage of the C5 TBS and C11 TES ethers and gave, after purification, a complex mixture of products. The ^{1}H NMR spectrum ($CDCl_3$) of this mixture indicated the presence of compounds resembling hemiacetals (such as **165** and **166**, Scheme 3.19), that unfortunately rapidly dehydrated in the slightly acidic $CDCl_3$. Hoping that the mixture might have contained hemiacetal **166**, a subsequent product mixture from the deprotection reaction was dissolved in C_6D_6 in an NMR tube and treated with a

catalytic amount of DBU.[16] Intriguingly, this resulted in rapid conversion (< 5 minutes) of the mixture to a single observable compound (^{1}H NMR spectrum). The product was isolated by column chromatography and subsequent spectroscopic analysis identified the compound as elaborate 2,4,6-trioxaadamantane **167** (78% from **160**). The rationale for the formation of this complex polycycle is given in Scheme 3.19. It appears that desilylation at C5 and C11 leads to the formation of an equilibrium mixture of hemiacetals **165** and **166**. Under the action of base (DBU), the acetal hydroxyl of hemiacetal **165** engages the C3 carbonyl, which in turn attacks the C7 carbonyl in a cascade cyclisation, leading to trioxaadamantane **167**. Interestingly, neither hemiacetal **166**, resulting from cyclisation of the C11 hydroxyl onto the C7 carbonyl, nor spiroacetal **168**, resulting from cyclisation of the acetal hydroxyl of hemiacetal **166** onto the C3 carbonyl, was isolated.

In other experiments it was found that reaction of trione **160** with buffered pyridinium hydrofluoride[42,60] at room temperature for 1 week also gave trioxaadamantane **167**.



Reagents and conditions: a. TAS-F (5.0 eq), H_2O (10.0 eq), DMF, rt, 2 h; **b.** DBU (cat.), C_6D_6, rt, 5 min; **c.** HF·pyr/pyr, H_2O (cat.), THF, rt, 7 days.

Scheme 3.19: *Formation of elaborate trioxaadamantane* ***167*** *from trione* ***160****.*

The ^{1}H NMR spectrum of compound **167** in C_6D_6 (Figure 3.12) shows the loss of the TES protecting group (no quartet at ~δ 0.7 or triplet at ~ δ 1.0) and one of the TBS moieties (only two singlets at ~δ 0.2 and one singlet at ~ δ 1.0). The remaining silyloxymethine resonates as a doublet of doublets at δ 4.27 (*J* = 5.1, 2.1 Hz) and shows coupling to the methyl methine resonances at δ 2.54 (m) and δ 2.32 (apt hept d, *J* = 6.9, 2.1 Hz). The signal at δ 2.32 is part of an isopropyl group, as evidenced by coupling to the two methyl doublets at δ 1.15 (*J* = 6.9 Hz) and δ 1.10 (*J* = 6.9 Hz), and hence confirms the location of the silyloxy group at C13. The hydroxymethine proton resonates as an apparent doublet of triplets at δ 3.84 and shows coupling to the hydroxy proton signal at δ 4.23 (d, *J* = 5.1 Hz), in addition to the methyl methine multiplet at δ 2.54 and methyl methine quartet of doublets at δ 2.10 (*J* = 7.2, 3.9 Hz). The remaining oxymethine resonance appears as a broad multiplet at δ 3.26 and couples to the methyl methine signals at δ 1.45 (qd, *J* = 7.2, 4.2 Hz) and δ 1.17 (br q, *J* = 7.2 Hz), which in turn couple to their respective methyl doublets. The methyl triplet at δ 0.97 (*J* = 6.9 Hz) couples to the methyl methylene multiplets at δ 1.73-1.61 and δ 1.44-1.36 which show reciprocal coupling. The chemical shift of these methylene protons indicates the loss of a carbonyl moiety at C3.

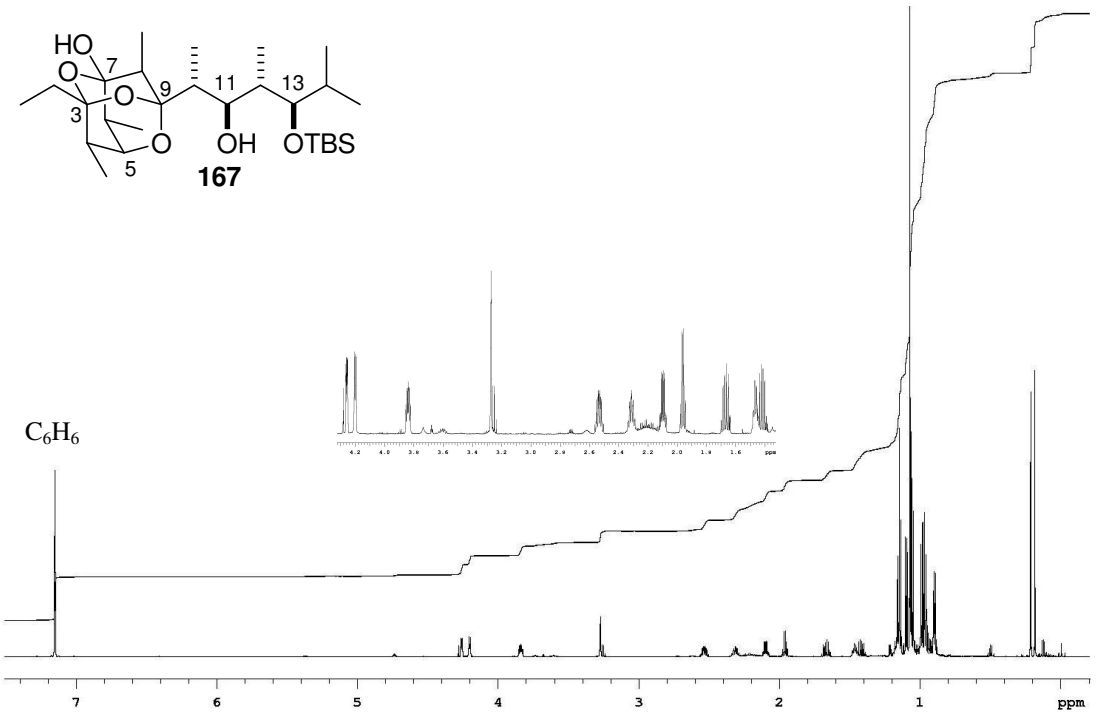


Figure 3.12: *600 MHz ^{1}H NMR spectrum of trioxaadamantane **167** in C_6D_6*

The presence of a trioxaadamantane moiety in **167** was confirmed by analysis of the ^{13}C NMR spectrum (Figure 3.13), which showed three signals at δ 106.5, δ 102.4 and δ 97.1, in the characteristic region of acetal carbon centres (*i.e.* C3, C7 and C9). Indeed the 2,4,6-trioxaadamantane ring system has been observed in a number of polypropionate natural products,[66-68] and comparisons of the spectral data for compound **167** with that reported for these natural products aided structural elucidation. Additionally, the oxidation state of the remaining oxygen bearing centres was suggested by the three oxymethine carbons that appeared at δ 79.1, δ 78.8 and δ 77.0 and the absence of any carbonyl carbon signals. Analysis of the infrared spectrum of compound **167** showed a broad band at 3506 cm^{-1}, indicating the presence of the hydroxyl groups and high resolution mass spectrometry confirmed the expected molecular formula $C_{26}H_{50}O_6Si$.

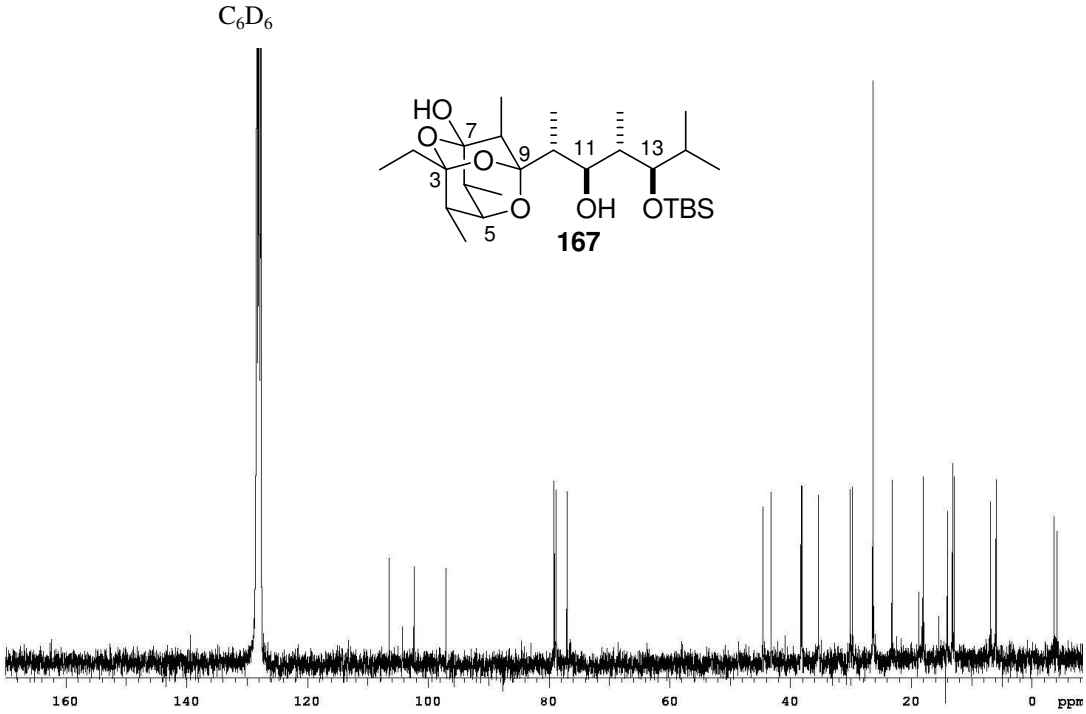
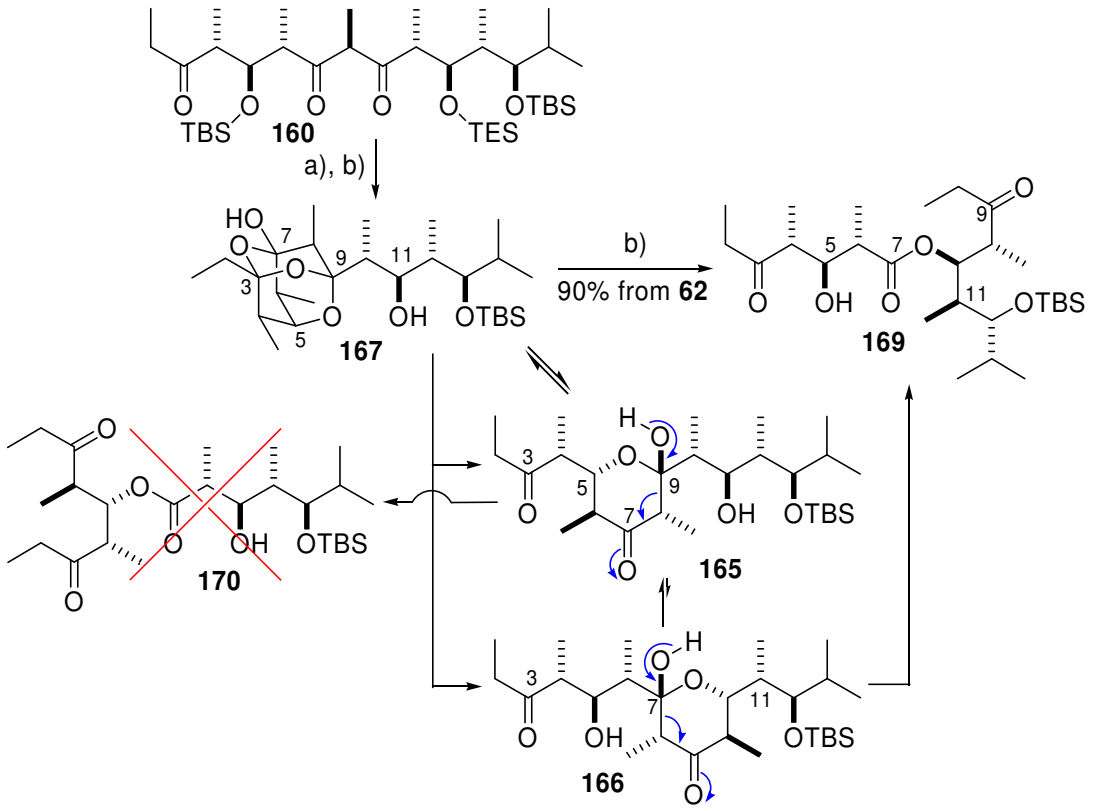


Figure 3.13: *75.5 MHz ^{13}C NMR spectrum of trioxaadamantane **167** in C_6D_6*

Although the acquisition of the unusual trioxaadamantane **167** was an intriguing result, this elaborate compound did not seem a likely precursor to the desired ester **169**, especially considering that its formation was from the incorrect hemiacetal **165**. Fortunately, this conjecture proved incorrect as either treatment of the isolated

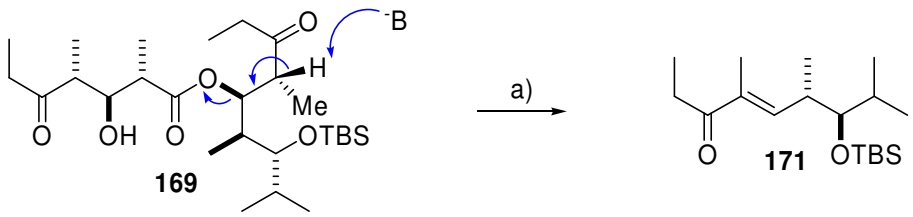
trioxaadamantane **167** with DBU or alternatively, prolonging exposure of the original hemiacetal mixture **165** and **166** to DBU, furnished ester **169** in good yield (90% from **160**, Scheme 3.20). It was apparent that under basic conditions, trioxaadamantane **167** unravels to re-establish the original hemiacetal mixture, where rapid cyclisation of hemiacetal **165** back to trioxaadamantane **167** prohibits retro-Claisen fragmentation of this transient species to ester **170**. The gradual formation and subsequent fragmentation of hemiacetal **166**, giving ester **169** however, proceeds uninhibited. In effect the thermodynamic stability of trioxaadamantane **167** (triple anomeric stabilization) and hence its rapid formation from hemiacetal **165**, enabled this elaborate compound to act as a protecting group, prohibiting the formation of the competing hemiacetal.



Reagents and conditions: a. TAS-F (5.0 eq), H_2O (10.0 eq), DMF, rt, 2 h; **b.** DBU (cat.), C_6D_6, rt, 6 h.

Scheme 3.20: *Acquisition of coveted ester* ***169*** *from trioxaadamantane* ***167****.*

Constant monitoring of the fragmentation reaction was critical, as over time ester **169** underwent β-elimination to give enone **171**, whose formation, while deleterious, helped confirm the identity of ester **169** (Scheme 3.21).



Reagents and conditions: a. excessive exposure to DBU.

Scheme 3.21: *The deleterious formation of enone **171** from ester **169**.*

The ^{1}H NMR spectrum of ester **169** (Figure 3.14) depicts an oxymethine resonance at δ 5.28 (dd, *J* = 9.0, 4.2 Hz), which shows coupling to the methyl methine protons resonating at δ 2.92 (qd, *J* = 7.2, 4.2 Hz) and δ 2.06 (dqd, *J* = 9.0, 7.2, 3.6 Hz). The downfield shift of this oxymethine resonance is indicative of an ester moiety. The methyl methine signals at δ 2.92 and δ 2.06 show coupling to the respective methyl doublets (δ 1.14 and δ 0.91), while the resonance at δ 2.06 shows additional coupling to the TBS oxymethine at δ 3.53 (apt t, *J* = 3.6 Hz). The TBS oxymethine shows the expected coupling to the dimethyl methine resonance at δ 1.81 (apt hep d, *J* = 7.2, 3.6 Hz), whose coupling to the methyl doublets at δ 0.90 (*J* = 7.2 Hz) and δ 0.87 (*J* = 7.2 Hz) completes the isopropyl group. The remaining oxymethine resonates at δ 3.72 (apt t, *J* = 6.6 Hz) and shows coupling to the two methyl methine signals at δ 2.82 (apt qn, *J* = 6.9 Hz) and δ 2.65 (qd, *J* = 7.2, 6.6 Hz), whose downfield shifts indicate their location adjacent to carbonyl moieties. The signals at δ 2.82 and δ 2.65 show coupling to the respective methyl doublets (δ 1.25 and δ 1.17) and hetero-nuclear multiple bond connectivity (HMBC) experiments (see Appendix A) showed coupling of the signal at δ 2.65 to the ester carbonyl at ~δ 176 and δ 2.82 to the ketone carbonyl at ~δ 217. The remaining resonances at δ 2.61-2.47 (4H m), δ 1.052 (3H, t, *J* = 7.2 Hz) and δ 1.048 (3H, t, *J* = 7.2 Hz) account for the two ethyl ketone groups and the signals for the TBS group are evident at δ 0.91 (9H, s), δ 0.054 (3H, s) and δ 0.047 (3H, s). Unfortunately, the ^{1}H NMR spectrum presented in Figure 3.14

shows a small unidentified impurity (~δ 1.4, ~ δ 2.1-2.2 and ~ δ 5.4), which was due to an inseparable by-product of the retro-Claisen reaction.

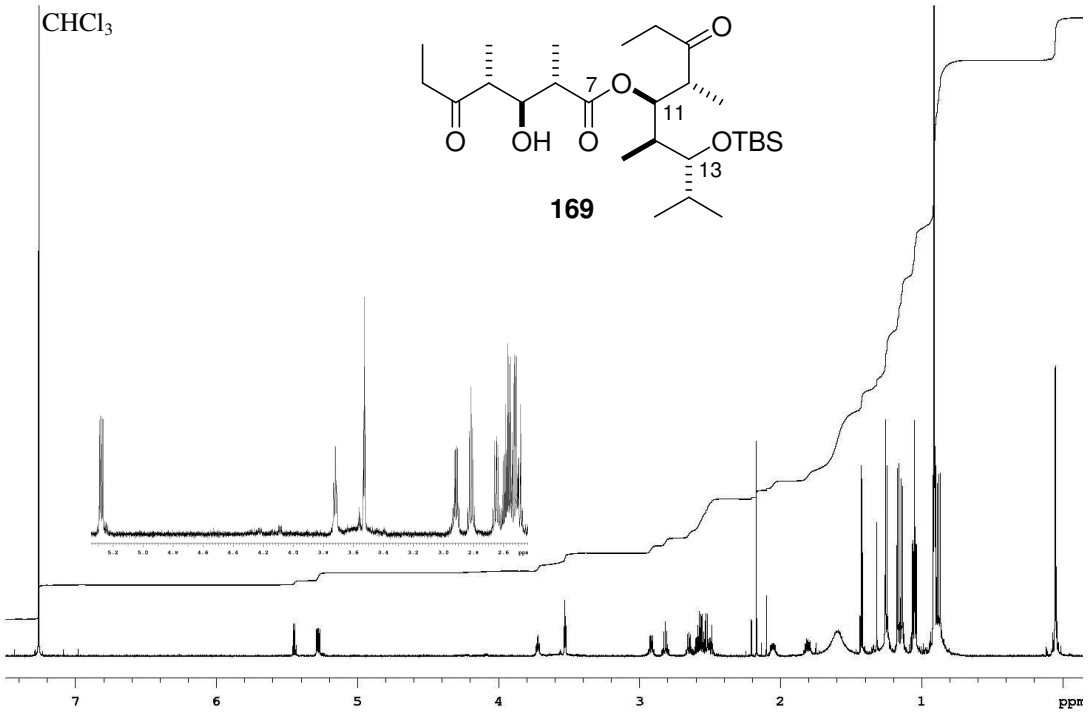
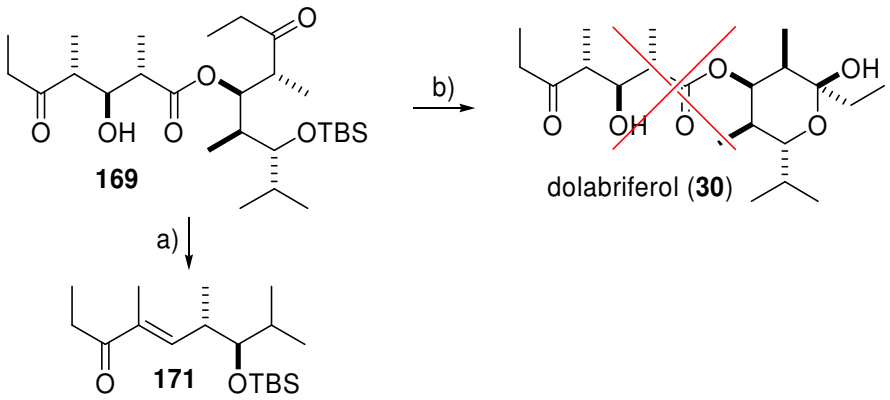


Figure 3.14: *600 MHz ^{1}H NMR spectrum of ester **169** in $CDCl_3$*

The ^{13}C NMR spectral data acquired for compound **169** was in accordance with that expected for the structure and high resolution mass spectrometry confirmed a molecular formula of $C_{26}H_{50}O_6Si$.

3.6 Attempted Deprotection of Ester 169

With ester **169** in hand, and possessing one less protecting group than was originally anticipated (compare with ester **128** from retro-synthetic analysis, Scheme 3.6), attention focussed on removal of the C13 TBS ether and completion of the total synthesis of dolabriferol (**30**). This deprotection reaction was expected to be inherently difficult given the robust character of the TBS moiety in previous steps (after 7 days exposure to HF·pyr/pyr this group remained intact in compound **167**, Scheme 3.19). Scheme 3.22 delineates the attempts made to deprotect ester **169**.



Reagents and conditions: a. TAS-F (5.0-10.0 eq), H_2O (10.0-20.0 eq), DMF, rt; or TBAF (5.0 eq), THF, rt; **b.** HF·pyr, THF, rt; or HF·pyr/pyr, THF, H_2O, rt; or HF·Et_3N, Et_3N, CH_3CN, rt; or $NaIO_4$ (2.5 eq), THF, rt, 1 week.

Scheme 3.22: *Attempted deprotection of ester **169** to give dolabriferol (**30**).*

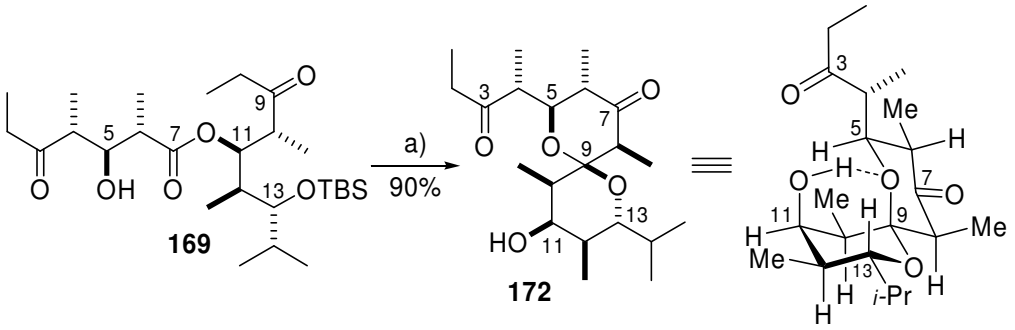
The base sensitivity of the ester **169** (in particular the C11 oxygen substituent) was reinforced when reaction with TBAF[61] at room temperature for 1 h resulted in exclusive formation of enone **171**. Moreover, reaction of ester **169** with TAS-F[64,65] at room temperature overnight also gave enone **171**, with recovered starting material. This result showed both the exceptional sensitivity of ester **169**, given the extremely mild nature of TAS-F, and also the incredible stability of the TBS group, as even after elimination the protecting group remained attached to enone **171**.

Recently[69] Wang and co-workers identified $NaIO_4$ as a mild reagent for the deprotection of hindered silyl ethers. However, exposure of ester **169** to $NaIO_4$ in THF at room temperature for 1 week failed to effect deprotection, giving only recovered starting material.

Hydrofluoric acid has been widely employed, in its various forms, for the removal of silicon protecting groups.[70] Borrowing from this wealth of precedent, multiple sources of HF were trialled to affect cleavage of the C13 TBS ether. To this end, ester **169** was treated with HF·pyr at 0 °Cfor 1 hour.[71] Under these conditions rapid decomposition of the starting material was observed. The very mild pyridine buffered HF·pyr[42,60] and triethylamine buffered HF·Et_3N[72-74] were trialled next.

Unfortunately, over short periods neither reagent caused cleavage of the TBS group and over longer intervals, or at elevated temperatures, extensive decomposition was observed.

Given these failures, an aqueous source of HF[75] was trialled. In practise, a solution of ester **169** in 1:1 CH_3CN/CH_2Cl_2 was reacted with 30% aqueous HF at room temperature for 4 hours (Scheme 3.23).[76] Analysis of the reaction by tlc indicated the formation of a single compound. However, inspection of the ^{1}H NMR spectrum of the purified product immediately ruled out the presence of an ester moiety and thus, the formation of dolabriferol (**30**). Further analysis, aided by 2D NMR experiments (nOe correlations), identified the product as (*E*,*Z*)-spiroacetal **172**.[Ψ]



Reagents and conditions: a. 30% aq HF, 1:1 CH_3CN/CH_2Cl_2, rt, 4 h.

Scheme 3.23: *Unexpected isolation of spiroacetal* ***172*** *from ester* ***169****.*

The outcome of this highly unusual reaction was confirmed by analysis of the spectral data obtained for compound **172**. The ^{1}H NMR spectrum displayed in Figure 3.15 shows an oxymethine proton resonating as a doublet of doublets at δ 3.72 (*J* = 10.8, 2.4 Hz), which shows coupling to the dimethyl methine signal at δ 1.73 (apt qn d, *J* = 6.6, 2.4 Hz) and the methyl methine multiplet at δ 1.29-1.23. The large coupling constant (10.8 Hz) indicates an *anti*-periplanar relationship between the C12 and C13 protons. The oxymethine signal at δ 3.60 (dd, *J* = 10.8, 3.0 Hz) showed

[Ψ] The relative stereochemistry of the spiroacetal ring is defined using the *E* and *Z* system defined by Blackwood *et al.* for the naming of double bonds.[77] With the plane of the ring considered the reference plane, a ring is deemed to have the *E*-configuration if the group of highest priority (usually methyl) bonded to the α-carbon (in this case C10) and the other ring oxygen are on opposite sides of the reference plane, and *Z* if these substituents are on the same side.

coupling to the methyl methine resonances at δ 2.65 (dq, *J* = 10.8, 7.2 Hz) and δ 2.25 (qd, *J* = 7.2, 2.4 Hz) whose shifts are indicative of protons adjacent to a carbonyl moiety. Again the large coupling constant (10.8 Hz) suggests an *anti*-periplanar relationship between the C5 and C6 protons. The remaining oxymethine resonance at δ 3.37 (apt dt, *J* = 10.8, 2.7 Hz) shows coupling to the methyl methine signal at δ 1.39 (qd, *J* = 7.2, 2.7) and the multiplet at δ 1.29-1.23, in addition to the hydroxyl proton at δ 3.05 (d, *J* = 10.8 Hz). The small coupling constant (2.7 Hz) is consistent with the protons at C10 and C12 adopting axial positions and the C11 proton being in the equatorial position. This places the hydroxyl substituent in the axial position, enabling the alcohol proton to participate in a hydrogen bond with the C5-acetal oxygen (Scheme 3.23). This rigidifies the system and positions the hydroxyl proton *anti*-periplanar to the C11 proton, which leads to the large coupling constant observed (10.8 Hz). The remaining signals account for the C8 methyl methine, which resonates as a quartet at δ 2.33 (*J* = 6.6 Hz) and couples to the methyl doublet at δ 1.05 (*J* = 6.6 Hz) and the diastereotopic C2 methyl methylene protons, which appear as doublets of quartets at δ 2.06 (*J* = 18.6, 7.2) and δ 1.99 (*J* = 18.6, 7.2) and show coupling to the methyl triplet at δ 0.94 (*J* = 7.2 Hz).

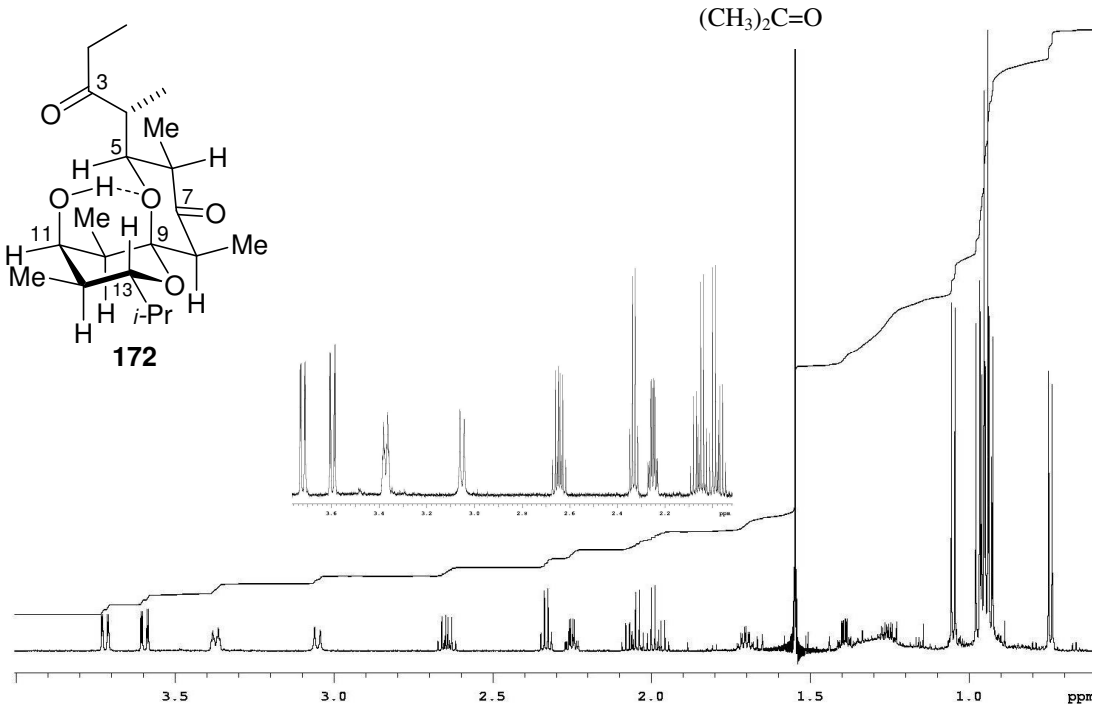
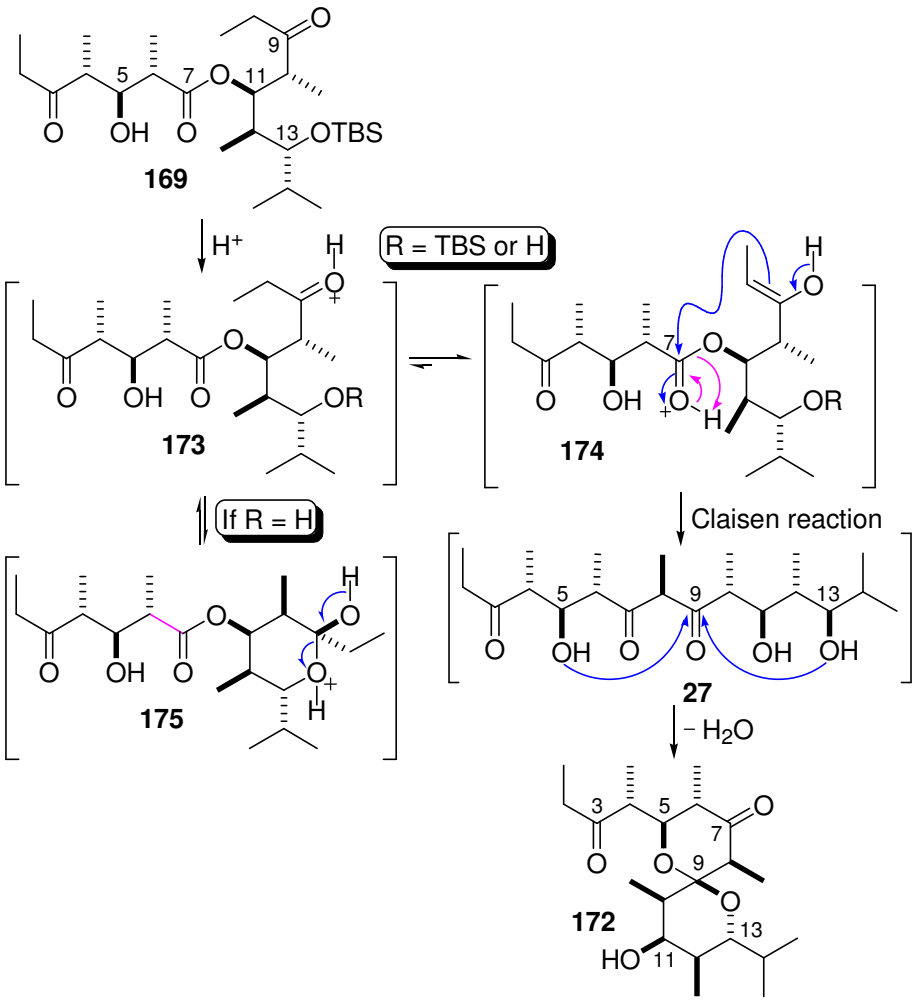


Figure 3.15: *600 MHz ^{1}H NMR spectrum of spiroacetal* ***172*** *in $CDCl_3$*

Unfortunately, due to the small quantity of material isolated, only a partial ^{13}C NMR spectrum could be obtained, which showed all but the C3 and C7 carbonyls and C9 dioxaspiro carbon resonances. However, HMBC experiments (see Appendix A) showed coupling of the C1, C2, C3 and C4 protons to an unsighted signal at ~ δ 210. Additionally, the C6, C8, C19 and C20 protons couple to an unsighted signal at ~ δ 208 and the C8, C18 and C19 protons show coupling to an unsighted signal at ~ δ 105. This confirms the presence of the expected two carbonyl carbons and the spiroacetal centre; in addition to high resolution mass spectrometry, which confirms the expected molecular formula of $C_{21}H_{36}O_5$ (and thus, the loss of H_2O), this secures the structure as depicted for **172**.

A plausible mechanism for the astonishing transformation of ester **169** to spiroacetal **172**, in which three new bonds are forged (and one broken) and two stereocentres are introduced, is presented in Scheme 3.24. Under the acidic reaction conditions, protonation of the C9 carbonyl of ester **169** led to enol **174** *via* tautomerisation of compound **173**. Enol **174** then presumably participated in an intra-molecular Claisen reaction with the ester carbonyl (C7) to give acyclic compound **27**. Finally, reaction of the C5 and C11 hydroxyl groups upon the C9 carbonyl, with loss of H_2O, gave spiroacetal **172**. It was unclear at what stage the TBS group was cleaved, however it was plausible that the silyl ether was removed first, in which case protonated dolabriferol (**30**) could have formed in solution, only to unravel, enolise and progress to the spiroacetal *via* the Claisen reaction. Regardless, it is clear that spiroacetal **172** can only form from cyclisation of deprotected acyclic precursor **27**. This suggests that under acidic conditions the favoured product from reaction of compound **27** is spiroacetal **172** and contradicts the proposed 'biosynthetic' mechanism for the synthesis of dolabriferol (**30**) (Section 3.1.2).[2,78] Further evidence for the favourable formation of spiroacetal **172** from acyclic precursor **27** was given by Goodman *et al.* in their analysis of the reaction pathway for dolabriferol (**30**) using ROBIA (Section 3.2.2).[7] A review of the results of this investigation, supplied as supplementary information, revealed that at the RHF/3-21G level of calculation, spiroacetal **172** was predicted as a possible product with an optimised energy of −1183.947 hartrees.[7] If the energy of water (−75.604 hartrees, calculated by Goodman at RHF/3-21G[79]) was added (which must be done to allow a meaningful comparison to be made with

dolabriferol) the energy is −1259.551 hartrees. Interestingly, this energy value is lower than that calculated for the structure of dolabriferol (**30**, −1259.549 hartrees) and of similar magnitude to other structures whose energy was calculated[7] to be comparable to that of dolabriferol (**30**).



Scheme 3.24: *Rationalisation of the formation of spiroacetal **172** from ester **169**.*

3.7 Directions for a Synthesis of Dolabriferol (30)

Exhaustive attempts to deprotect ester **169** to complete the first total synthesis of marine natural product dolabriferol (**30**) have proven unsuccessful. The combination of an extremely robust TBS group at C13 (presumably due to steric hindrance) and the tremendous sensitivity of ester **169** to even the most mild of

reagents, has prevented the current approach (with a TBS group at C13) from yielding dolabriferol (**30**). It is anticipated that a slight modification in the protecting group strategy, namely replacing the troublesome C13 TBS ether with a benzyl ether, would be compatible with the early stages of the strategy and would not compromise the overall efficiency. With a benzyl ether at C13 in ester **169**, hydrogenation of this protecting group should proceed smoothly to afford dolabriferol (**30**).

Unfortunately, a completely depleted stock of starting materials, limited time and a simultaneous investigation directed toward the first total synthesis of auripyrone A (Chapter 4) meant that the revised approach to dolabriferol (**30**) could not be initiated. However, a highly efficient strategy had been devised, which after modification through replacement of the TBS ether with a benzyl ether should permit the first asymmetric synthesis of dolabriferol (**30**) to be accomplished.

3.8 Natural Product Status of Dolabriferol (30)

The natural product status of dolabriferol (**30**) remains uncertain. The synthetic study delineated above has shown that the ester moiety of dolabriferol (**30**) can be formulated from a hemiacetal intermediate (**166**). Significantly, the approach yielded the correct carbogenic skeleton for dolabriferol (**30**) as the only product from reaction of a mixture of hemiacetals **165** and **166** (Scheme 3.20). This result is in line with the pathway that has been suggested[2,78] for the formation of dolabriferol (**30**) from acyclic precursor **27** (Scheme 3.1). However, the strategy is not truly representative of the proposed pathway as the C13 alcohol remained protected. Of great significance was the isolation of spiroacetal **172**. This compound can only form from double cyclisation of fully deprotected acyclic precursor **27** (Scheme 3.24), and hence the formation of this product does not support the proposed uncontrolled synthesis of dolabriferol (**30**) from compound **27**. Additionally, results published by Goodman *et al.*[7] suggest that dolabriferol (**30**) is not the lowest energy product from reaction of acyclic precursor **27** (indeed spiroacetal **172** is predicted to be lower in energy). This perhaps suggests that the formation of dolabriferol (**30**) as the major product from uncontrolled reaction of unprotected precursor **27** is unlikely. And

given that dolabriferol (**30**) was shown to be the main metabolite in the parapodia and hepatopancreas, but not the digestive glands of *D. dolabrifera*,[2] it is plausible that dolabriferol (**30**) is a true secondary metabolite and not an artefact. It seems possible that the ester linkage of dolabriferol (**30**) could be forged from the union of the appropriate alcohol and acid polypropionate fragments.

3.9 Conclusion

The work communicated above constitutes an efficient and high yielding asymmetric approach to the unusual marine natural product dolabriferol. Despite falling short of its goal, the devised strategy afforded ester **169** as a direct precursor to dolabriferol (**30**), as a single stereoisomer in 36% overall yield from lactate derived[14] ketone (*S*)-**67** and aldehyde (*R*)-**133** (16 linear steps). The approach used ketone (*S*)-**67** in three separate substrate controlling *anti*-aldol reactions to install all but one of the stereocentres found in dolabriferol (**30**). Notably, the synthesis followed a 'pseudo biomimetic' route,[2,78] such that the ester moiety was forged from an acyclic precursor through deprotection of triketone **160** and retro-Claisen fragmentation of the resulting hemiacetal **166** (masked as trioxaadamantane **167**). This novel approach to the formation of the ester moiety suggests that the synthesis of dolabriferol (**30**) from an intermediate hemiacetal is plausible, and thus supports the proposition that dolabriferol (**30**) could form from the retro-Claisen fragmentation of a hemiacetal intermediate (Section 3.1.2). However, the formation of spiroacetal **172** from fully deprotected acylic precursor **27** (*via* ester **169**) suggests that the proposed formation of dolabriferol (**30**) from the same precursor needs review.

In general terms however, the strategy presented above recognised the dependence organic synthesis has on formal protecting groups, and the problems that are encountered when such moieties display unexpected robustness. Although not anticipated, trioxaadamantane **167** adopted the role of a protecting group in the retro-Claisen fragmentation reaction leading to ester **169** (Scheme 3.21). This fortuitous reactivity was suggestive of the efficiency and control that can be achieved by

employing inherent structural functionality to replace formal protection sequences. The following chapter will elaborate on this point and show that the synthesis of complex natural products can be achieved with minimal influence from formal protecting groups.

3.10 References

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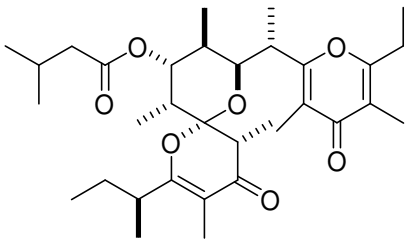
Chapter Four

Asymmetric Total Synthesis of Cytotoxic Marine Polypropionate Auripyrone A

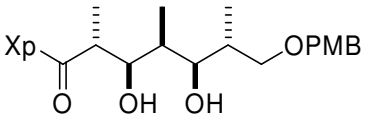
Chapter Four

Asymmetric Total Synthesis of Cytotoxic Marine Polypropionate Auripyrone A

This chapter describes the first total synthesis of the cytotoxic marine natural product auripyrone A (**78**). The evolution of this endeavour from a model system, into a highly efficient strategy for the synthesis of this natural product in enantiopure form is delineated. Key to this achievement were construction of the requisite stereopentad, utilising chiral auxiliary (*R*)-**100**, differentiation of the diol system in compound **206**, optimising formation of spiroacetal **274** and the discovery of a novel γ-pyrone forming reaction.



auripyrone A (**78**)



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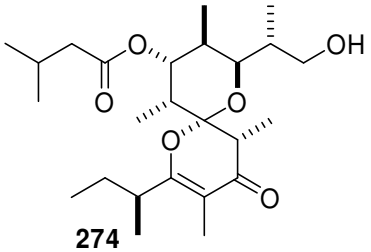

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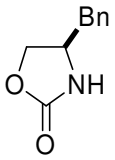


(*R*)-**100**

4.1 Introduction

4.1.1 *Dolabella auricularia* and the Isolation of the Auripyrones

Typically found in shallow (<2 m) subtidal, circumtropical seas, *Dolabella auricularia* (Figure 4.1) is a large (to ~1 kg wet mass), herbivorous, opisthobranch gastropod (sea hare),[1] with an impressive reputation for yielding bioactive metabolites.[2,3] Indeed, since 1965, specimens of *D. auricularia*, collected from the

Indo-Pacific region, have yielded a vast variety of potent metabolites ranging from peptides and depsipeptides to terpenes and polyketides.[2,3] Recent reports suggest that the majority of bioactive compounds isolated from *D. auricularia* are not produced *de novo* or through symbiosis with microbacteria, but are merely sequestered by the organism from algal grazing;[1-3] hence their confinement to the internal organs.

Figure 4.1: *Dolabella auricularia*

No fewer than 30 bioactive depsipeptides designated dolastatins (and isodolastatins) 1-20 and A-H[2] as well as the aurilides[2] have been isolated from *D. auricularia*, with dolastatin 10 (**2**)[4] and dolastatin 15 (**176**)[5] (Figure 4.2) showing such potent anti-tumour activity (0.45 and 2.4 ng/mL, respectively) that they have both entered phase II clinical trials.[6] In fact, when first discovered, dolastatin 10 (**2**) was claimed to be the most active neoplastic substance known.[4] Bioactive terpenoids are much less prolific, with examples including the cytotoxic dolatriols (**177** and **178**)[7,8] and bromotriterpene, aurilol (**179**)[9] (Figure 4.2). The polyketides are well represented with the cytotoxic macrolides auriside A (**180**) and B (**181**)[10] and the 22- and 24-membered macrocyclic dolabelides A-D (**182**-**185**)[11,12] (Figure 4.2), being but a few examples. It was in to this last grouping that auripyrones A (**78**) and B (**186**) (Figure 4.3) were assigned when they were isolated from the ether soluble acetone extracts of specimens of *D. auricularia*, collected from Mie Prefecture, Japan, by Suenaga and co-workers in 1996.[13] Auripyrone A and B displayed significant cytotoxicity towards HeLa S_3 cells with IC_{50} values of 0.26 and 0.48 μg/mL, respectively.[13] Unfortunately, both compounds were isolated in exceedingly small quantities, with 452 kg (wet wt.) of organism yielding just 1.0 mg (2.2×10^{-7}%) and 1.7 mg (3.8×10^{-7}%) of auripyrone A and B, respectively.[13]

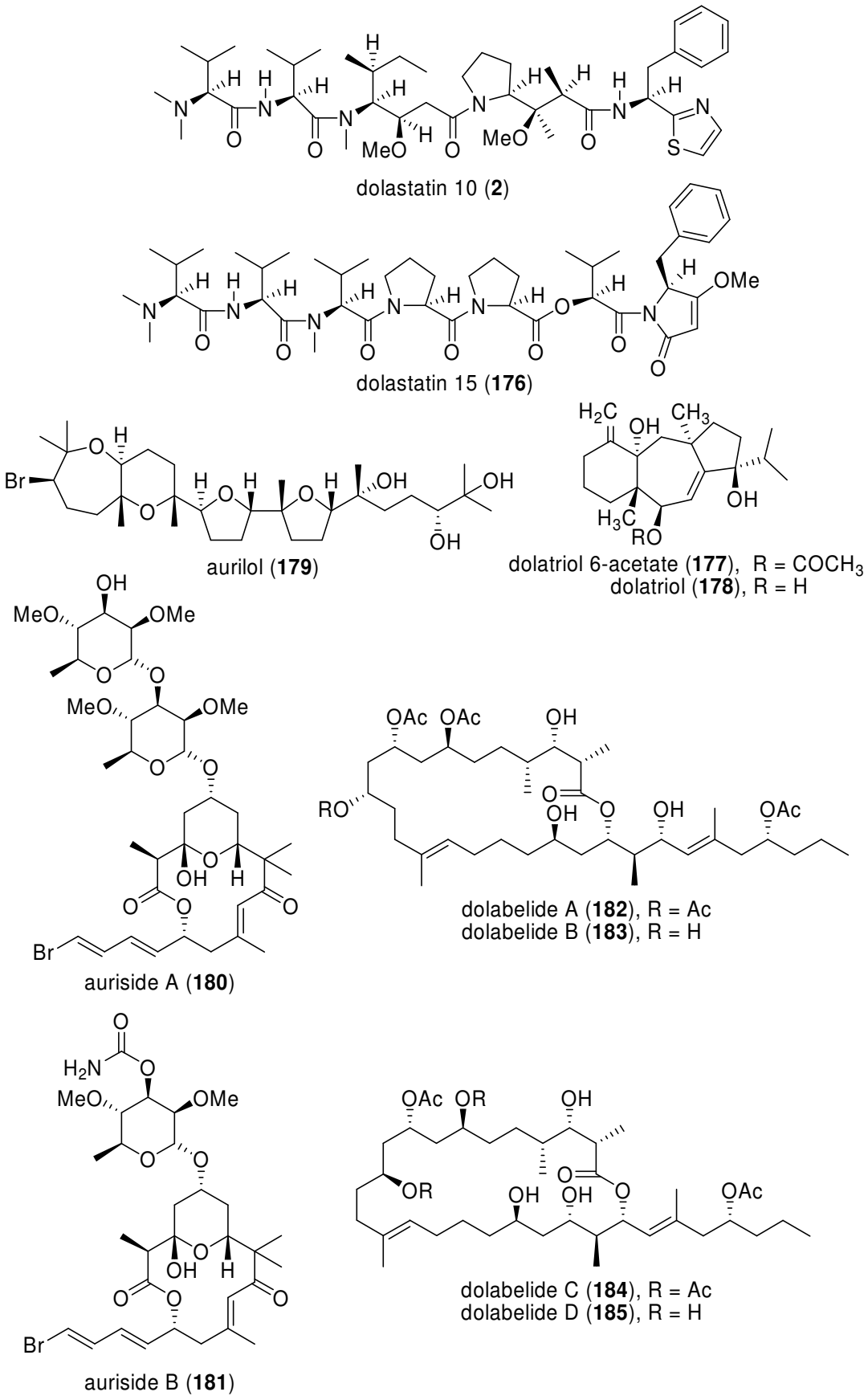


Figure 4.2: *Cytotoxic metabolites isolated from D. auricularia.*

4.1.2 Structural Elucidation

Extensive NMR studies by Suenaga *et al.*[13] showed that auripyrones A (**78**) and B (**186**) comprised characteristic polypropionate architecture, encompassing a unique spiroacetal dihydropyrone core tethered to a γ-pyrone ring, and that the two compounds differed only in the substitution of their respective C11 acyloxy side chains. Two-dimensional NMR techniques (nOe experiments) allowed Suenaga *et al.*[13] to deduce the complete relative stereochemistry of the natural products, with the exception of the C2` stereocentre in auripyrone B (**186**). As such, it was shown that the spiroacetal core exhibited a double anomeric, diaxial-dioxaspiro centre, an axial methyl substituent at C10 and an axial acyloxy group at C11 (Figure 4.3). Unfortunately, the absolute stereochemistry of the natural products was unable to be assigned and as such the enantiomer depicted by Suenaga in the isolation communication[13] was arbitrary.

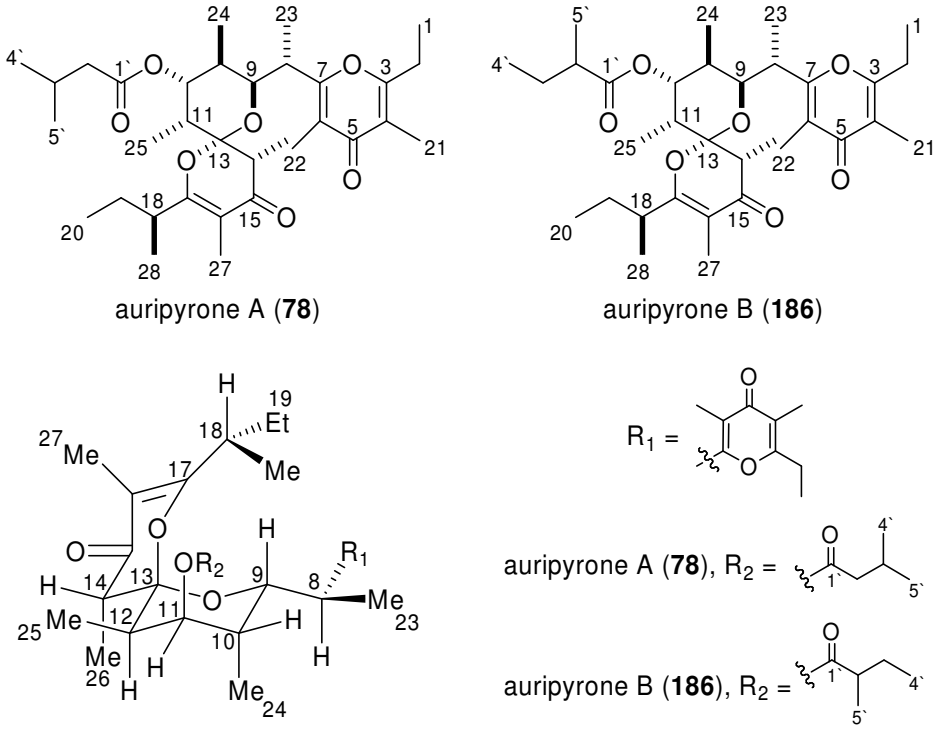
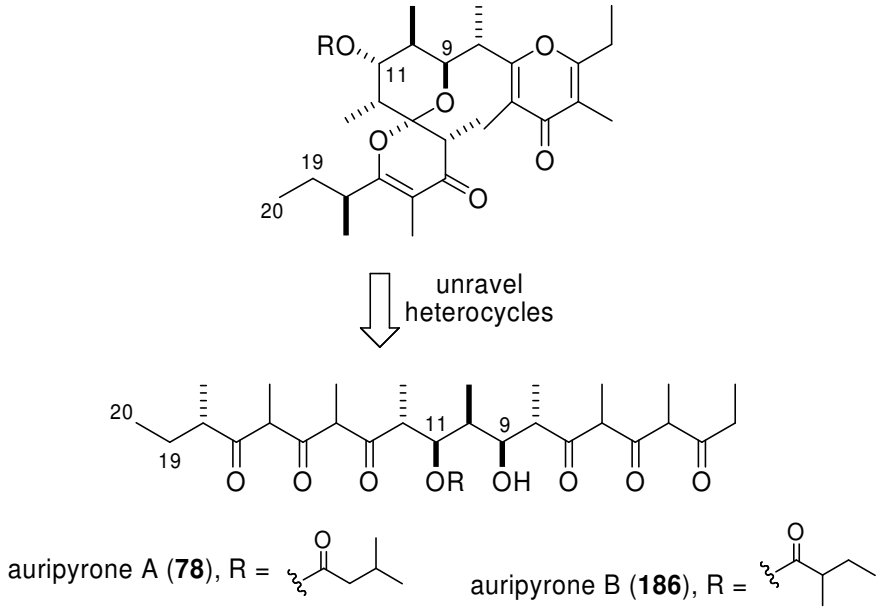


Figure 4.3: *Auripyrone A and B*

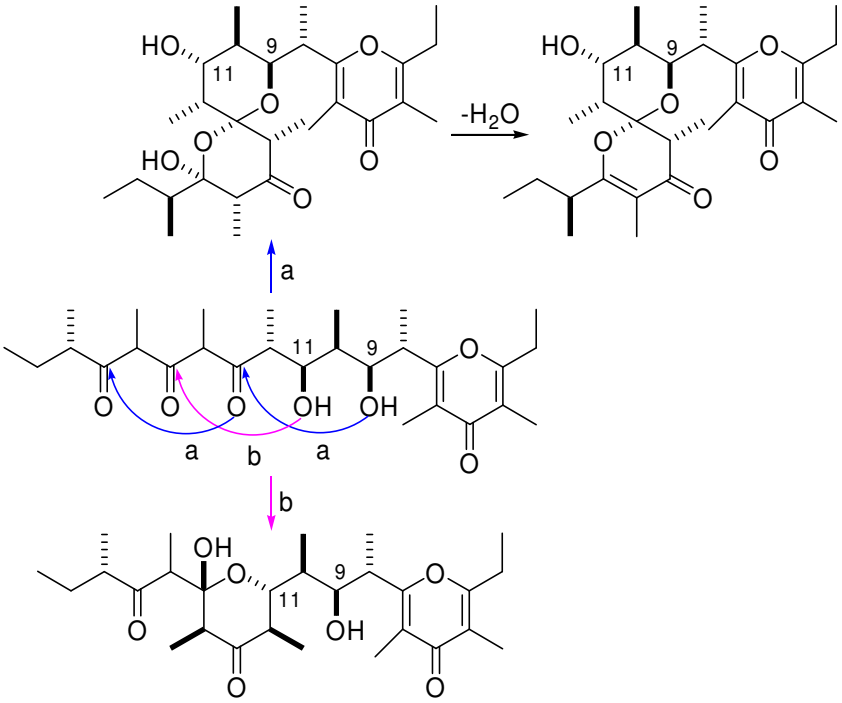
Unravelling the heterocycles in the generic auripyrone skeleton (Scheme 4.1) permits immediate recognition of both the polypropionate lineage and the arrangement of the stereochemical array. The C8-C12 'meso' stereopentad lies at the heart of the

auripyrones and is flanked on either side by a tricarbonyl system. Despite the near perfect C2 symmetry that this combination confers on the structure, the C19-C20 ethyl extension and the differentiation of the C9 and C11 oxygen bearing centres impart a crucial asymmetry on the system.



Scheme 4.1: *'Meso' stereopentad of the auripyrones*

If one considers a likely precursor to the auripyrones (where the pyrone unit is already installed, Scheme 4.2) and the acyloxy group at C11 is not present, it is clear that the position of the ester moiety at C11 prohibits a competing cyclisation mode (mode b). Indeed, if this group was introduced during biosynthetic homologation, prior to spiro-cyclisation, it would likely constitute a biological protecting group, used to promote efficient metabolite formation. The auspicious placement of the acyloxy moiety and the consequences of its use as a potential protecting group were given ample thought when planning a synthetic strategy towards auripyrone A, as will be shown in the coming sections.



Scheme 4.2: *Competing cyclisation modes if the C11 acyloxy group was omitted.*

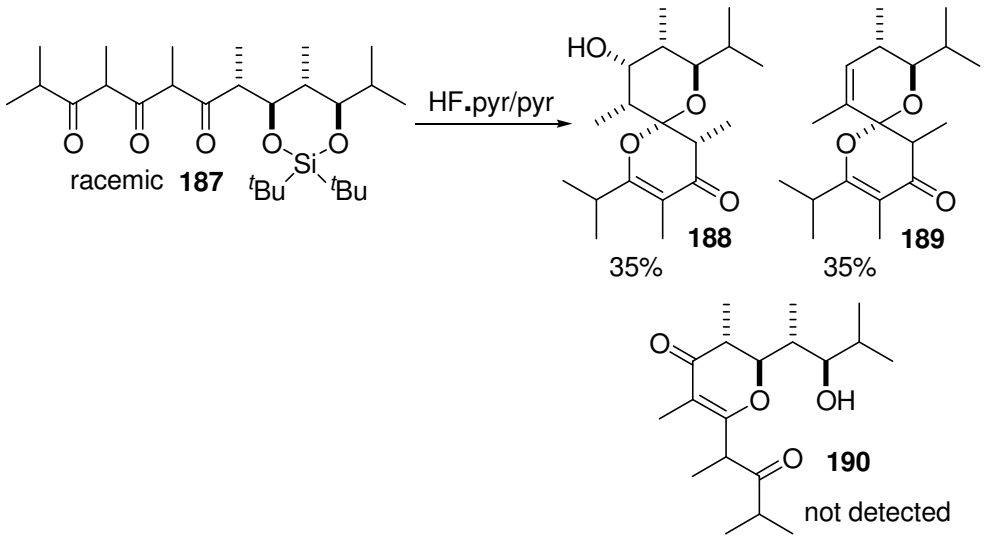
4.2 Previous Work

Despite displaying moderate levels of cytotoxic activity and a unique structure, the auripyrones have seemingly escaped the attention of the synthetic community. Indeed, outside of the Perkins laboratory (Flinders University), there does not appear to have been any significant studies towards a chemical synthesis of these natural products.

The auripyrones have been a keen focus for the Perkins group for some time, with previous studies constituting two model systems[14,15] and an attempted total synthesis.[15] The model studies were devised to probe spiroacetal dihydropyrone formation and its dependence on the relative stereochemistry of the requisite stereoarray. Neither of these strategies had the scope to be extended to a total synthesis; however a further study borrowed extensively from the model systems in an endeavour to target the auripyrones. Schemes 4.3-4.5 show the final stages of each strategy, where liberation of the respective protecting groups was directed towards spiroacetal dihydropyrone formation.

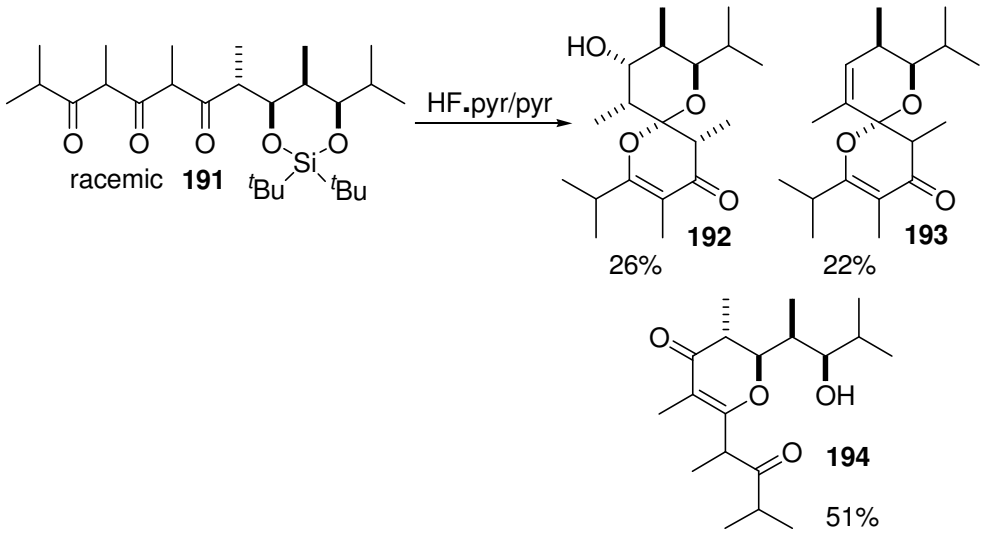
Jahangiri and Joannou studied very similar, racemic systems where the γ-pyrone tether and the C19-C20 ethyl extension were each replaced by isopropyl groups.[14,15] The central difference in these strategies was the design of the stereochemical array in each substrate. Jahangiri designed a stereotetrad where, upon cyclisation, the C10 methyl substituent was anticipated to adopt the equatorial position.[14] In contrast, Joannou developed a stereoarray that mimicked the auripyrones, where the C10 methyl substituent would adopt the axial position after cyclisation.[15] Schemes 4.3-4.5 show the product distribution after removal of the respective bis-silylene protecting groups and subsequent cyclisation.

Jahangiri observed exclusive spiroacetalisation after deprotection of compound **187** giving **188** (following path a, as shown in Scheme 4.2) with half the cyclised material lost to undesired dehydration at C11 (**189**) as shown in Scheme 4.3. None of dihydropyrone **190** was detected.[14]



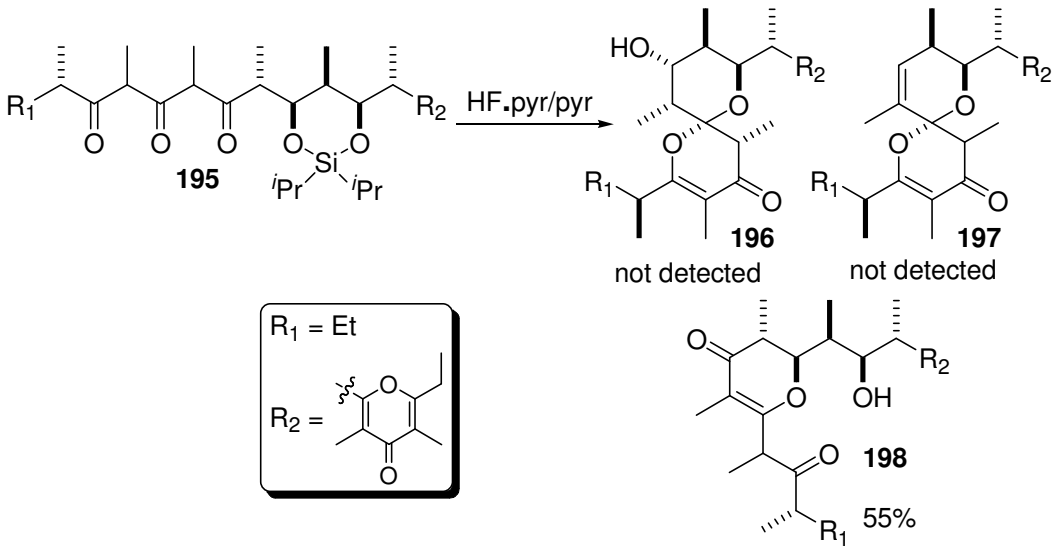
Scheme 4.3: *Studies in spiroacetal formation by Jahangiri.*

After deprotection of racemic β-triketide **191** Joannou observed a 1:1 distribution of products arising from cascade cyclisation leading to **192** (path a) and undesired dihydropyrone formation giving **194** (path b, followed by dehydration). The yield of the desired spiroacetal dihydropyrone **192** was diminished by uncontrolled dehydration giving compound **193** as shown in Scheme 4.4.[15]



Scheme 4.4: *Studies in spiroacetal formation by Joannou.*

Sampson targeted a diastereoselective synthesis of auripyrone A employing a similar protection strategy to that encountered in the model systems. Unfortunately, upon final stage deprotection of precursor **195**, none of the desired spiroacetalisation (**196** or **197**) was observed with only dihydropyrone **198** (path b, followed by dehydration) resulting (Scheme 4.5).[15]



Scheme 4.5: *Studies in spiroacetal formation by Sampson*

These results suggested that as the system is elaborated to more closely mimic the natural product, the balance between spirocyclisation (path a) and dihydropyrone formation (path b) is shifted drastically away from the desired result. The clear

connection of these past studies was the employment of bis-protection of the C9 and C11 hydroxyl groups.[14,15] It was apparent that such a protection strategy was not compatible with controlled spiroacetalisation of a fully elaborated auripyrone precursor.

Hence, despite significant information having been gleaned from the previous studies,[14,15] a different strategy was required to pursue a stereoselective synthesis of the auripyrones. As such, a new methodology was devised that utilised differential protection of the C9 and C11 oxygen bearing centres.

4.3 Strategies Towards a Synthesis of Auripyrone A

Of the two natural products isolated, auripyrone A was chosen as the initial target, given its less ambiguous structure (known relative stereochemistry) and more potent biological activity than auripyrone B. However, it was anticipated that the devised strategy would be applicable to both natural products by interchange of the required acyloxy group.

As with all targeted syntheses, there was a multitude of ways to dissect and retro-synthetically cleave auripyrone A to achieve a convergent, stereoselective synthesis. However, two broad approaches seemed clear. Either the formation of the spiroacetal dihydropyrone moiety would be left as the last synthetic operation to be performed, thus requiring installation of the γ-pyrone tether at an early stage, or the unique spirocycle could be assembled prior to a late stage pyrone formation. In terms of greatest number of steps, neither strategy significantly outranked the other, but it appeared likely that a γ-pyrone moiety would be considerably more robust and hence more capable of surviving multiple transformations intact, rather than the spiroacetal. For this reason, the strategy as depicted retro-synthetically in Scheme 4.6 was pursued as a first approach.

4.4 A First Approach to Auripyrone A

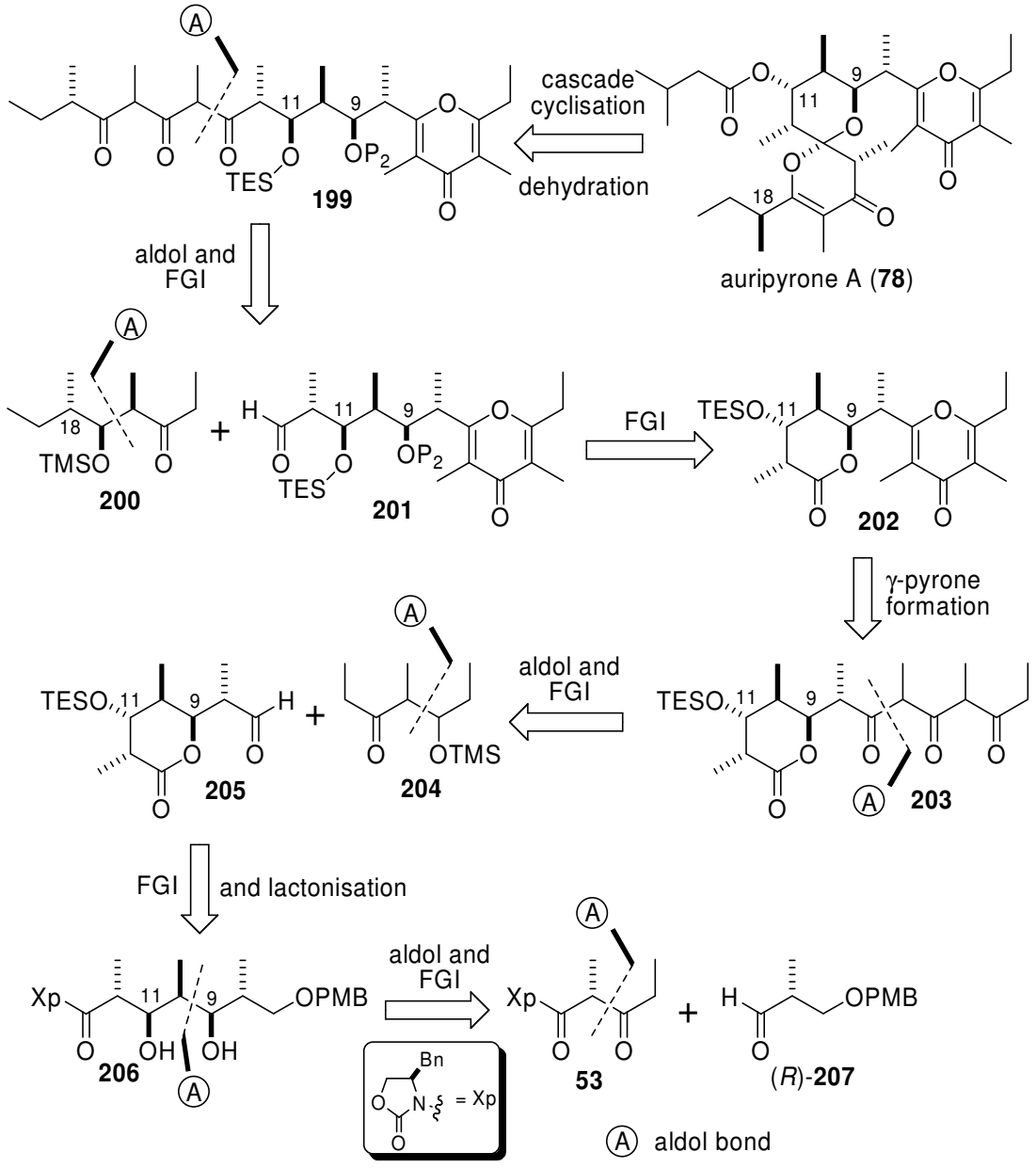
4.4.1 Retro-Synthetic Analysis

Due to the inherent symmetry of the acyclic precursor to the auripyrones and the desire to have absolute control over spirocyclisation, the critical operation in the synthesis was anticipated to be achieving differential protection of the C9 and C11 oxygen bearing centres. It was predicted, therefore, that protecting group selection and manipulation would play a crucial role in the synthesis. For simplicity, all compounds depicted hence forth are numbered in accordance with the numbering of auripyrone A (**78**).[13]

As delineated in Scheme 4.6 the final steps in the synthesis of auripyrone A (**78**) called for cascade cyclisation/dehydration of precursor tricarbonyl **199**, upon liberation of protecting group P_2, followed by installation of the required ester at C11. The tricarbonyl moiety of **199** was anticipated to be formulated from an initial aldol coupling of β-silyloxy ketone **200** with suitably protected aldehyde **201**, followed by removal of the TMS group and double oxidation. It was envisaged that differential protection could be achieved through ring opening of β-lactone **202** and subsequent protection of the liberated C9 alcohol. The γ-pyrone unit in **202** was accessible from β-triketide **203**, which in turn was available from an initial aldol reaction between ketone **204** and β-lactone aldehyde **205**, followed by standard functional group manipulations. It was foreseen that lactonisation of diol **206** would provide the means for differential protection by tying up the C9 oxygen and allowing the C11 oxygen to be protected independently. Subsequent functional group manipulations would afford aldehyde **205**. Critical to synthesising auripyrone A as a single enantiomer was the stereocontrolled synthesis of diol **206** containing the requisite C8-C12 stereopentad. The use of Evans' dipropionate equivalent,[16] β-ketoimide **53** in an aldol coupling with known[17] aldehyde (*R*)-**207** followed by *syn*-selective reduction,[18] was envisaged to accomplish this goal, admirably.

At this point it is pertinent to note that β-silyloxy ketone **200** would act as a surrogate for the remote C18 stereocentre of auripyrone A. To ensure a diastereoselective synthesis of the natural product was achieved, the formation of this fragment

required an aldol union of pentan-3-one with a single enantiomer of 2-methylbutanal (see Scheme 4.29). Given the commercial availability (Sigma-Aldrich Chemical Co.) of only the (*S*)-enantiomer of 2-methylbutanol (the intended precursor to 2-methylbutanal), it was deemed that the most accessible enantiomer of auripyrone A would be that depicted for **78** (Scheme 4.6), where C18 has (*S*)-configuration. Notably, this corresponds to the enantiomer of auripyrones A (**78**) and B (**186**) as arbitrarily depicted by Suenaga and co-workers in the isolation paper.[13]



Scheme 4.6: *Retrosynthetic analysis of auripyrone A (**78**).*

4.5 Model Studies

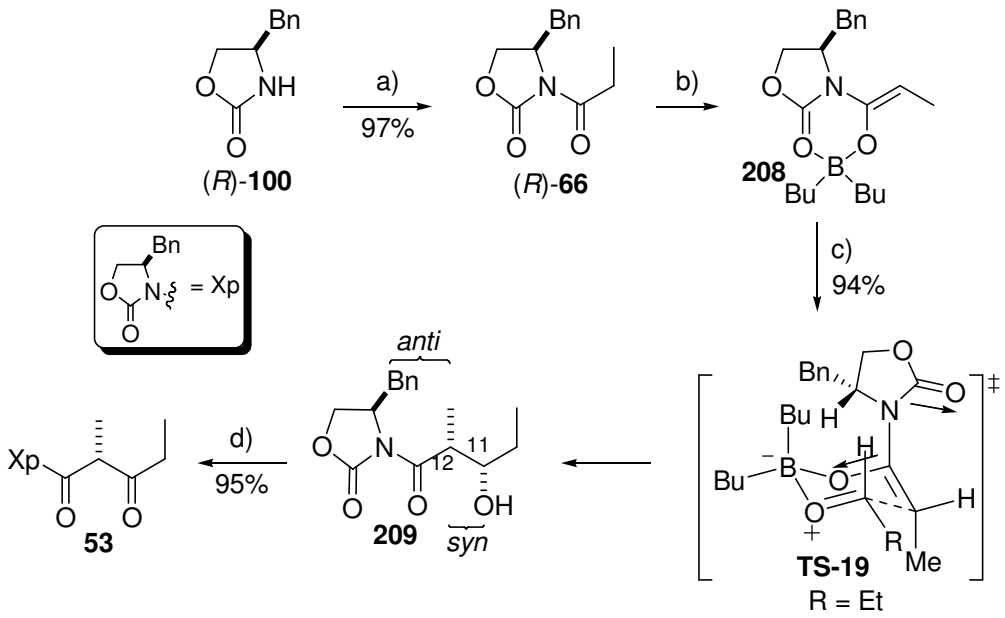
A model system was devised to probe the utility of the lactone moiety as an intermediary protecting group and to assess conditions for its formation. The model strategy followed the initial stages of the sequence depicted retro-synthetically for auripyrone A (**78**) (Scheme 4.6), but omitted the γ-pyrone moiety and utilised commercially available (Sigma-Aldrich Chemical Co.) methacrolein in place of aldehyde (*R*)-**207**. It was anticipated that the sequence formulated in the model study would be reproducible for a synthesis of auripyrone A upon incorporation of the correct chiral aldehyde.

4.5.1 Acquisition of Model Diol 211

Substantial quantities of β-ketoimide **53** (~10 g) were required to sustain the anticipated synthetic endeavours. To this end, the previously discussed (Scheme 2.4, Chapter 2) (*R*)-4-benzyl-2-oxazolidinone [(*R*)-**100**)][19] was treated with butyl lithium, followed by propionyl chloride to afford *N*-acyl oxazolidinone (*R*)-**66**[19] in excellent yield as shown in Scheme 4.7. Exposure of the *N*-acylated material to dibutylboron triflate and triethylamine forged the *Z*-(O)-boron enolate **208**, which smoothly reacted with propanal to afford, after oxidative work-up and purification, 11,12-*syn*-oxazolidinone,12-*anti*-β-hydroxyimide **209** as white needles.[19]

Transition state[20] **TS-19** explains the exceptional level of diastereoselectivity (>95%) observed for this substrate controlled aldol reaction. In **TS-19** the preferred conformation of the N-C bond is adopted, where the dipoles of the enolate oxygen and the carbonyl group of the auxiliary are opposed (as shown by the arrows in Scheme 4.7). Also, the rotamer of the N-C bond projects the small hydrogen (as opposed to the large benzyl group) towards the centre of the sterically demanding transition state.

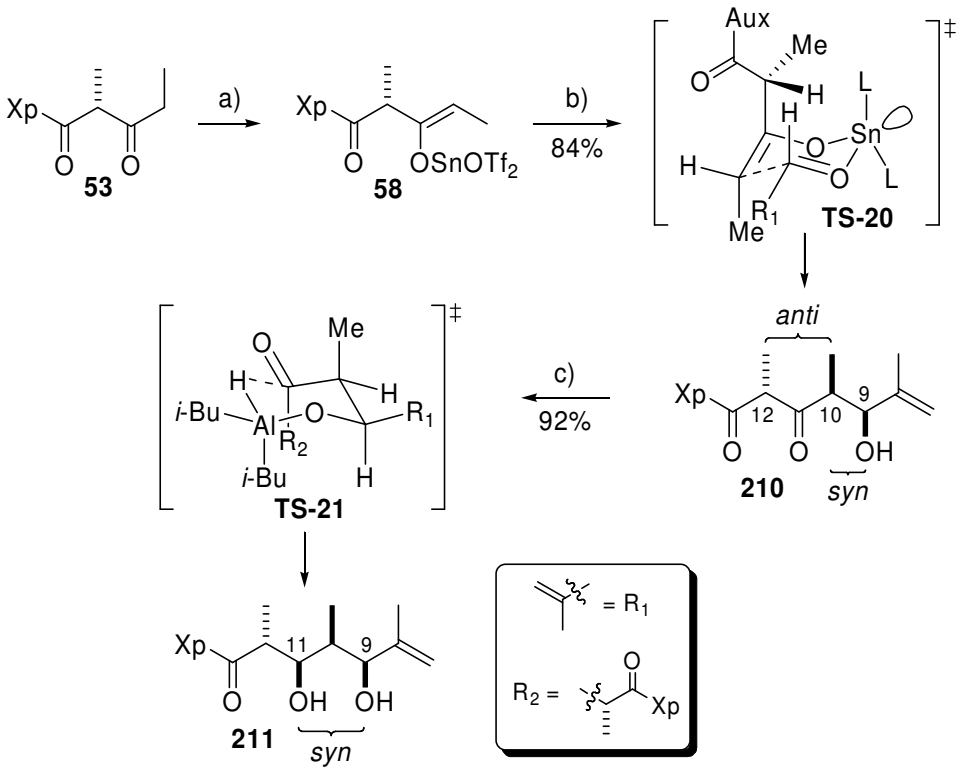
With aldol adduct **209** in hand, reaction with SO_3·pyr and DMSO under Parikh and Doering conditions[21] afforded dipropionate equivalent **53** as a white solid in excellent yield (95%) as shown in Scheme 4.7.



Reagents and conditions: a. i. *n*-BuLi (1.01 eq), THF, −78 °C; ii. EtCOCl (1.1 eq), −78 °C, 30 min to rt; **b.** i. Bu_2BOTf (1.2 eq), CH_2Cl_2, 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; **c.** propanal (2.0 eq), −78 °C, 30 min to 0 °C, 1 h; **d.** SO_3·pyr (3.0 eq), Et_3N (3.0 eq), DMSO/CH_2Cl_2, rt, 3 h.

Scheme 4.7: *Sequence for the synthesis of β-ketoimide* ***53****.*

Reaction of β-ketoimide **53** with premixed stannous triflate and Et_3N at −20 °C for 1 hour formed *Z*-(O)-tin(II) enolate **58**,[18] which reacted with freshly distilled methacrolein at −78 °C for 30 minutes, giving the 9,10-*syn*-10,12-*anti*-aldol adduct **210** in good yield and excellent selectivity (>95% ds, Scheme 4.8). Transition state model (**TS-20**)[18] rationalizes the high level of diastereofacial selectivity observed. The conformation formed projects the least bulky hydrogen substituent towards the sterically demanding centre of transition state. The success of this reaction was strongly dependant on the quality of the $Sn(OTf)_2$, which was prepared from reaction of tin chloride ($SnCl_2$) with triflic acid (TfOH) at 85 °C for 16 hours,[22,23] followed by isolation of the white solid with a Schlenk tube and handling in an argon glove bag. Finally, hydroxyl directed DIBAL-H reduction[18] (**TS-21**) of the aldol adduct afforded the 9,11-*syn*-diol **211** in high diastereoselectivity (>95%), thus completing installation of the required stereotetrad.



Reagents and conditions: a. i. $Sn(OTf)_2$ (1.3 eq), CH_2Cl_2, 0 °C; ii. Et_3N (1.3 eq), 10 min; iii. imide **53**, CH_2Cl_2, −20 °C, 1 h; **b.** methacrolein, (1.5 eq); −78 °C, 30 min; **c.** DIBAL-H (4.0 eq), Et_2O, −78 °C, 1 h.

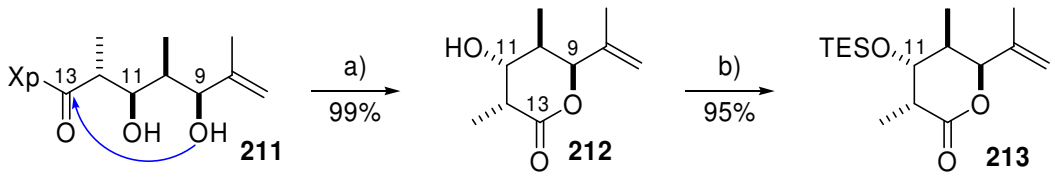
Scheme 4.8: *Sequence for the synthesis of diol **211** from β-ketoimide **53**.*

Despite the exceptional efficiency and control exhibited by the Evans' protocol depicted above, the final reduction step displays limitations when confronted with a system like auripyrone A, which necessitated differential protection. Attempts to either perform the reduction in the presence of a preinstalled protecting group at C9 or to achieve chemoselective silyl protection at C9 in the presence of the free diol failed. A Tishchenko-type reaction, where reduction occurs with simultaneous protection of the initial alcohol,[24] appeared the perfect solution. However, there are currently no known *syn*-variants of such a transformation. As such, an intramolecular protection strategy was devised, with its implementation delineated below.

4.5.2 Lactonisation of Diol 211 as a Protecting Group Mimic

Focus now centred on effecting lactonisation of diol **211** to temporarily 'desymmetrise' the system. Initial reactions of **211** with a variety of acids (HCl,

TFA, CSA) gave very poor results due to both decomposition of the starting material and complex product mixtures. Interestingly, lactone **212** was routinely isolated in small quantities in the high R_f fractions from chromatographic purification (silica gel) of diol **211**. With this in mind **211** was deposited onto silica gel (~ 50 times by weight) with CH_2Cl_2 (slurry) and allowed to stir overnight, as depicted in Scheme 4.9. This simple procedure afforded the desired lactone **212** in near quantitative yield and recovered oxazolidinone (*R*)-**100**, which could be recycled. Protection of the free alcohol in **212** as a triethylsilyl ether under standard conditions (TESOTf, 2,6-lutidine)[25] then afforded silyl lactone **213** in excellent yield (95%).



Reagents and conditions: a. SiO_2, CH_2Cl_2, rt, o/n; **b.** i. 2,6-lutidine (4.0 eq), CH_2Cl_2, −78 °C; ii. TESOTf, (3.0 eq), −78 °C, 30 min.

Scheme 4.9: *Cyclisation of diol **211** and protection of γ-hyroxylactone **212**.*

The ^{1}H NMR spectrum of lactone **212**, shown in Figure 4.4, displays one vinyl proton as a multiplet at δ 5.11 and the other as a quartet at δ 4.97 (J = 1.5 Hz) with both showing coupling to the vinyl methyl singlet at δ 1.68. The allylic oxymethine proton resonates as a multiplet at δ 5.17 and shows coupling to the methyl methine multiplet at δ 2.34 (qdd, J = 7.2, 3.6, 3.6 Hz), which in turn couples to the methyl doublet at δ 0.83 (J = 7.2 Hz). The remaining oxymethine resonates as an apparent triplet at δ 3.98 (J = 3.6 Hz) and shows coupling to the methyl methine quartet of doublets at δ 2.64 (J = 4.2, 3.6 Hz), which itself couples to the remaining methyl doublet at δ 1.31 (J = 7.2 Hz). The hydroxyl proton appears as a broad singlet at δ 2.79.

The ^{13}C NMR spectrum (Figure 4.5) shows a characteristic ester carbonyl resonance at δ 174.1 and olefinic resonances at δ 140.1 and δ 111.4. Analysis of the infrared spectrum of **212** revealed a broad hydroxyl stretch at 3448 cm^{-1} and a strong

carbonyl band at 1715 cm^{-1} and high resolution mass spectrometry confirmed the expected molecular composition of $C_{10}H_{16}O_3$.

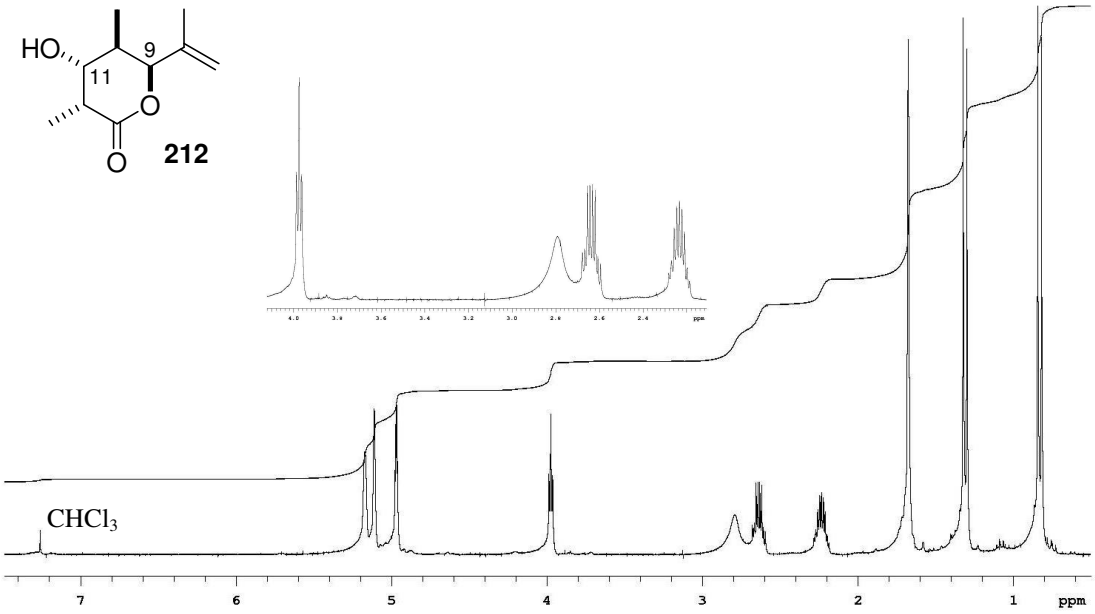


Figure 4.4: *300 MHz ^{1}H NMR spectrum of lactone* ***212*** *in $CDCl_3$*

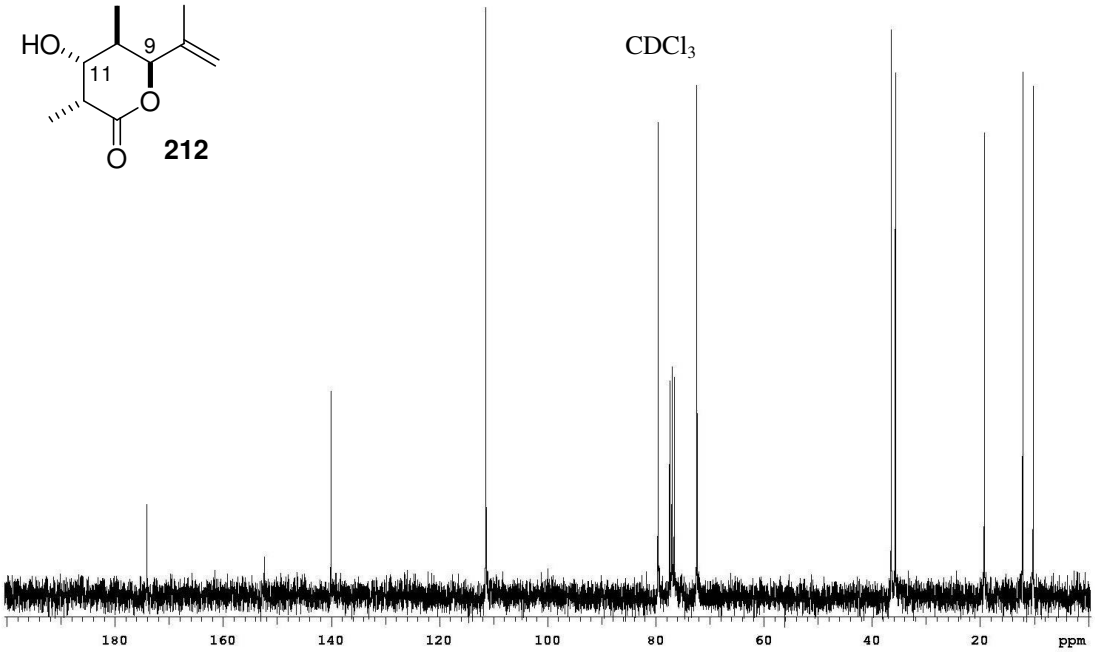
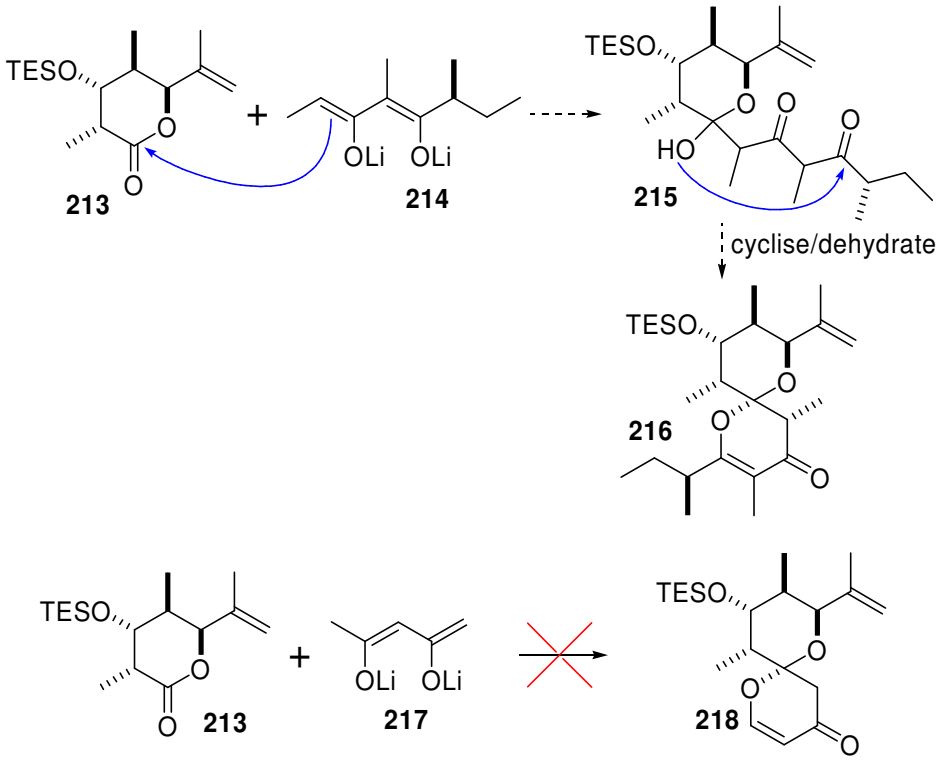


Figure 4.5: *75.5 MHz ^{13}C NMR spectrum of lactone* ***212*** *in $CDCl_3$*

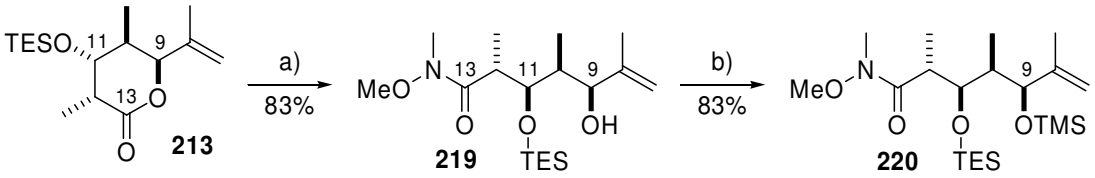
Having successfully differentiated the diol system, attention was turned to replacement of the temporary lactone protecting group with a more formal group. However, it was anticipated that this manipulation could be avoided if instead the lactone was reacted with the dienolate **214** of the required C14-C20 dione to give spiroacetal **216** *via* hemiacetal **215** (Scheme 4.10). If successful, this transformation would potentially afford the spiroacetal dihydropyrone core in **216** in a single operation. To test this theory, lactone **213** was first reacted with the lithium dianion **217** of pentan-2,4-dione (which would act as a model for the true dione) as depicted in Scheme 4.10. Unfortunately, under various conditions no reaction was observed, most likely due to a combination of steric hindrance and the poor electrophilic character of the lactone carbonyl.



Scheme 4.10: *Attempted addition of dienolate **217** to lactone **213**.*

In light of this, the β-lactone had to be opened both to liberate the C9 alcohol and provide access to a more reactive electrophile. Ultimately, this had to be achieved in such a manner as to completely prohibit re-cyclisation. A convenient solution was found by treating lactone **213** with *N*,*O*-hydroxylamine hydrochloride and ^{i}PrMgCl under modified[26,27] Weinreb conditions[28] to generate stable amide **219** in good yield

as shown in Scheme 4.11. The addition of the Weinreb amine to ester carbonyls involves an intermediate quaternary carbon centre, which in this case prohibits attack from the generated C9 alkoxide. Additionally, Weinreb amides are less reactive to nucleophilic attack than aldehydes, which rendered **219** more stable than the aldehyde equivalent. Subsequent protection (TMSCl, HMDS, rt, 1 h)[29] of the liberated alcohol afforded bis-silyl amide **220**. As such, the C9 and C11 alcohols had been successfully differentiated and importantly, the more labile group had been positioned at C9 to permit selective deprotection and controlled cyclisation (see Section 4.2).

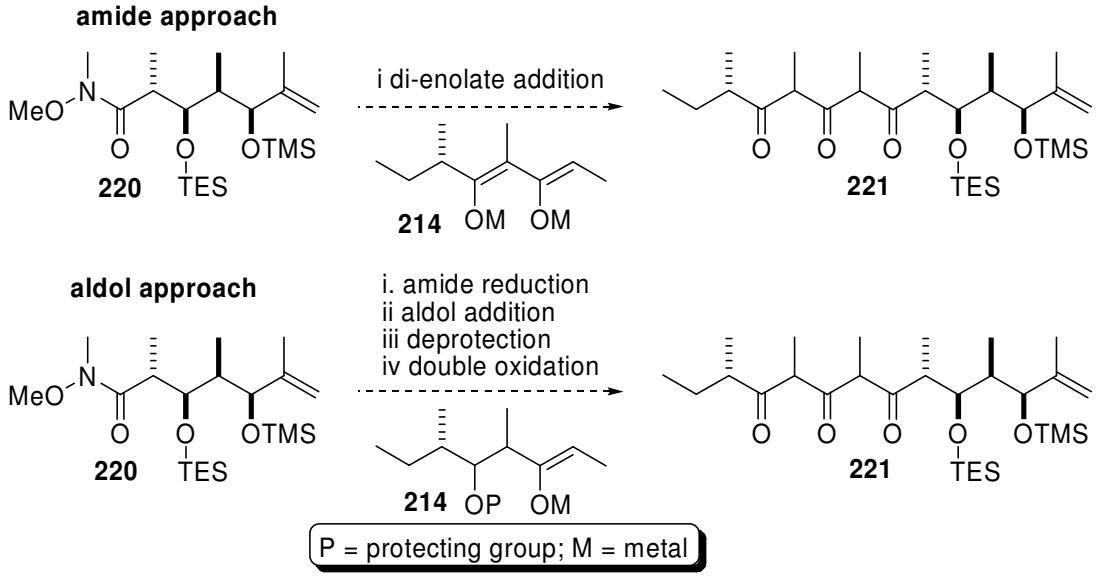


Reagents and conditions: a. MeN(OMe)H·HCl (2.5 eq), ^{i}PrMgCl (5.0 eq), THF, −20 °C, 30 min to 0 °C, 30 min; **b.** TMSCl, (3.0 eq), HMDS (3.0 eq), pyr, rt, 1 h.

Scheme 4.11: *Formation of Weinreb amide **220** from lactone **213**.*

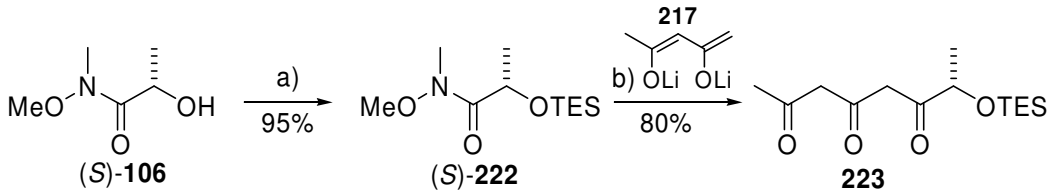
4.5.3 Addition of Enolates to Weinreb Amides

Weinreb amides are readily converted to the corresponding aldehydes or ketones under the influence of hydride sources or Grignard reagents, respectively.[28,30] However, the addition of enolates to give the corresponding β-polycarbonyl compounds is scarcely documented.[30-32] Scheme 4.12 shows that transforming amide **220** to β-triketide **221** (spiroacetal precursor) *via* a traditional aldol sequence would require four steps. This is a consequence of aldol additions proceeding relatively poorly with either β-dienolates or unprotected β-hydroxyenolates.[33,34] Therefore, additional steps to remove the protecting group and subsequently oxidise both the liberated alcohol and the alcohol generated in the addition reaction would be necessary. However, such problems are not encountered when β-dienolates are reacted with Weinreb amides and as such, it was anticipated that β-triketide **221** could be realised in a single step utilising this protocol.



Scheme 4.12: *Alternative routes to the synthesis of β-triketide* ***221****.*

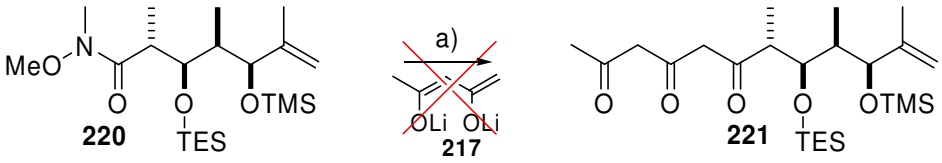
In light of the limited evidence available pertaining to the reaction of sterically demanding β-dienolates with Weinreb amides, the model study was extended to investigate the potential of such transformations. As depicted in Scheme 4.13, a simple system was first trialled to probe the reactivity of amides with lithium dienolates. To this end, amide (*S*)-**106** (Scheme 2.5, Chapter 2) was first protected at the free hydroxyl (TESOTf, 2,6-lutidine),[25] to give amide (*S*)-**222**, which was then reacted with the preformed lithium dianion **217** of pentan-2,4-dione.[35,36] Flash chromatography of the crude mixture afforded β-triketide **223** in good yield (80%), as a bright red oil, in a mixture of keto and enol forms.



Reagents and conditions: a. i. 2,6-lutidine (4.0 eq), −78 °C; ii. TESOTf, (3.0 eq), −78 °C, 30 min; **b.** i. pentan-2,4-dione (2.0 eq), NaH (2.0 eq), *n*-BuLi (2.0 eq), THF, −10 °C to 0 °C, 20 min; ii. amide **222**, −78 °C, 30 min.

Scheme 4.13: *Addition of the lithium dianion of pentan-2,4-dione to amide* ***222****.*

Given this success, efforts were made to couple **217** with amide **220** to give trione **221**, as shown in Scheme 4.14. Unfortunately, under various conditions (including stirring at room temperature) none of expected product **221** was observed, with only starting material being recovered. This suggested that the reactivity of Weinreb amides with enolates was strongly dependent on steric congestion and that amide **220** was too sterically demanding to participate in such a reaction to afford the desired β-triketide **221**.



Reagents and conditions: a. i. pentan-2,4-dione (2.0 eq), NaH (2.0 eq), *n*-BuLi (2.0 eq), THF, −10 °C to 0 °C, 20 min or LDA (4.3 eq), THF; ii. amide **220**.

Scheme 4.14: *Attempted reaction of dienolate **217** with amide* **220**.

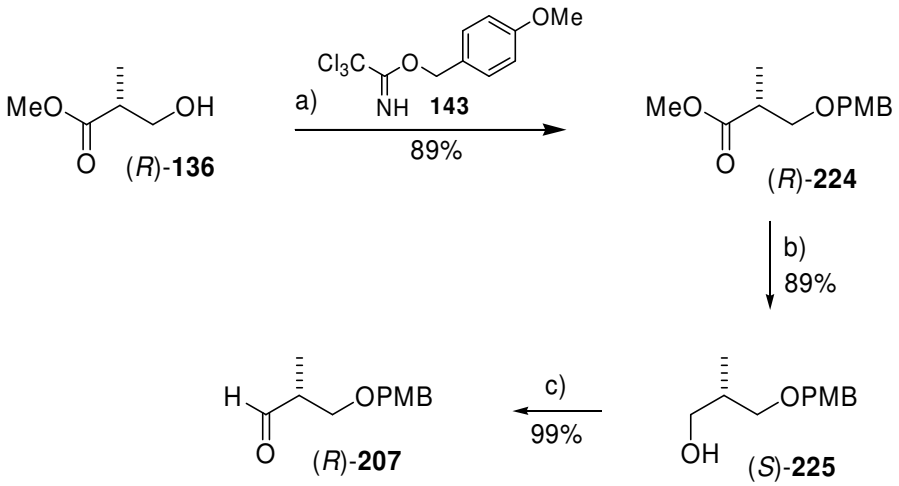
Despite this disappointment, it was anticipated that the aldol strategy shown in Scheme 4.12, used to homologate a Weinreb amide to a β-triketide *via* the intermediate aldehyde, would be successful. With a high level of confidence in an aldol approach, it seemed unwarranted to test this strategy in the context of a model system. Therefore, having achieved its goal of showing that intramolecular lactonisation would provide a means to differentiate the troublesome diol system, the model studies were terminated and exploration of the fully elaborated system was initiated.

4.6 Pursuing the Lactone Approach to Auripyrone A

4.6.1 The Synthesis of Diol 206

Access to the full stereopentad of auripyrone A would follow the protocol utilised in the model study (Scheme 4.8), employing known[17] α-methyl aldehyde (*R*)-**207** in place of methacrolein for the initial aldol coupling reaction. To this end, chiral aldehyde (*R*)-**207** was synthesised using the same procedure as described for

the synthesis of aldehyde (*R*)-**133** (Scheme 3.7, Chapter 3), using a *para*-methoxybenzyl protecting group in place of the benzyl group. Serendipitously, this slight variation in the protecting moiety proved crucial in latter endeavours (see Scheme 4.26). In practice, (2*R*)-3-hydroxy-2-methylpropionate [(*R*)-**136**] was protected as the known[17] *p*-methoxybenzyl ether (*R*)-**224** after reaction with PMB-acetimidate **143**[37] and catalytic triflic acid,[17] as depicted in Scheme 4.15. Subsequent reduction of the ester with lithium aluminium hydride ($LiAlH_4$), followed by Swern oxidation[38,39] of the primary alcohol (*S*)-**225**, afforded known aldehyde (*R*)-**207** in excellent overall yield (78% over three steps).

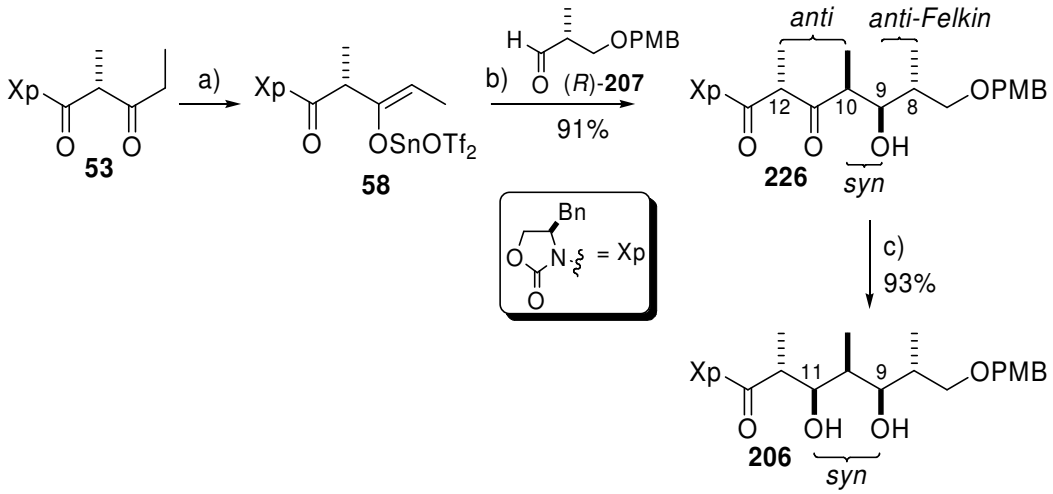


Reagents and conditions: a. imidate **52** (1.51 eq), TfOH (0.3 mol%), Et_2O, rt 2 h; **b.** $LiAlH_4$ (1.2 eq), THF, 0 °C to rt 30 min; **c.** i. DMSO (3.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (1.5 eq), −78 °C, 30 min; iii. alcohol (*S*)-**225**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (6.0 eq), −78 °C, 30 min to rt.

Scheme 4.15: *Acquisition of α-methyl aldehyde (R)-**207** from Roche ester (R)-**136**.*

Scheme 4.16 shows that the *Z*-(O)-enolate **58** of β-ketoimide **53** discussed in Section 4.5.1 was again formed under the action of $Sn(OTf)_2$ and Et_3N.[18] Addition of a slight excess (1.5 eq) of freshly prepared chiral aldehyde (*R*)-**207** afforded the 8,9-*anti*-Felkin-9,10-*syn*-10,12-*anti*-aldol adduct **226** as a clear oil after purification, in excellent yield (91%) on a 6-gram scale. NMR spectral analysis of the crude reaction mixture identified **226** as a single stereoisomer. As before (Section 4.5.1), the

powerful diastereofacial preference exhibited by the enolate resulted in excellent levels of stereocontrol. In this particular case, the reaction selectivity was likely enhanced by a reinforcing π-facial preference of the aldehyde for the *anti*-Felkin product. The requisite stereopentad of auripyrone A was subsequently completed upon reduction of β-hydroxyketone **226** with an excess of DIBAL-H,[18] giving 9,11-*syn* diol **206** as the major stereoisomer (>95% ds).



Reagents and conditions: a. i. $Sn(OTf)_2$ (1.3 eq), CH_2Cl_2, 0 °C; ii. Et_3N (1.3 eq), 10 min; iii. imide **53**, CH_2Cl_2, −20 °C, 1 h; **b.** aldehyde (*R*)-**207**, (1.5 eq) CH_2Cl_2, −78 °C, 30 min; **c.** DIBAL-H (4.0 eq), Et_2O, −78 °C, 1 h.

Scheme 4.16: *Synthesis of syn-diol **206** from imide **53** and construction of the stereopentad in auripyrone A.*

The ^{1}H NMR spectrum of aldol adduct **226** (Figure 4.6) displayed the expected resonances as single peaks, indicating a high level of isomeric purity. Notably, the hydroxymethine proton appears as a doublet of doublets at δ 3.90 (*J* = 8.7, 3.0 Hz) and shows coupling to both methyl methine protons at δ 2.91 (qd, *J* = 7.2, 3.0 Hz) and δ 1.95-1.83. The PMB oxymethylene protons appear as a 2H doublet at δ 3.54 (*J* = 5.4 Hz) and show coupling to the methine proton at δ 1.95-1.83. The quartet at δ 4.94 (*J* = 7.2 Hz) is consistent with the methine situated between the β-dicarbonyl and shows coupling to the methyl doublet at δ 1.47 (*J* = 7.2 Hz). The other methyls appear as doublets at δ 1.18 (*J* = 7.2 Hz) and δ 0.90 (*J* = 6.9 Hz) and show coupling to the expected methines. The remaining peaks are attributed to the oxazolidinone

auxiliary and PMB protecting group. Absorptions in the infrared spectrum at 3479, 1778, 1713 and 1692 cm^{-1} were indicative of the hydroxyl, auxiliary carbonyl and two ketone carbonyl groups, respectively and high resolution mass spectrometry confirmed the expected molecular formula of $C_{28}H_{35}NO_7$.

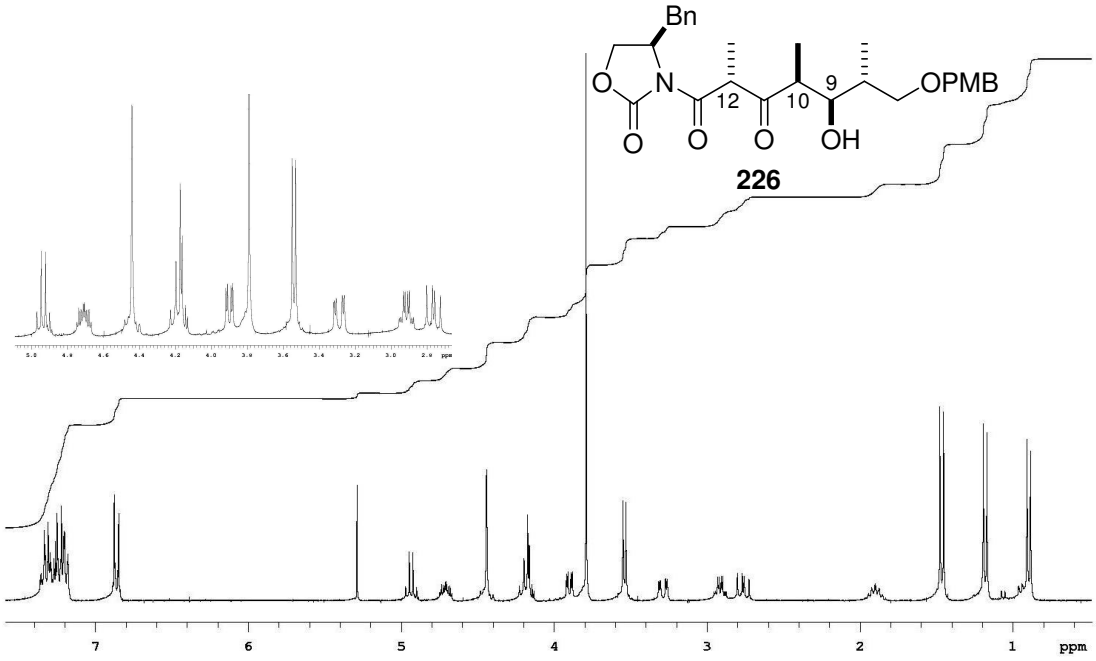
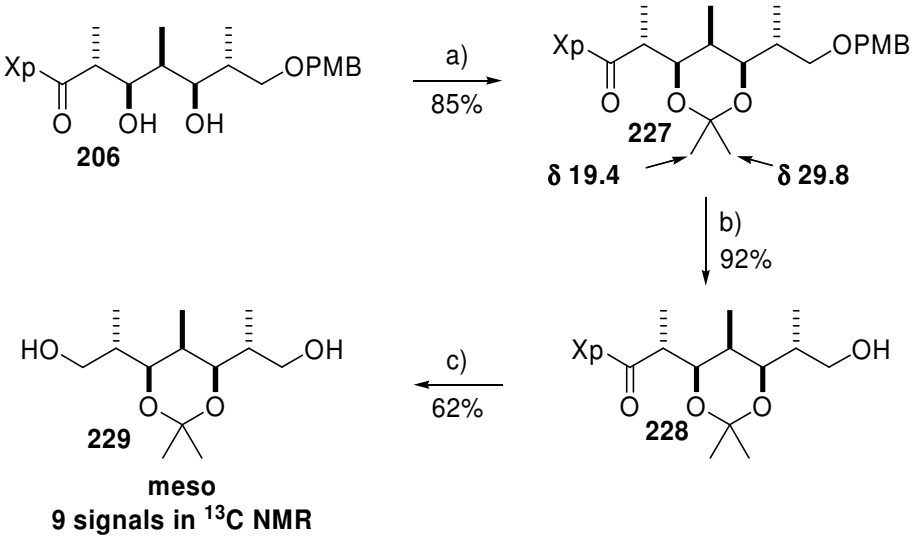


Figure 4.6: *300 MHz ^1H NMR spectrum of aldol adduct* ***226*** *in $CDCl_3$*

4.6.2 Confirmation of Relative Stereochemistry of Diol 206

Despite strong literature precedence[18] suggesting that the selectivity of both the aldol addition and DIBAL-H reduction were assured, it seemed prudent to confirm the stereochemical integrity of diol **206**. This was accomplished in a convenient three step sequence as delineated in Scheme 4.17. Initially, diol **206** was reacted with dimethoxypropane in the presence of catalytic PPTS[40] at room temperature for 3 hours to afford the 1,3-diol acetonide **227** in good yield. In 1990, Rychnovsky[41] suggested that *syn*- and *anti*-1,3-diol acetonides could be readily differentiated by analysis of the ^{13}C NMR spectral shifts for the acetonide methyl signals. As he noted, acetonides derived from *syn*-1,3-diols adopt a chair conformation, thus positioning one alkyl substituent in an equatorial position and the other in an axial position (Figure 4.7).[41] Alternatively, *anti*-1,3-diol acetonides will exist in a twist conformation in order to avoid *syn*-pentane interactions that would prevail in the chair conformation.[41] As such, the ^{13}C NMR spectra for *syn*-1,3-diol

acetonides display an axial methyl group at ~δ 19 and an equatorial methyl group at ~δ 30. In contrast, the ^{13}C NMR spectra for *anti*-1,3-diol acetonides show two methyl groups at ~δ 25.[41-43] Pleasingly, 1,3-diol acetonide **227** displayed signals for the acetonide methyl groups in the ^{13}C NMR spectra at δ 29.8 and δ 19.4, thus confirming the *syn*-diol relationship.



Reagents and conditions: a. $(MeO)_2C(CH_3)_2$, PPTS (cat.), CH_2Cl_2, rt, 3 h; **b.** DDQ (1.5 eq), pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 3 h; **c.** $LiBH_4$ (2.4 equiv), EtOH (2.4 equiv), Et_2O, −10 °C, 1.5 h.

Scheme 4.17: *Synthesis of meso diol* ***229*** *from diol* ***206*** *to confirm the relative stereochemistry of the stereopentad.*

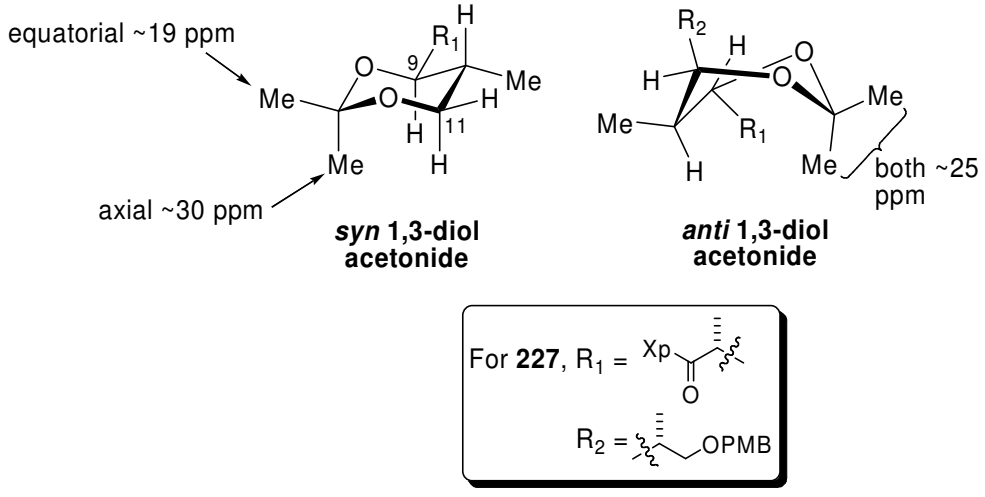


Figure 4.7: *Distinguishing ^{13}C NMR signals for syn- and anti-1,3-diol acetonides.*

With the relative stereochemistry of the two hydroxyl groups secure, the *p*-methoxybenzyl ether was cleaved under the action of DDQ[44] in pH 7 buffered aqueous CH_2Cl_2[45] to afford primary alcohol **228** in good yield (92%). Finally, reductive cleavage of the chiral auxiliary ($LiBH_4$, Et_2O, −10 °C)[46] gave diol **229**.

As displayed in Figure 4.8, the ^{1}H NMR spectrum for bis-alcohol **229** shows just 9 signals. In particular, the 2H oxymethine doublet of doublets at δ 3.74 (*J* = 9.9, 2.1Hz) shows coupling to both the 2H methyl methine multiplet at δ 2.00-1.86 and the 1H methyl methine multiplet at δ 1.59-1.51. The signal at δ 1.59-1.51 in turn shows coupling to the 3H methyl doublet at δ 0.91 (*J* = 6.9 Hz), whilst the multiplet at δ 2.00-1.86 couples to the 6H methyl doublet at δ 0.78 (*J* = 7.2 Hz) and both 2H methylene doublet of doublets at δ 3.61 (*J* = 10.8, 7.5 Hz) and δ 3.55 (*J* = 10.8, 3.6 Hz). The remaining broad 2H singlet at δ 2.88 and the 3H singlets at δ 1.49 and δ 1.40 are consistent with the hydroxyl and acetonide methyl groups, respectively.

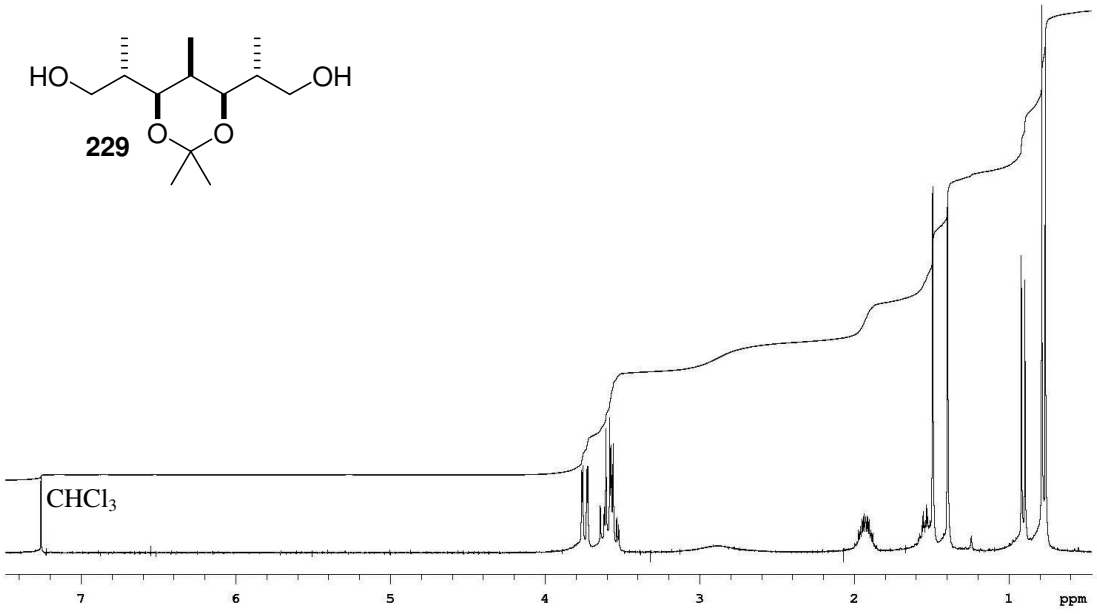


Figure 4.8: *300 MHz ^{1}H NMR spectrum of meso diol **229** in $CDCl_3$*

The ^{13}C NMR spectrum (Figure 4.9) shows only 9 signals of which the quaternary acetal signal at δ 99.0 is most pertinent. Note also the relative intensity of the methyl signal at δ 12.0 and the methine signal at δ 36.3 compared to the other methyl and methine signals at δ 31.0, δ 29.9, δ 19.8 and δ 4.7. This double intensity is indicative

of a meso compound, where the signals at δ 36.3 and δ 12.0 account for two equivalent carbon centres. A solution of the compound in $CHCl_3$ gave no optical rotation and high resolution mass spectrometry confirmed a molecular composition of $C_{13}H_{26}O_4$. Thus, the assorted data supports the isolation of a meso compound, which was expected if the relative stereochemistry of the stereopentad was as depicted for diol **206**.

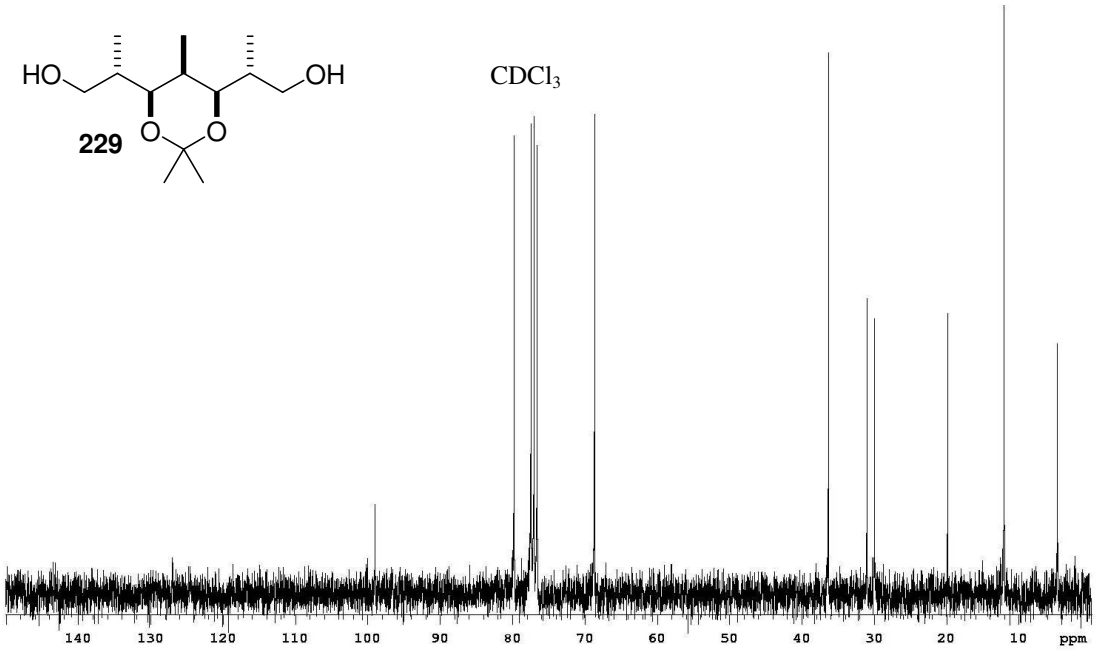
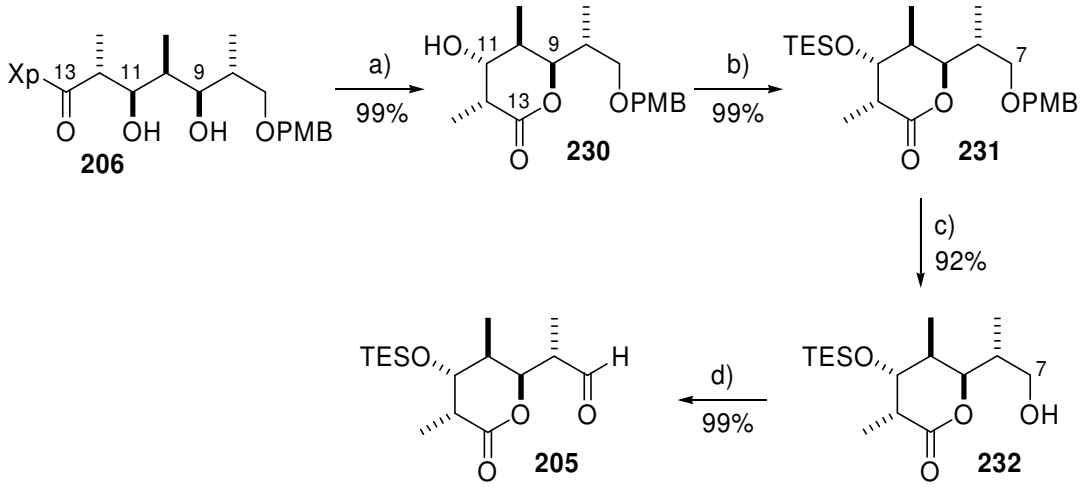


Figure 4.9: *75.5 MHz ^{13}C NMR spectrum of meso diol **229** in $CDCl_3$*

4.6.3 Synthesis of β-Triketide 203

In accordance with the model study, Scheme 4.18 shows that diol **206** was smoothly converted to β-lactone **230** after stirring in a slurry of silica gel (CH_2Cl_2) overnight. Standard silylation with TESOTf and 2,6-lutidine[25] dutifully protected the free secondary alcohol and subsequent exposure of silane **231** to DDQ[44,45] liberated alcohol **232** after *p*-methoxybenzyl ether cleavage. Finally, reaction of alcohol **232** with Dess-Martin periodinane[47,48] furnished lactone aldehyde **205** in excellent overall yield (89% over four steps).



Reagents and conditions: a. SiO_2, CH_2Cl_2, rt, o/n; **b.** i. 2,6-lutidine (4.0 eq), CH_2Cl_2, −78 °C; ii. TESOTf, (3.0 eq), −78 °C, 30 min; **c.** DDQ (1.5 eq), pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 3 h; **d.** DMP (1.5 eq), CH_2Cl_2, rt, 1 h.

Scheme 4.18: *Synthesis of lactone aldehyde* ***205*** *from diol* ***206****.*

Analysis of the ^{1}H NMR spectrum of primary alcohol **232** (Figure 4.10) revealed the oxymethylene protons to be diastereotopic and resonate as doublet of doublets at δ 3.79 (*J* = 11.1, 5.1 Hz) and δ 3.70 (*J* = 11.1, 4.2 Hz). In addition to reciprocal coupling, these signals shows coupling to the 2H multiplet at δ 2.04-1.92 which in turn couples to the methyl doublets at δ 0.97 (*J* = 7.2 Hz) and δ 0.88 (*J* = 7.2 Hz). The multiplet at δ 2.04-1.92 shows further coupling to the ester oxymethine doublet of doublets at δ 4.61 (*J* = 10.8, 2.7 Hz) and the oxymethine apparent triplet at δ 3.87 (*J* = 3.6 Hz), and thus comprises the C8 and C10 methyl methine protons. The methyl and methylene protons of the TES protecting group resonate as a 9H triplet at δ 0.95 (*J* = =7.8 Hz) and a 6H quartet at δ 0.60 (*J* = 7.8 Hz), respectively.

The ^{13}C NMR spectrum (Figure 4.11) shows the expected ester resonance at δ 173.4 and the three oxymethine signals at δ 81.1, δ 73.8 and δ 66.0. Also evident are the large TES methyl and methylene resonances at δ 6.8 ad δ 4.8.

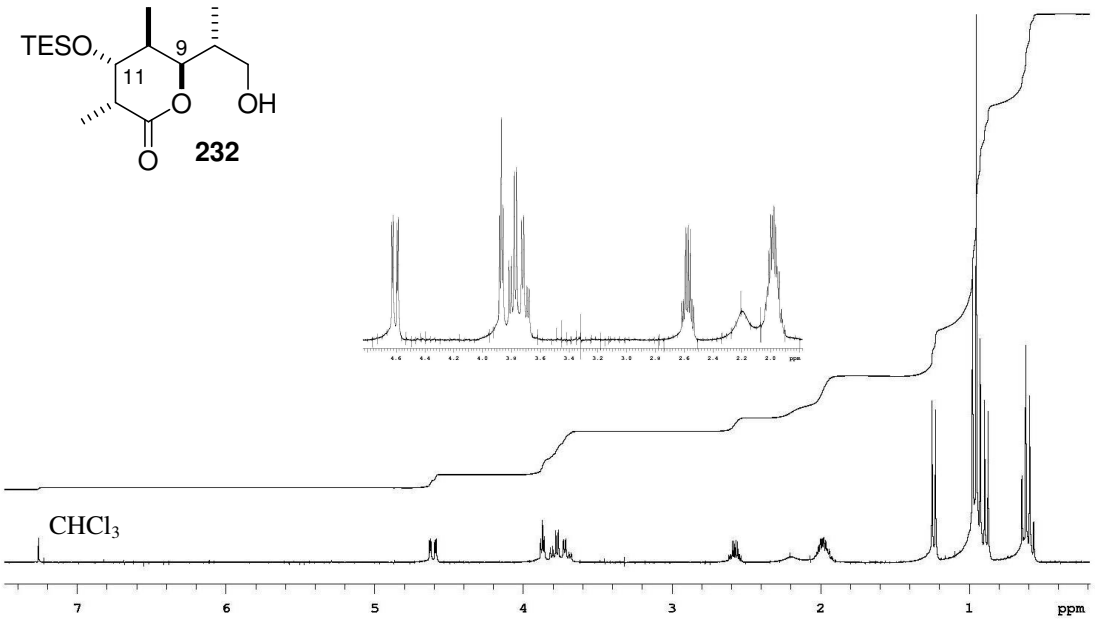


Figure 4.10: *300 MHz ^{1}H NMR spectrum of lactone alcohol* ***232*** *in $CDCl_3$*

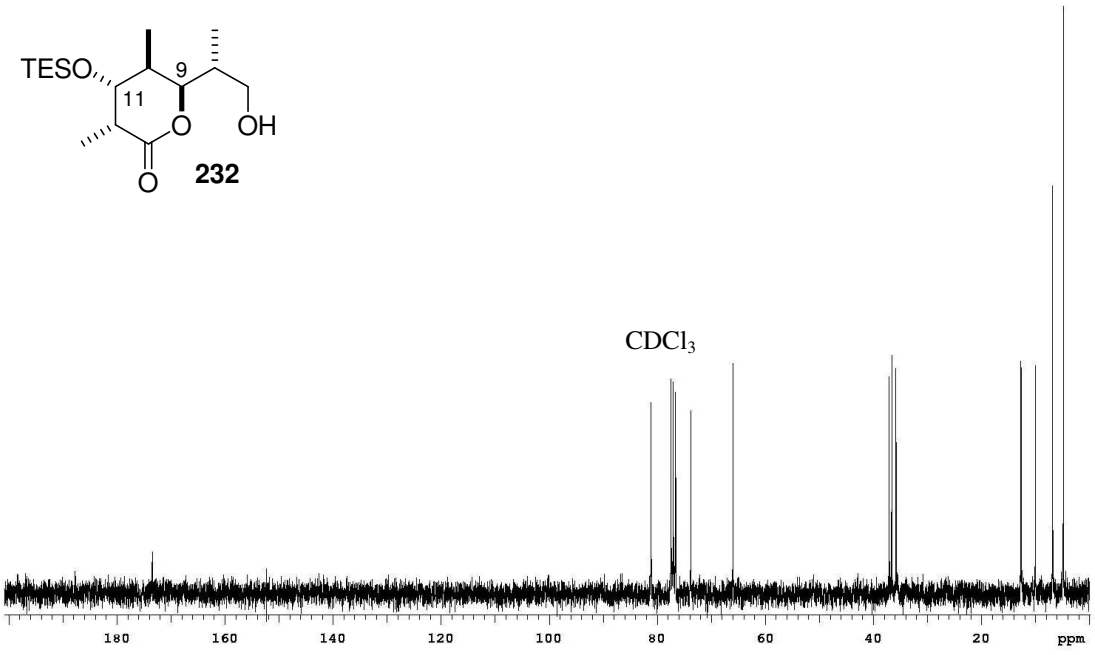


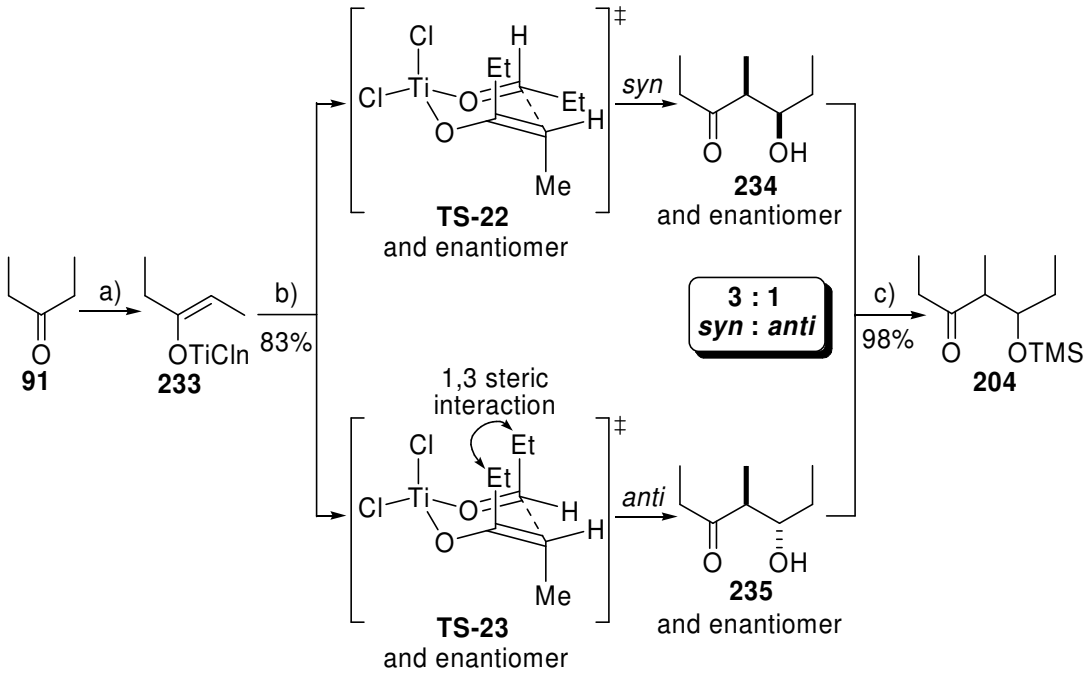
Figure 4.11: *75.5 MHz ^{13}C NMR spectrum of lactone alcohol* ***232*** *in $CDCl_3$*

An aldol addition to aldehyde **205** was foreseen to initiate construction of the desired β-tricarbonyl moiety in **203** (Section 4.4.1). Typically, β-tricarbonyl systems are uncontrollably enolisable and as such exist as mixed keto and enol isomers.[49] Hence, any stereochemical integrity in the precursors to such systems would be completely

lost upon oxidation. As such, pursuing a stereoselective synthesis of the precursor's to the β-triketone moiety in **203** was considered unnecessary and thus, a non-diastereoselective approach to β-silyoxyketone **204** was employed as delineated in Scheme 4.19.

Pentan-3-one (**91**) was treated with titanium tetrachloride ($TiCl_4$) at −78 °C for 30 minutes, followed by the addition of *N*,*N*-diisopropylethylamine (DIPEA) to forge the characteristic deep red coloured *Z*-(O)-titanium(IV) enolate **233** (Scheme 4.19).[18,50,51] Pre-complexation of the ketone with the Lewis acid was essential as $TiCl_4$ and DIPEA can complex irreversibly, minimising the extent of enolisation. After 1 hour at −78 °C, enolate **233** was reacted with freshly distilled propanal which, after product isolation and purification by flash chromatography, afforded a 3:1 ratio of inseparable *syn*- and *anti*-β-hydroxyketones **234** and **235** (and their respective enantiomers) in 83% yield. Interestingly, the *syn* vs. *anti* isomeric ratio was lower than might be expected. Generally, *Z*-(O)-enolates give exclusively *syn*-aldol products (**234**), as the chair transition state (**TS-22**, Scheme 4.19) leading to *anti*-adducts (**235**) is less favoured due to destabilising 1,3-steric interactions (see Section 1.5.2 for discussion). However, in cases where the steric demand of both the ketone and aldehyde is very low, the transition state leading to *anti*-adducts can adopt a twisted conformation, which relieves 1,3-interactions and increases the proportion of the *anti*-isomer in the product ratio. This would account for the *syn*:*anti* ratio observed in the synthesis of **234** and **235**, as propanal displays very little steric demand. One may suspect that the poor *syn*:*anti* ratio is more likely due to propanal reacting with a mixture of *cis*- and *trans*-enolates of pentan-3-one (**91**), which could result from a non-selective enolisation strategy. However, it has been shown that the enolate of pentan-3-one (**91**), produced in an identical manner to that discussed above, reacts with larger aldehydes (for instance isobutyraldehyde) to give the corresponding *syn*-adducts almost exclusively[51] (a further example of this point is delineated in Section 4.8.2, Scheme 4.29). These results confirm that under these specific enolisation conditions, the *Z*-(O)-enolate forms exclusively.[18,50,51] Fortunately, selectivity was of little consequence (for reasons previously discussed) and adducts **234** and **235** were subsequently protected with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine[52] to give β-ketosiloxane **204** in

good yield (98%, Scheme 4.19). Given the relatively easy enol silylation of such simple ethyl ketones (see discussion for β-hydroxyketone **98**, Scheme 2.7, Chapter 2), the mixed aldol adducts **234** and **235** were reacted with a reduced amount of TMSOTf and lutidine and at lower temperatures (−90 °C) than standard silyl protections to avoid this potential problem.[52]



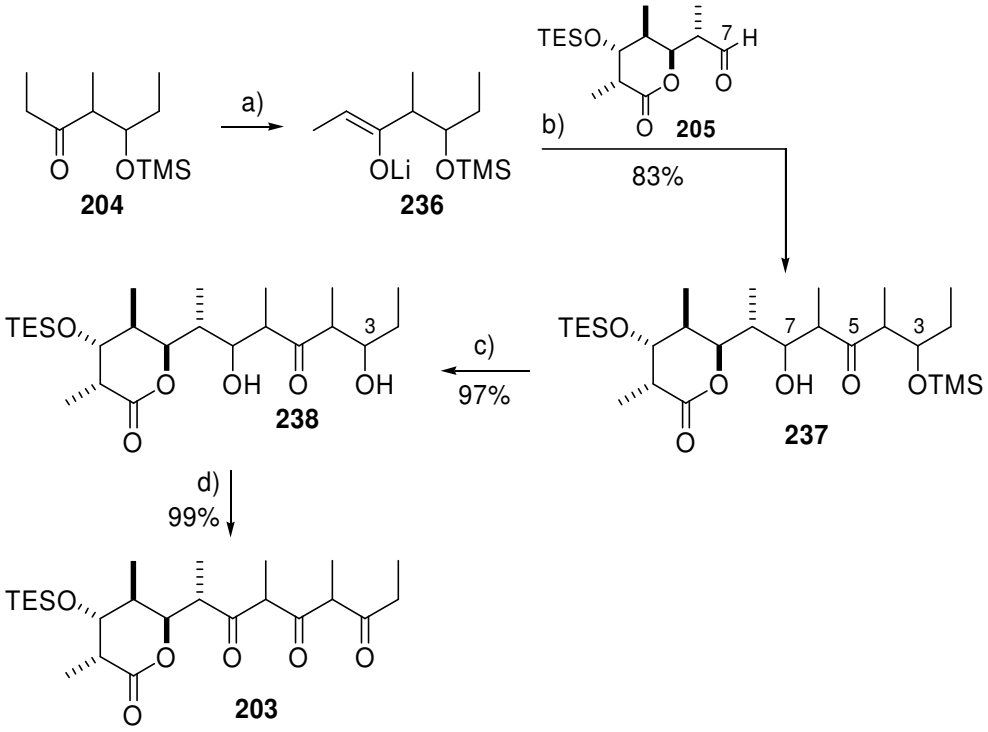
Reagents and conditions: a. i. $TiCl_4$ (1.2 eq), CH_2Cl_2, −78 °C, 30 min; ii. DIPEA (1.4 eq), −78 °C, 1 h; **b.** propanal (2.0 eq), −90 °C to −78°C, 1 h; **c.** i. 2,6-lutidine (2.0 eq), CH_2Cl_2, −90 °C; ii. TMSOTf, (1.5 eq), −90 °C, 10 min;

Scheme 4.19: *Synthesis of β-silyloxyketone* ***204*** *from pentan-3-one (****91****).*

With ketone **204** in hand, elaboration of aldehyde **205** into tricarbonyl **203** was completed as depicted in Scheme 4.20. Towards this end, ethyl ketone **204** was treated with LiHMDS[53-55] to generate the *Z*-(O)-lithium enolate **236** under the same conditions discussed previously (Section 3.4.4, Scheme 3.16). Subsequent addition of a solution of freshly prepared aldehyde **205** in THF to the enolate, followed by stirring at −78 °C for 2 hours, afforded aldol adduct **237** as a complex mixture of inseparable stereoisomers in good yield (83%). The decision to employ LiHMDS was based primarily on the reagent's compatibility with ketone **204**. The use of a

$TiCl_4$ for instance, in a Lewis acid/amine base aldol protocol would almost certainly have caused cleavage of the labile trimethylsilyl ether resulting in poor levels of enolisation and aldol reaction (see Section 3.4.4 for related discussion). Additionally, LiHMDS aldol reactions are experimentally much simpler than mixed reagent aldol procedures, so despite often lower levels of selectivity[20] (inconsequential in this particular case), it makes this protocol a convenient alternative.

Chemoselective desilylation of the TMS ether was achieved by treatment of the mixed isomers of aldol adduct **237** with PPTS in 1:9 MeOH/THF at room temperature for 45 minutes, which gave diol **238** in excellent yield (94%). Finally, oxidation of diol **238** using Schreiber's accelerated Dess-Martin protocol,[47,48,56] smoothly afforded β-triketone **203** as a mixture of keto and enol forms in near quantitative yield.

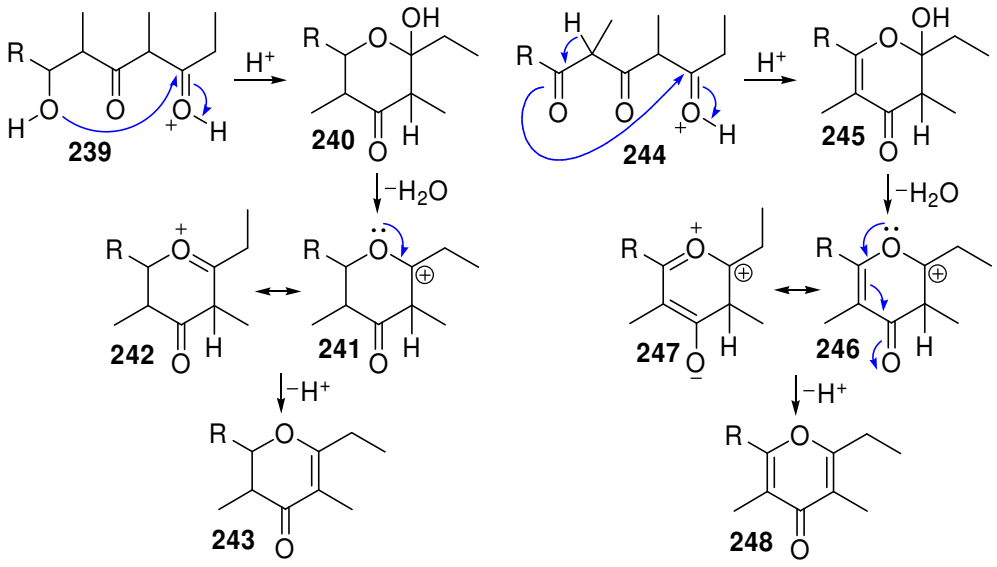


Reagents and conditions: a. LiHMDS (2.2 eq), THF −78 °C, 30 min to −50 °C 30 min; **b.** aldehyde **205** (0.5 eq), THF, −78 °C, 2 h; **c.** PPTS (cat.), MeOH/THF (1:9), rt, 45 min; **d.** i. DMP (3.0 eq), CH_2Cl_2, rt; ii. H_2O (2.0 eq), CH_2Cl_2, rt, 1 h.

Scheme 4.20: *Synthesis of β-triketone **203**.*

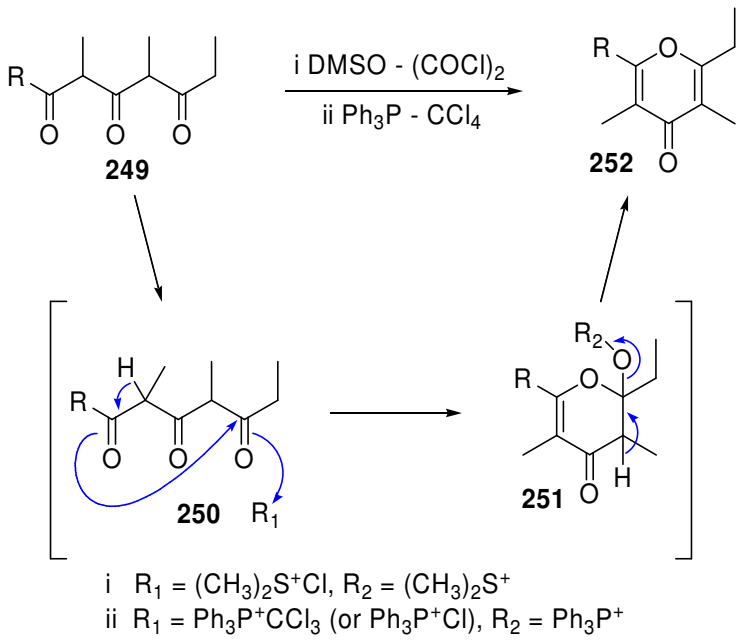
4.6.4 The Synthesis of γ-Pyrones from β-Triketides

From the earliest accounts, the formation of γ-pyrones from β-triketides had relied almost exclusively on the use of strongly acidic (HCl or H_2SO_4) conditions, often resulting in low yields and unpredictable product distributions.[57-60] In general, the acid catalysed formation of γ-pyrones from corresponding β-triketides is hard to achieve. This is in stark contrast to dihydropyrone synthesis, which occurs readily from β-hydroxy-β-dicarbonyl compounds. Rationale for this difference in reactivity, despite the similarity of the mechanism, is depicted in Scheme 4.21. Under acidic conditions compound **239** rapidly cyclises to generate hemiacetal **240**, whose subsequent dehydration leads to cationic tetrahydropyran **241**. This intermediate is stabilised by interaction of the lone pair on oxygen, leading to resonance contributor **242**. In a similar sequence, enol **244** cyclises to give α,β-unsaturated hemiacetal **245**, whose subsequent dehydration leads to intermediate resonance structures **246** and **247**. The initial cyclisation reaction leading to compound **245** is slow compared to the formation of hemiacetal **240**, due to the poor nucleophilic character and transient nature of the enol moiety compared to the alcohol group in **239**. Additionally, the lone pair on oxygen in compound **246** is less available to stabilise the positive charge due to a π-interaction with the enone system. This causes the energy barrier for dehydration leading to γ-pyrone **248** to be significantly greater than the corresponding barrier to dihydropyrone synthesis.



Scheme 4.21: *Comparison of γ-pyrone and dihydropyrone synthesis.*

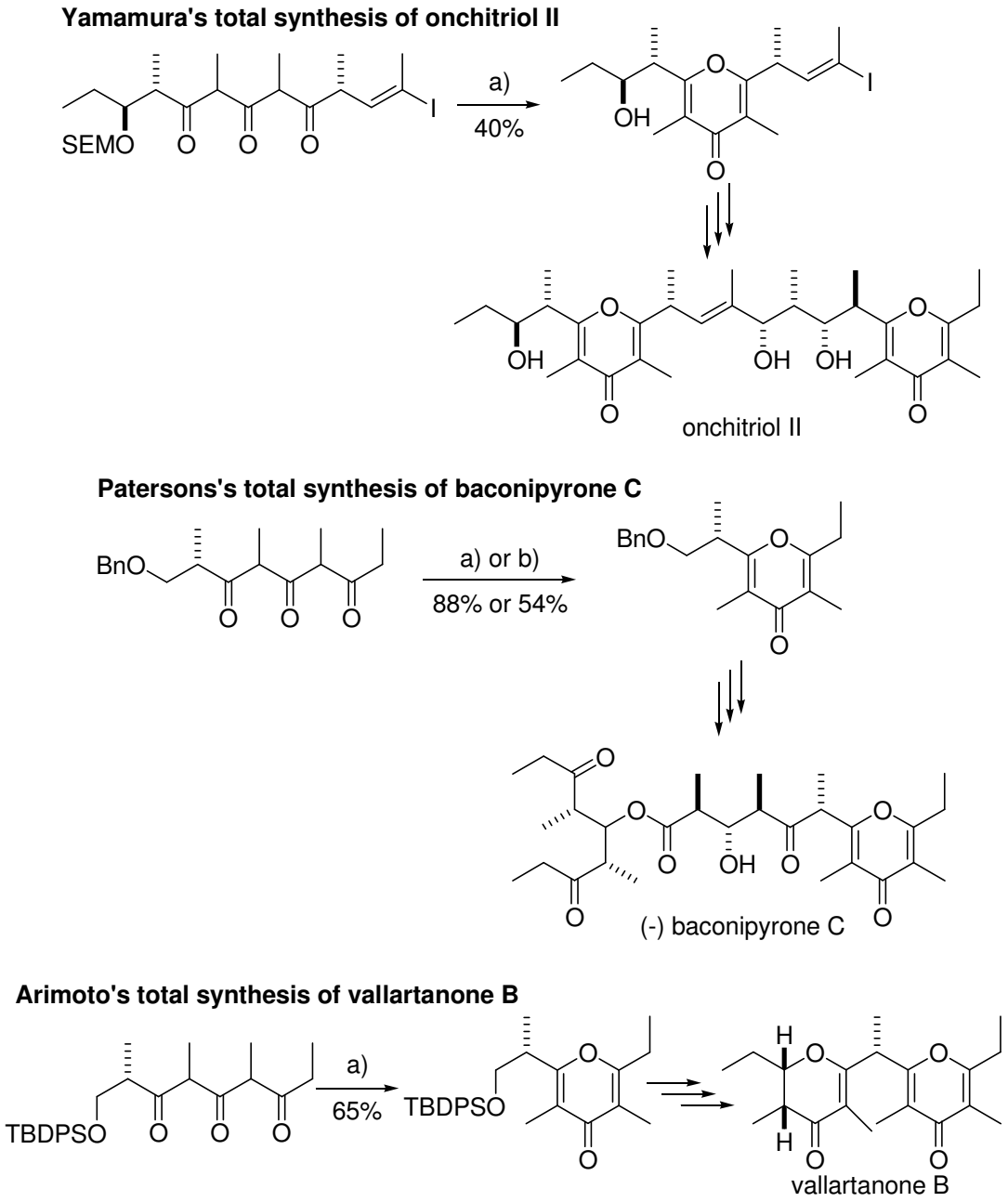
Realising the limitations of the current methods for γ-pyrone synthesis and in conjunction with his desires to formulate a γ-pyrone to complete a total synthesis of ilikonapyrone, Yamamura *et al.* devised a novel set of mild conditions to affect this transformation from substituted β-triketides.[61] Scheme 4.22 shows that application of the active species in Swern oxidations [$(CH_3S^+Cl]$ (method i) or phosphonium salts [$Ph_3P^+CCl_3(Ph_3P^+Cl)$ or $Ph_3P^+CBr_3(Ph_3P^+Br)$] (method ii) to polycarbonyls of type **249**, results in cyclisation to give the corresponding γ-pyrone **252**.[61] This process takes advantage of the readily enolisable nature of β-triketides, where by nucleophilic attack of the enol oxygen in **250** upon the carbonyl group five carbon atoms down the chain, and subsequent reaction of the generated alkoxide with the active reagent, gives an intermediate dihydropyrone **251**. Oxygen is then lost from **251** in the form of the phosphine oxide (method i) or sulfoxide (method ii) to furnish the γ-pyrone **252**.[61]



Scheme 4.22: *Yamamura's protocols for the synthesis of γ-pyrone* ***252*** *from β-triketone* ***249****.*

These new methods rendered synthesising highly substituted γ-pyrone rings from sensitive β-triketides (in good yield) possible and provided access to the ever growing number of γ-pyrone containing natural products.[62] Subsequently, application

of these methods by Yamamura,[63,64] Paterson[65,66] and Arimoto[67] in their total synthesis endeavours (Scheme 4.23) has validated the technology, although on relatively simple systems.

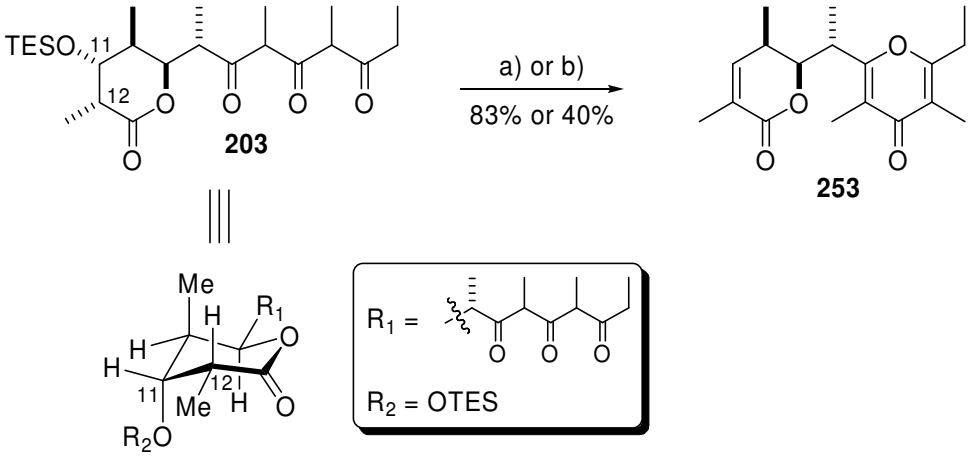


Reagents and conditions: a. Ph_3P, CCl_4, THF, rt, 3-5 days; **b.** DMSO, $(COCl)_2$, CH_2Cl_2, −20 °C, 2 h.

Scheme 4.23: *Yamamura's γ-pyrone protocol in natural product synthesis.*

4.6.5 Investigating the Synthesis of γ-Pyrone 202

As depicted in Scheme 4.24, β-triketide **203** was reacted with a mixture of Ph_3P/CCl_4 at room temperature for 3 days.[61] Continued monitoring by tlc indicated the gradual formation of a highly polar, UV active compound (consistent with a γ-pyrone) along with significant amounts of triphenylphosphine oxide (the expected by-product). Unfortunately, upon isolation and subsequent analysis of the reaction product by ^1H and ^{13}C NMR it was deduced that, despite excellent conversion of the triketone moiety to the corresponding γ-pyrone, the oxygen substituent at C11 had been lost to give enone **253**. Similar results were obtained when employing the Swern reagents ($DMSO/(COCl)_2$).[61] Clearly the reagent combinations were outstanding at promoting γ-pyrone formation but were not mild enough to prevent elimination of the triethylsilyl ether. It is likely that *in situ* generated HCl[61] initiates the elimination reaction which is favoured due to an *anti*–periplanar relationship that exists between the C12-hydrogen and C11-oxygen substituents (see Scheme 4.24) and the stabilising π-conjugation that develops with the lactone carbonyl.



Reagents and conditions: a. Ph_3P (5.0 eq), CCl_4 (5.0 eq), THF, rt, 3 days; **b.** DMSO (2.0 eq), $(COCl)_2$ (2.0 eq), CH_2Cl_2, −20 °C, 2 h.

Scheme 4.24: *Attempted γ-pyrone cyclisation of β-triketide* ***203****.*

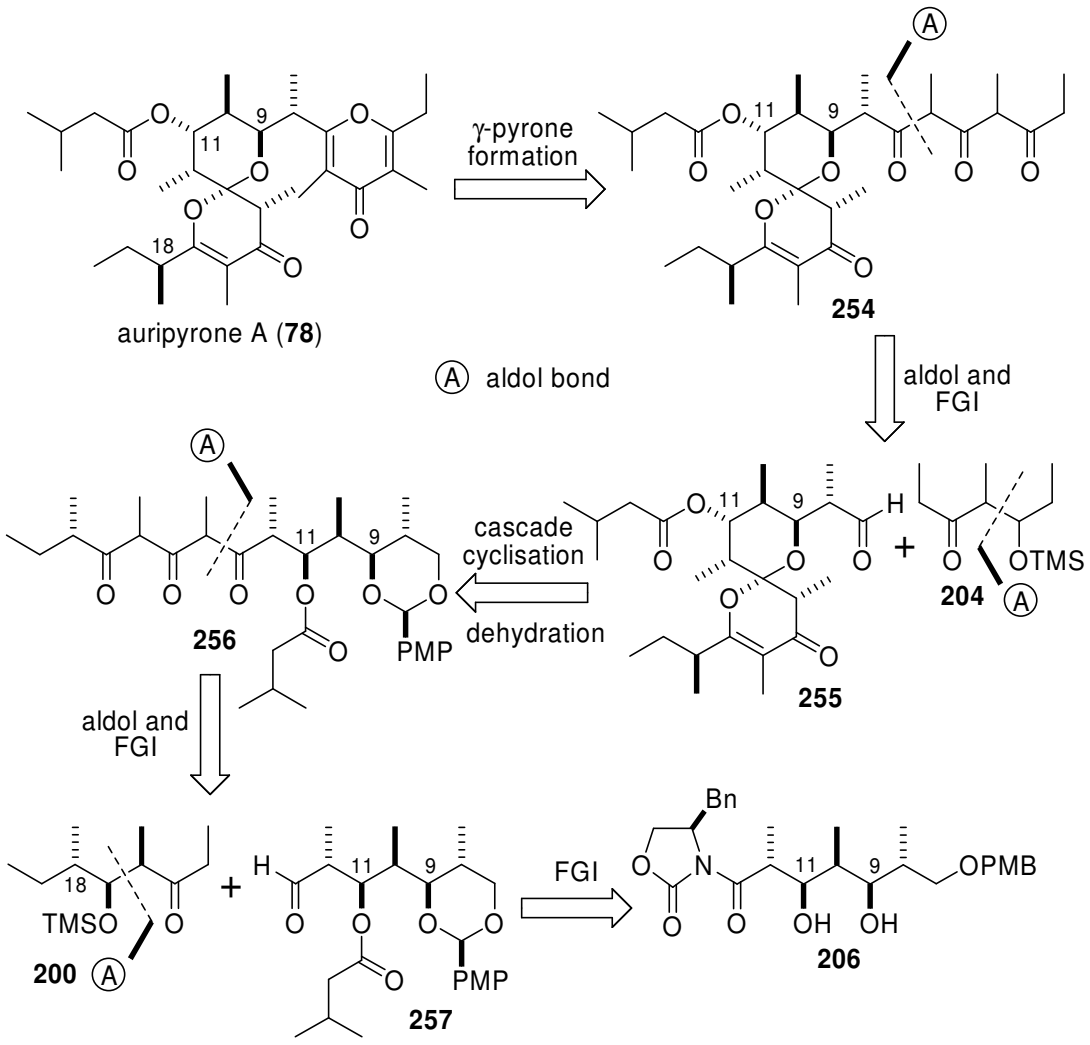
Despite not yielding the desired product, the success of the actual pyrone forming reaction was encouraging and it was anticipated that removal (masking) of the C13 carbonyl should overcome dehydration/elimination. However, it did not appear

practical to attempt this modification in the context of the lactone approach as it would require significant functional group manipulation. However, one strategy already discussed (Section 4.3) seemed to present an ideal solution. The alternative methodology presented for a synthesis of auripyrone A (Section 4.3) involved installing the spiroacetal dihydropyrone moiety before the γ-pyrone tether had been constructed. If indeed the spiroacetal core of auripyrone A could be developed and then extended to include the C1-C7 β-triketide, then γ-pyrone formation could be attempted on a substrate where C13 wielded a dioxaspiro group, not a carbonyl moiety. Whilst this potentially provided a solution to dehydration/elimination, this strategy was worrying. There was no way to confidently predict the stability of the spiroacetal to the conditions required for γ-pyrone formation and failure to affect this transformation at such a late stage would leave very little room to manoeuvre. However, if successful it would constitute the most complex example of γ-pyrone formation ever reported.

4.7 A Revised Approach to Auripyrone A

4.7.1 Retro-Synthetic Analysis

Scheme 4.25 displays the revised retro-synthetic analysis for auripyrone A (**78**). A significant amount of the methodology planned for the previous approach (Section 4.4) can be applied to this strategy. This particularly applies to the construction of the C1-C7 and C13-C20 β-triketide moieties and crucially, the development of the stereopentad surrogate, namely diol **206.** The key differences include: a) postponing pyrone formation to the final step, b) forging the spiroacetal dihydropyrone at an early stage through a cascade cyclisation/dehydration of β-triketide **256**, and c) the use of a *p*-methoxyphenyl acetal to differentially protect diol **206**. Noteworthy was the consistency of the use of the acyloxy group at C11 in a protecting role. It was anticipated that the ester group would replace a traditional protecting group and thus, differentiation of the diol could be completed with the natural products own functionality. Indeed, the proposed strategy does not require the introduction of a single protecting group within the linear sequence. The following sections will detail the successful implementation of this strategy to the synthesis of auripyrone A (**78**).



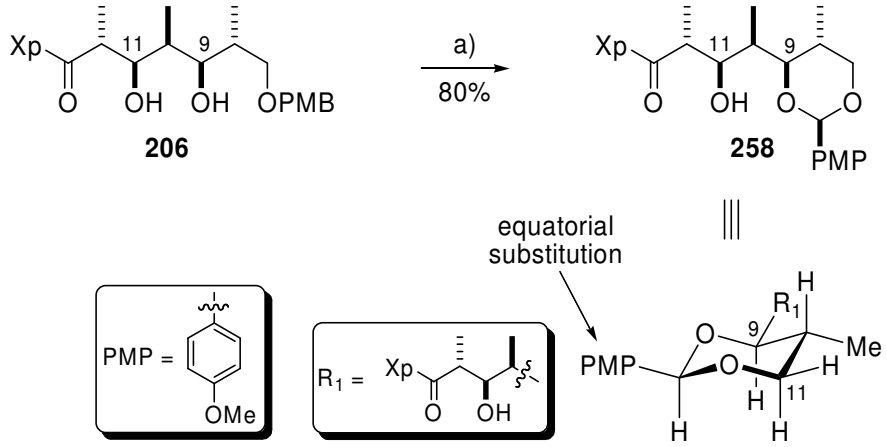
Scheme 4.25: *Revised retro-synthetic analysis of auripyrone A (**78**)*

4.8 Total Synthesis of Auripyrone A

4.8.1 Acquisition of Aldehyde 257

Starting from diol **206** (Scheme 4.16), migration of the *p*-methoxybenzyl group with DDQ[68] under anhydrous conditions,[69,70] conveniently and selectively protected the C9 alcohol as *p*-methoxybenzylidene acetal **258**, as depicted in Scheme 4.26. It was essential to use freshly baked (250 °C oven, 3 days), activated 4-angstrom molecular sieve powder in this radical migration, as even trace amounts of water resulted in cleavage of the PMB ether and correspondingly, substandard yields. Notably, acetal **258** was isolated as a single stereoisomer, presumably due to thermodynamic factors which favour adoption of the chair-like conformation with the *p*-methoxyphenyl substituent in the equatorial position. This has been confirmed

by Smith[39] and others,[70,71] with the aid of X-ray crystallography and nOe experiments on similar PMP acetal containing substrates.



Reagents and conditions: a. DDQ (1.2 eq), 4Å MS powder, CH_2Cl_2, 0 °C, 5 h.

Scheme 4.26: *Formation of p-methoxybenzilidene acetal* ***258****.*

The ^{1}H NMR spectrum of compound **258** (Figure 4.12) shows the characteristic features of a *p*-methoxybenzilidene acetal moiety, namely the acetal oxymethine singlet at δ 5.30, the oxymethyl singlet at δ 3.23 and the aromatic proton doublets at δ 7.45 (J = 8.7 Hz) and δ 6.69 (J = 8.7 Hz), which show reciprocal coupling. Noteworthy is the significant upfield shift of the C23 methyl group, which resonates at δ 0.27 (J = 6.6 Hz), which presumably results from solvent packing due π-interactions between the *p*-methoxybenzilidene moiety and the deuterated benzene solvent causing shielding of the methyl group. This seems likely, as the ^{1}H NMR spectrum of compound **258** recorded in $CDCl_3$ showed the C23 methyl resonanating at δ 0.80. Unfortunately, the acetal rapidly isomerised in $CDCl_3$, which meant that all subsequent NMR analysis of PMP-acetal containing compounds was performed in C_6D_6. The remaining signals are consistent with the oxazolidinone and carbon framework of the compound, and high resolution mass spectrometry indicated the expected loss of two hydrogen atoms from compound **206**.

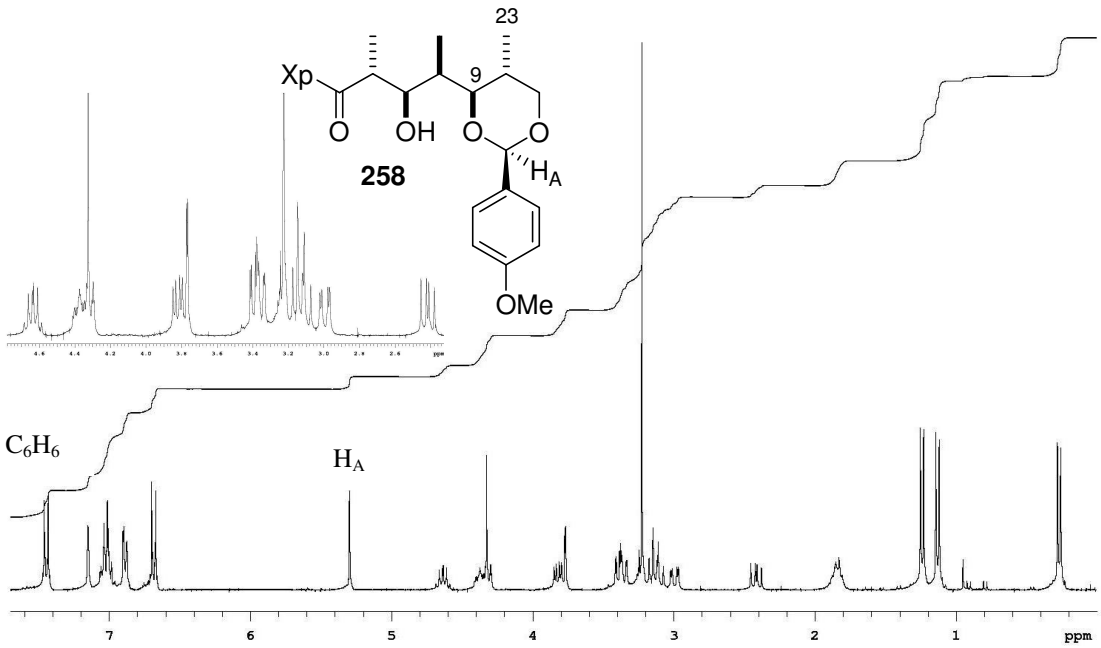
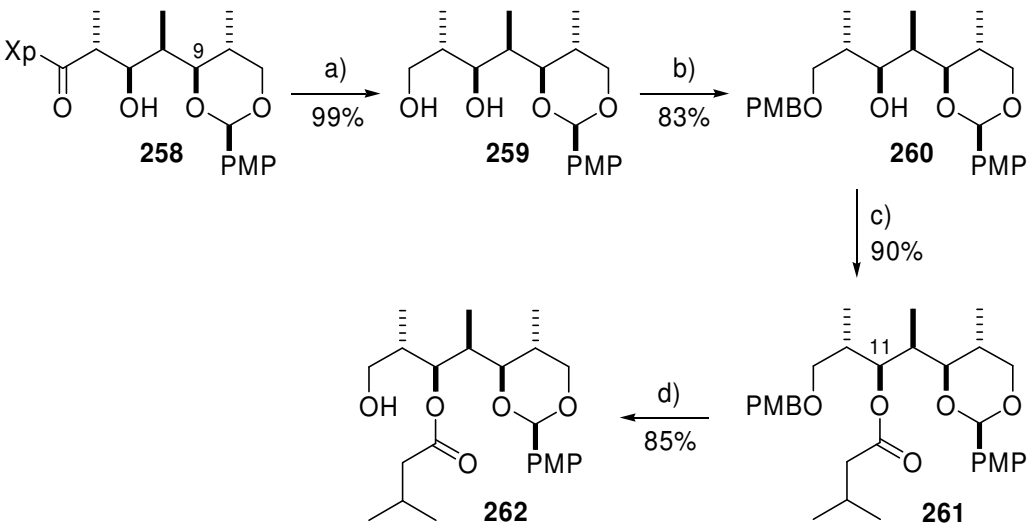


Figure 4.12: *300 MHz ^{1}H NMR spectrum of p-methoxybenzilidene acetal* ***258*** *in C_6D_6*

A sequence of manipulations was then implemented to install the desired acyloxy group at C11 and furnish alcohol **262**. As delineated in Scheme 4.27, this was achieved by first reductively cleaving the chiral auxiliary with $LiBH_4$,[46] which smoothly afforded crystalline diol **259** in near quantitative yield. Selective protection the of primary alcohol as the PMB ether was achieved by reacting diol **259** with NaH in THF at room temperature for 2 hours followed by addition of a limiting amount (1.2 eq) of *p*-methoxybenzyl chloride.[72] The reaction proceeded with complete regioselectivity giving **260** in good yield (83%). Acyl docking at the C11 oxygen was accomplished in good yield using Paterson's modification[66] of the Yonemitsu-Yamaguchi esterification protocol[35,73] with isovaleric acid to afford **261**. With the oxygen bearing centres of the stereopentad successfully differentiated, all that remained was unmasking of the primary alcohol, which was effortlessly accomplished through PMB ether cleavage with DDQ[44] leading to alcohol **262**. Crucially, the use of DDQ in aqueous media for this final deprotection reaction did not affect the integrity of the *p*-methoxybenzilidene acetal.[39]



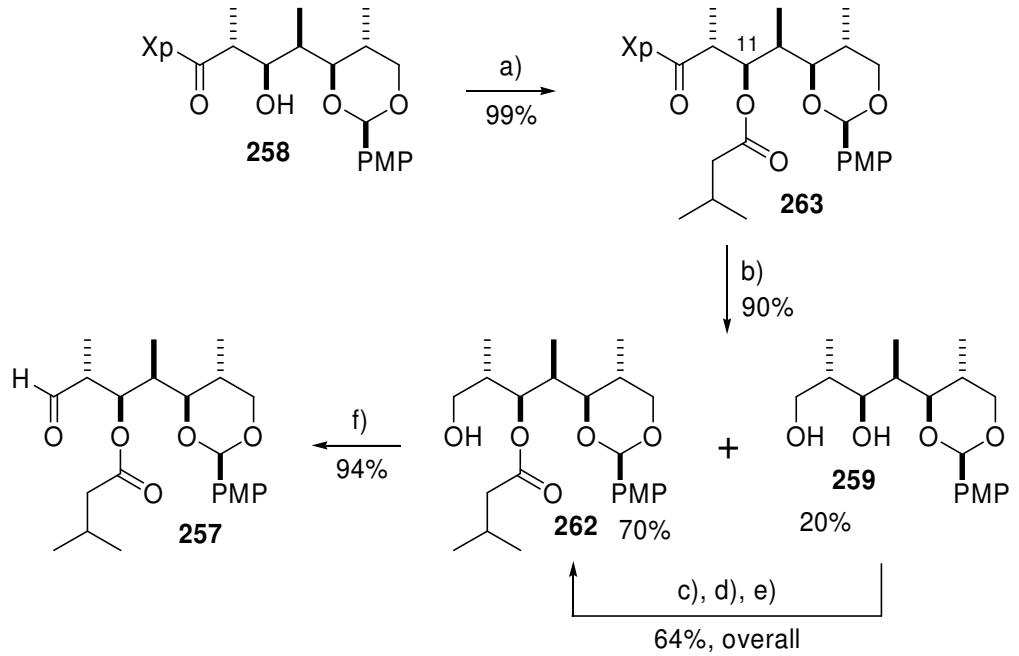
Reagents and conditions: a. $LiBH_4$ (1.2 eq), EtOH (1.2 eq), Et_2O, −10 °C, 3 h; **b.** i. NaH (3.0 eq), THF, rt, 2 h; ii. PMBCl (1.2 eq), rt, 3 h; **c.** i. isovaleric acid (10.0 eq), DMAP (38.0 eq), Et_3N (18.0 eq), toluene, −78 °C; ii. 2,4,6-trichlorobenzoyl chloride (17.0 eq), −78 °C, 15 min to 0 °C, 15 min to rt, 1 h; **d.** DDQ (1.2 eq), pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 3 h.

Scheme 4.27: *Completion of differential protection and formation of alcohol* ***262****.*

Despite its relative ease and efficiency (63% overall yield), this four step sequence seemed long winded and required a formal protection/deprotection manipulation, which was hoped to be avoided.

It was envisaged that primary alcohol **262** could be afforded in just two steps from secondary alcohol **258** if, upon acyloxy insertion at C11, chemoselective reduction/cleavage of the auxiliary amide could be achieved. To this end, alcohol **258** was 'protected' as ester **263** under identical conditions[66] as before (see Scheme 4.27), as shown in Scheme 4.28. This exceptional reaction proceeds virtually quantitatively, despite the sterically demanding reaction origin. Pleasingly, subsequent treatment with $LiBH_4$[46] afforded primary alcohol **262** in good yield (70%) with diol **259** accounting for the rest of the material (20%). The inertness of the *p*-methoxybenzylidene acetal moiety in **263** to the action of $LiBH_4$ was pleasing, given the documented susceptibility of such groups to ring opening with DIBAL-H.[39,74] The yield of alcohol **262** could be increased (83%) by processing the by-product diol **259** through the sequence delineated in Scheme 4.27. This modification

secured alcohol **262** in half the number of steps and higher overall yield than the previous method.



Reagents and conditions: a. i. isovaleric acid (10.0 eq), DMAP (38.0 eq), Et_3N (18.0 eq), toluene, −78 °C; ii. 2,4,6-trichlorobenzoyl chloride (17.0 eq), −78 °C, 15 min to 0 °C, 15 min to rt, 1 h; **b.** $LiBH_4$ (1.2 eq), EtOH (1.2 eq), Et_2O, −10 °C, 3.5 h; **c.** i. NaH (3.0 eq), THF, rt, 2 h; ii. PMBCl (1.2 eq), rt, 3 h; **d.** i. isovaleric acid (10.0 eq), DMAP (38.0 eq), Et_3N (18.0 eq), toluene, −78 °C; ii. 2,4,6-trichlorobenzoyl chloride (17.0 eq), −78 °C, 15 min to 0 °C, 15 min to rt, 1 h; **e.** DDQ (1.2 eq), pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 3 h; **f.** DMP (1.5 eq), CH_2Cl_2, rt, 1 h;

Scheme 4.28: *Acquisition of aldehyde **257** via an improved synthesis of alcohol **262**.*

The key aldehyde fragment **257** was then accessed by Dess-Martin periodinane oxidation[47,48] of primary alcohol **262**, which proceeded in excellent yield (94%). In some instances (when an older batch of DMP was used), this oxidation reaction produced small quantities of *p*-methoxyanisaldehyde (as evidenced by tlc and isolation by column chromatography), due to acetal cleavage and resulted in more moderate yields (~80%). It seems apparent that built-up acetic acid (caused by slow hydrolysis of the Dess-Martin reagent over time due to exposure to moisture) was the likely cause of the observed acetal cleavage. This problem was easily circumvented

by either extensively drying the reagent on a high vacuum pump prior to use or more drastically, washing the entire batch of reagent with anhydrous ether and drying under high vacuum prior to use (in reality, the compatibility of the Dess-Martin reagent to a large number of functional groups is unmatched and this slight acid build-up was only witnessed in batches that had been stored for long periods).[λ]

Characterisation of compound **257** was aided by ^{1}H NMR (Figure 4.13) and ^{13}C NMR (Figure 4.14) spectroscopy. The ^{1}H NMR spectrum shows that the expected aldehydic proton resonates as a doublet at δ 9.61 (J = 2.0 Hz) and shows coupling to the methyl methine multiplet at δ 2.60 (dqd, J = 7.6, 7.0, 2.0 Hz). The signal at δ 2.60 in turn couples to the methyl doublet at δ 0.94 (J = 7.0 Hz) and the ester oxymethine at δ 5.54 which resonates as a doublet of doublets (J = 7.6, 4.6 Hz). The remaining oxymethine signal appears as a doublet of doublets at δ 3.40 (J = 10.0, 2.2 Hz), while the doublet of doublets at δ 3.83 (J = 11.2, 4.6 Hz) and the apparent triplet at δ 3.14 (J = 11.2 Hz), which show reciprocal coupling, account for the oxymethylene protons. The 5H multiplet at δ 2.13-1.71 comprises the C8 and C10 methyl methine protons in addition to the methylene and dimethyl methine protons of the ester side chain. The characteristic *p*-methoxybenzilidene resonances are also evident (as previously discussed).

Pertinent peaks in the ^{13}C NMR spectrum are the aldehydic and ester carbonyl resonances at δ 201.3 and δ 171.9, respectively and the acetal oxymethine resonance at δ 101.5. A broad band at 1731 cm^{-1} in the infrared spectrum recorded for **257** was indicative of overlapping aldehyde and ester carbonyl signals, while high resolution mass spectrometry confirmed a molecular composition of $C_{23}H_{34}O_6$.

[λ] The Dess-Martin reagent was made in large batches (~ 30-50 g) and was stored in amber bottles that were placed in the freezer. Handling was conducted under normal conditions and the bottle was flushed with N_2 prior to re-sealing and storage.

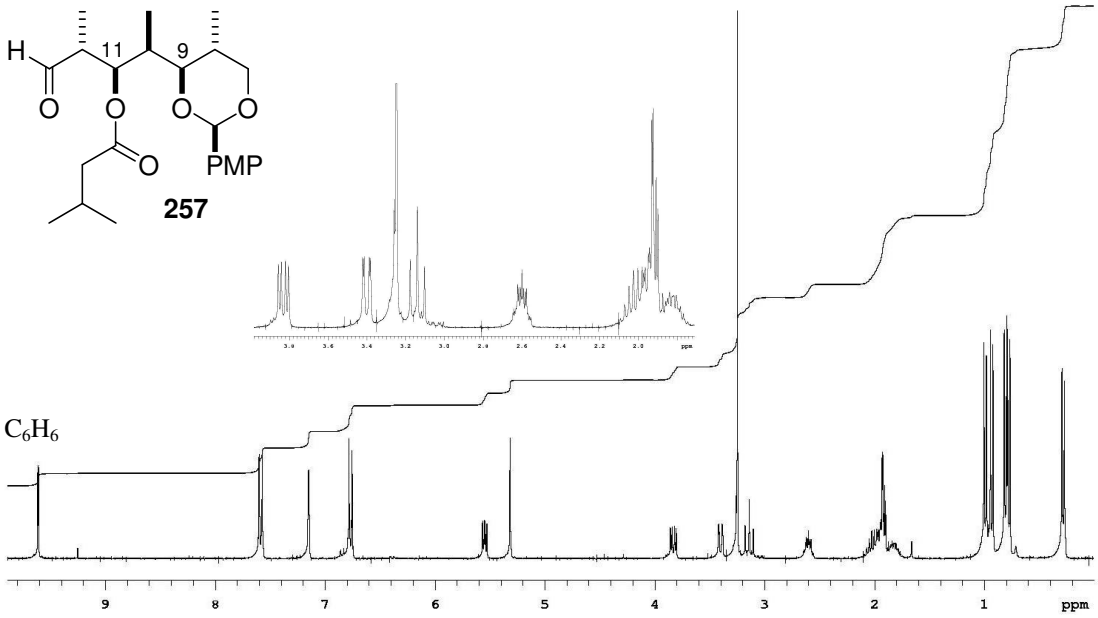


Figure 4.13: *300 MHz ^{1}H NMR spectrum of aldehyde* ***257*** *in C_6D_6*

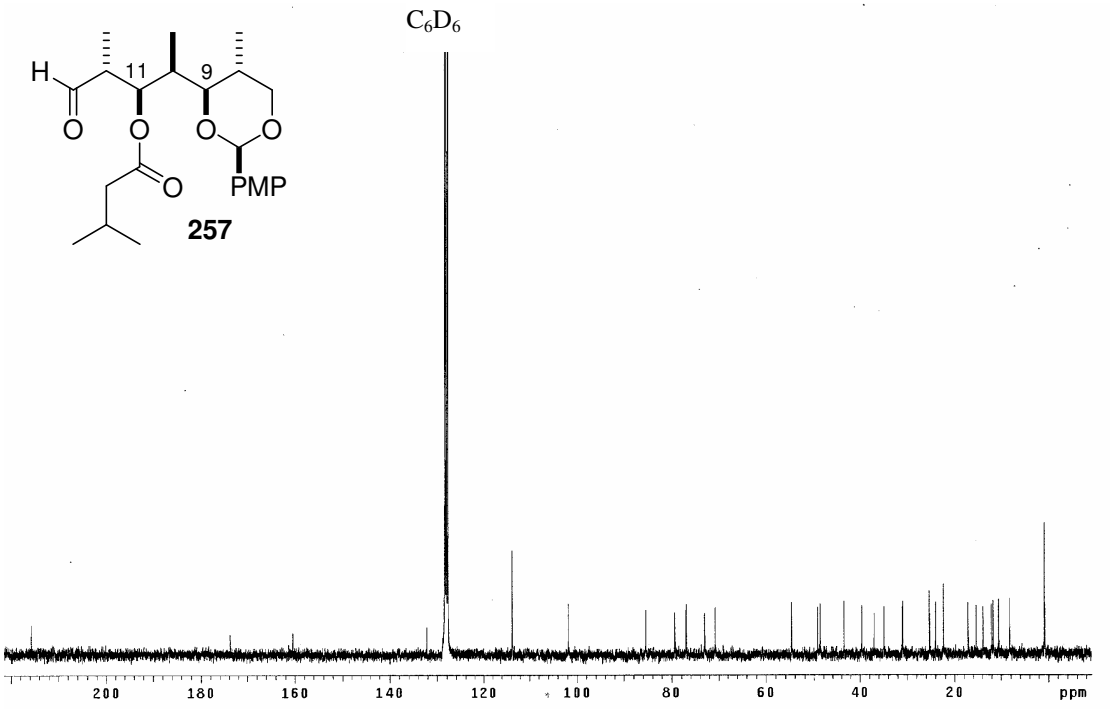
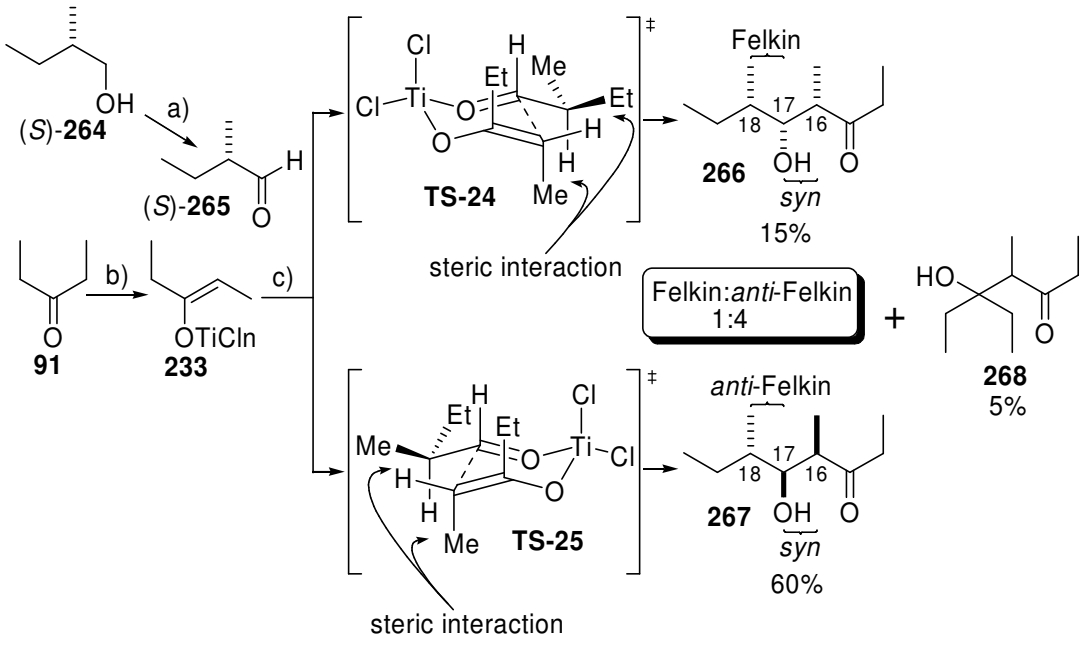


Figure 4.14: *75.5 MHz ^{13}C NMR spectrum of aldehyde* ***257*** *in C_6D_6*

4.8.2 The Synthesis of Ketone 200 as a Single Stereoisomer

The synthesis of β-silyloxy ketone **200**, which is the aldol coupling partner to aldehyde **257**, commenced with the acquisition of compound **267** as depicted in Scheme 4.29. Although a stereoselective synthesis of ketone **200** was not essential,

given the removal of its C16 and C17 stereocentres in a future oxidation reaction, it was anticipated that the reaction of α-methyl aldehyde (*S*)-**265** with pentan-3-one (**91**) would potentially allow a single isomer of adduct **267** to be isolated. This would lead to the acquisition of ketone **200** as a single diastereomer, which in turn would enable easier compound characterisation in later steps. In practice, aldehyde (*S*)-**265** was synthesised from commercially available (*S*)-2-methylbutanol [(*S*)-**264**] through Swern oxidation.[38] The extreme volatility of the product (bp ~55 °C) dictated that standard reaction quench and product isolation could not be conducted without significant loss of material. Instead, after the customary Swern protocol,[38] the reaction mixture was fractionally distilled to afford (*S*)-2-methylbutanal [(*S*)-**265**] as a solution in residual CH_2Cl_2. Without storage, the aldehyde was added to a preformed solution of the *Z*-(O)-titanium(IV) enolate **233**[18,50,51] of pentan-3-one (**91**) in CH_2Cl_2 at −100 °C. Isolation and purification of the reaction mixture revealed three products.



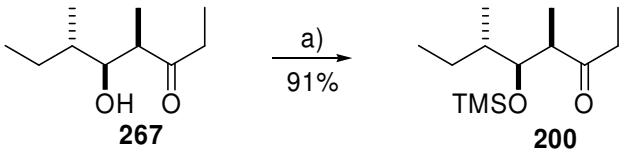
Reagents and conditions: a. i. DMSO (3.0 eq), CH_2Cl_2 −78 °C, 30 min; ii. $(COCl)_2$ (1.5 eq), −78 °C, 30 min; iii. alcohol (*S*)-**284**, CH_2Cl_2, −78 °C, 45 min; iv. Et_3N (6.0 eq), −78 °C, 30 min to rt; **b.** i. $TiCl_4$ (1.2 eq), CH_2Cl_2, −90 °C, 30 min; ii. DIPEA (1.4 eq), −90 °C, 1 h; **c.** aldehyde (*S*)-**285** (~1.5 eq), −100 °C to −90 °C, 1 h.

Scheme 4.29: *Aldol reaction of chiral aldehyde (S)-**265** with pentan-3-one (**91**).*

A minor component of the products was identified as tertiary alcohol **268**, which formed upon reaction of enolate **233** with unreacted pentan-3-one (**91**). The percentage of this by-product was found to significantly increase when the reaction temperature was allowed to rise above −90 °C. The remaining products were characterised as being a 4:1 ratio of stereoisomers of (5*S*)-5-hydroxy-4,6-dimethyloctan-3-one. It was assumed that the major isomer was the 16,17-*syn*-17,18-*anti*-Felkin-adduct **267** given both the typical *anti*-Felkin π-facial discrimination[75-77] that α-methyl aldehydes display in aldol reactions with *Z*-(O)-titanium enolates and the inherent *syn*-selectivity of *Z*-(O)-enolates.[51] The minor isomer is thus assigned the structure of **266** which corresponds to 16,17-*syn*-17,18-Felkin selectivity. Although only a tentative assignment, literature precedent suggests that the isomeric ratio should favour this designation.[51] Scheme 4.29 depicts transition states leading to the observed products. It is evident that both transition states experience steric interactions between the enolate methyl and the hydrogen of the lone stereocentre in the aldehyde and the enolate hydrogen and the nearest substituent of the stereocentre of the aldehyde. However, in **TS-24** the steric interaction is between the enolate hydrogen and the ethyl group as opposed to the the methyl group for **TS-25**. Additionally, **TS-24** experiences a steric interaction between the ethyl group of the aldehyde and the methyl of the enolate. These various interactions destabilise **TS-24** and as a consequence this transition structure is less stable than **TS-25**. Hence, only a small proportion of material reacts *via* transition state **TS-24**, which directly affects the product ratio. It is interesting to note the vast effect on transition state stability that an increase in the steric demand of the aldehyde has in aldol additions. Aldehyde (*S*)-**265** and propanal differ by C_2H_5 (an ethyl group), yet in the aldol reaction of propanal with pentan-3-one (Scheme 4.19) the product ratio included nearly 1/4 *anti*-adducts, whereas the same reaction with (*S*)-**265** gave no *anti*-isomers.

Pleasingly, isomers **266** and **267** could be separated with careful column chromatography and as such, the major adduct **267** was taken through the remaining sequence in isomerically pure form. While not critical, the well defined stereogenicity of ketone **267** would hopefully aid future spectroscopic analysis. In any case, pure β-hydroxyketone **267** was protected with TMSOTf under careful

conditions[52] (to avoid silyl enol ether formation) to give silane **200** in excellent yield (91%) as shown in Scheme 4.30.



267 **200**

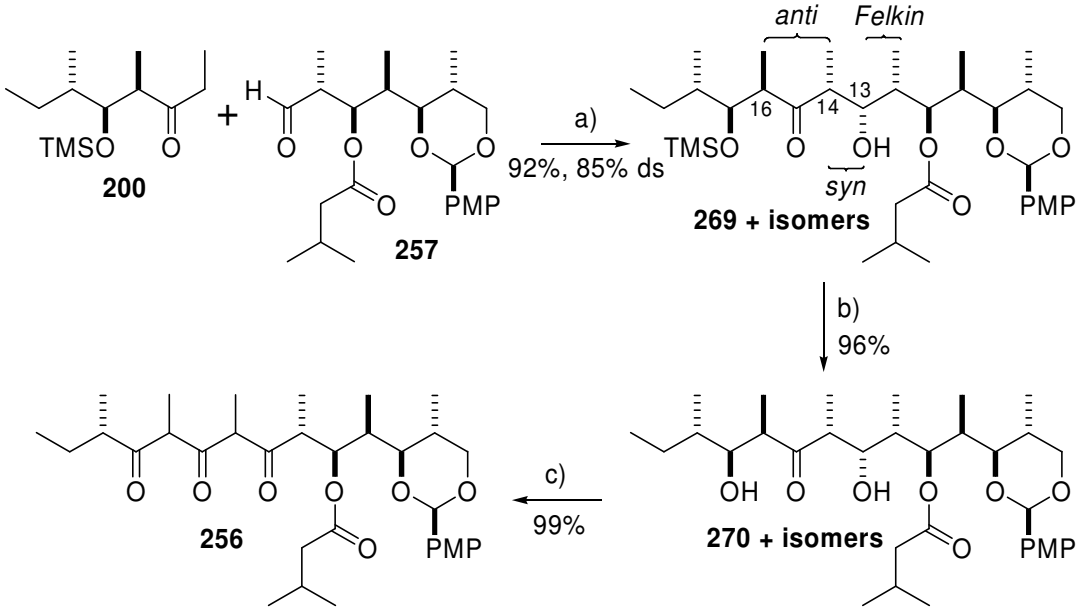
Reagents and conditions: a. i. 2,6-lutidine (2.0 eq), CH_2Cl_2, –90 °C; ii. TMSOTf, (1.5 eq), –90 °C, 10 min.

Scheme 4.30: *Synthesis of β-silyloxyketone **200**.*

4.8.3 Aldol Extension and Formulation of β-Triketide 256

With the two aldol fragments in hand, attention was turned to their union in a homologation reaction and ultimately, acquisition of spiroacetal dihydropyrone precursor, β-triketide **256**. Scheme 4.31 shows that the aldol bond forming reaction was mediated by enolisation of ketone **200** with LiHMDS[53-55] in an identical manner to that already discussed (Sections 3.4.4 and 4.6.3). Interestingly, this double stereodifferentiating reaction proceeded with very high levels of stereoselectivity (ds >85%) to give a major isomer tentatively assigned the structure depicted for **269**. This tentative stereochemical assignment was based on similar double stereodifferentiating lithium aldol reactions conducted by Masamune *et al.*[53] (see also Section 3.4.4 for additional discussion). Namely, that ketone **200** displays a dominating preference for the 13,14-*syn*,14,16-*anti*-adduct. In this instance however, such π-facial discrimination forces aldehyde **257** to accept Felkin attack.[75-77] Despite the fact that α-methyl aldehydes show a persistent *anti*-Felkin preference in aldol reactions with *Z*-(O)-enolates, it was expected that any such preference would be largely overwhelmed by a dominating preference from the enolate, resulting in the stereochemistry as drawn. In certain instances the β-stereocentre of chiral aldehydes can influence the stereochemical outcome of aldol reactions,[78] but again in this case it was anticipated that any β-stereocentre effect would be dominated by the enolate selectivity. In any case the configuration of these new stereocentres is not critical as they are either lost on oxidation or become epimerisable in subsequent steps.

To that end, desilylation of major aldol adduct **269** under the action of fluoride ion (HF·pyr/pyr)[49,79] afforded dihydroxy ketone **270**, and subsequent double oxidation with Dess-Martin reagent[47,48] afforded β-triketide **256** as a complex mixture of keto and enol isomers in excellent overall yield (95% after both steps, Scheme 4.31). The deprotection reaction was only conducted on isomerically pure material once to obtain full spectroscopic data. In general, it proved much more efficient not to separate the isomers before deprotection and oxidation, but rather perform these reactions on the mixed isomeric material. This was viable given that all the compounds eventually converge to the same product upon oxidation.



Reagents and conditions: a. i. LiHMDS (1.1 eq), THF −78 °C, 30 min to −50 °C 30 min; ii. aldehyde **257** (0.5 eq), THF, −78 °C, 2 h; **b.** HF·pyr/pyr, THF, rt, 45 min; **c.** i. DMP (3.0 eq), CH_2Cl_2, rt; ii. H_2O (2.0 eq), CH_2Cl_2, rt, 1 h.

Scheme 4.31: *Synthesis of β-triketone* ***256*** *from aldehyde* ***257*** *and ketone* ***200****.*

The ^{1}H NMR (Figure 4.15) and ^{13}C NMR (Figure 4.16) spectra acquired for compound **269** indicate the growing complexity of the system. Importantly, both spectra show single resonances for all peaks indicating the presence of a single stereoisomer. In particular, the ^{1}H NMR spectrum displays peaks consistent with those encountered in Figure 4.13, which can thus be attributed to the aldehyde

portion of the compound. However, the proton at C13 now resonates as an oxymethine broad doublet of doublets at δ 4.12 (J = 9.6, 2.1 Hz) and shows coupling to the methyl methine doublet of quartets at δ 2.86 (J = 9.6, 6.9 Hz), the 4H multiplet at δ 2.10-1.83 and the hydroxyl doublet at δ 3.05 (J = 3.6 Hz). With the aid of COSY NMR the multiplet at δ 2.10-1.83 was shown to correspond to resonances for the protons in the aldehyde portion of **269**, namely the protons at C8, C10, C12 and C3`. Correlations of the signals with other resonances allowed the remainder of the aldehyde fragment to be confirmed. The remaining peaks could be attributed to the ketone derived portion of the molecule, which could be deduced by following couplings extending from the TMS oxymethine doublet of doublets at δ 3.99 (J = 6.6, 3.9 Hz). The dominant 9H singlet at δ 0.15 is due to resonance of the equivalent methyl groups of the trimethylsilyl protecting group.

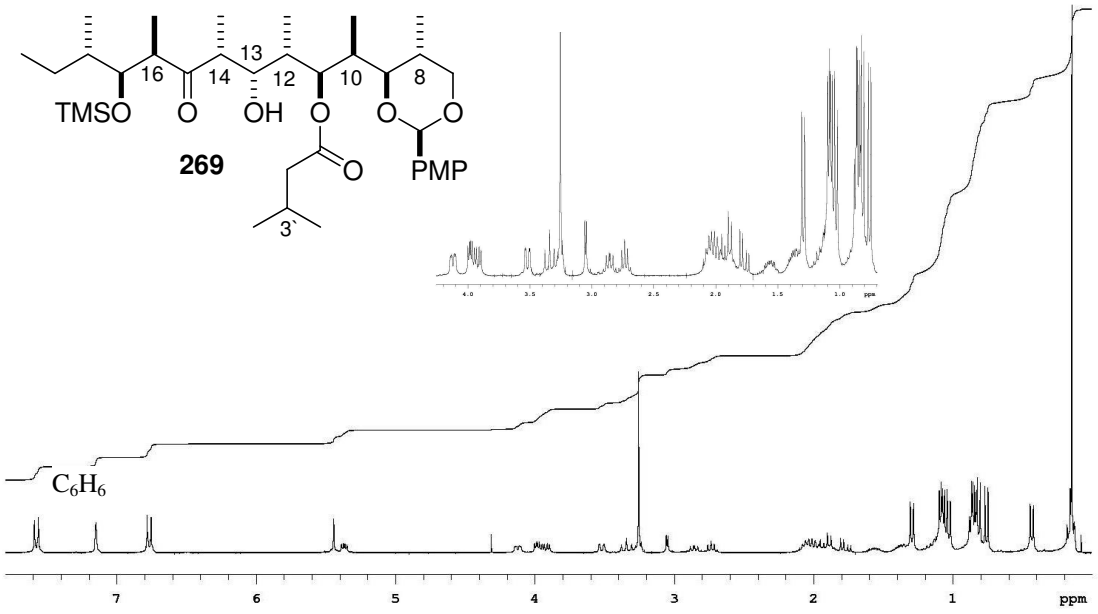


Figure 4.15: *300 MHz ^{1}H NMR spectrum of aldol adduct* ***269*** *in C_6D_6*

The ^{13}C NMR displays the correct number of signals in the expected regions for compound **269**, particularly a carbonyl resonance at δ 215.7, five oxymethine resonances at δ 85.4, δ 79.3, δ 76.9, δ 73.1 and δ 70.8 and the TMS resonance at δ 0.86. High resolution mass spectrometry identified an accurate mass of 673.4105 which confirmed a molecular formula of $C_{32}H_{68}O_6SiNa$.

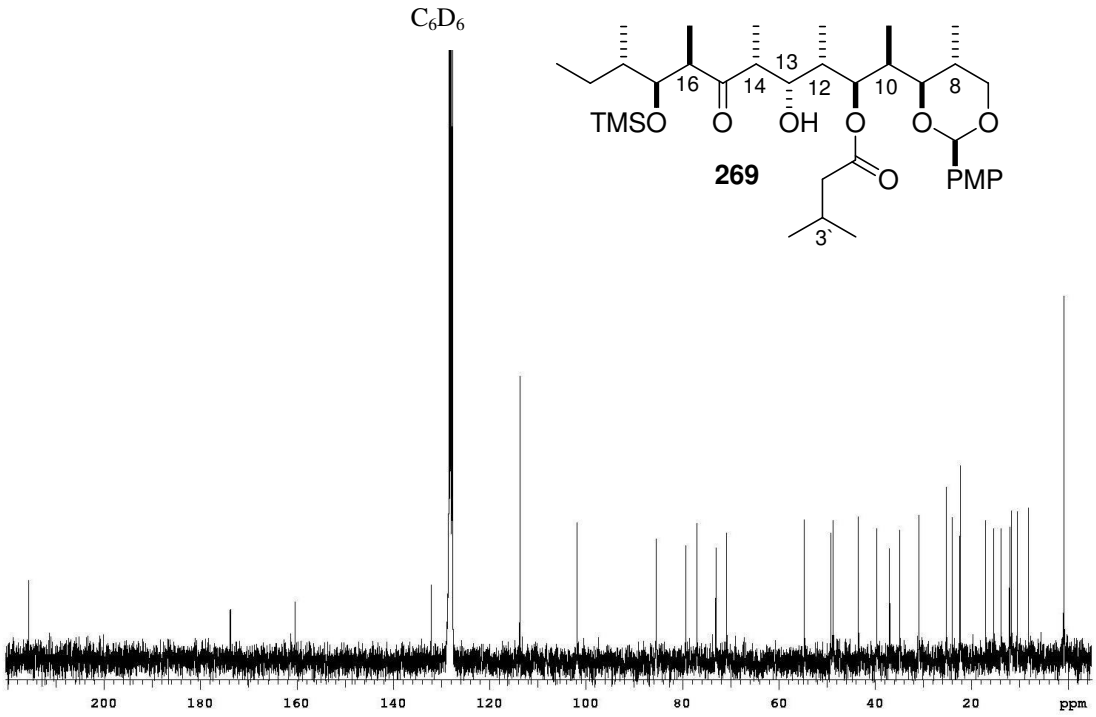


Figure 4.16: *75.5 MHz ^{13}C NMR spectrum of aldol adduct* ***269*** *in C_6D_6*

4.8.4 The Synthesis of Spiroacetal Dihydropyrone 274

Having completed construction of crucial β-triketide **256**, the much anticipated spirocyclisation reaction was at hand. Given the predicted sensitivity of the PMP acetal protecting group to acid, early attempts to construct the spiroacetal revolved around treating tricarbonyl compound **256** directly with acid. Simply adding successively stronger acids (PPTS to *p*-TsOH to TFA) to a small amount of **256** in $CDCl_3$ in an NMR tube and analysing the ^1H NMR spectrum over time gave a good indication of both the sensitivity of the *p*-methoxybenzilidene group to acid and also the propensity for spirocyclisation to occur upon deprotection. Unfortunately, none of these experiments proved very successful. It was apparent that a very fine balance of acidity had to be reached, such that acetal cleavage was achieved and cyclisation/dehydration occurred, but that hydrolysis of the ester was avoided.

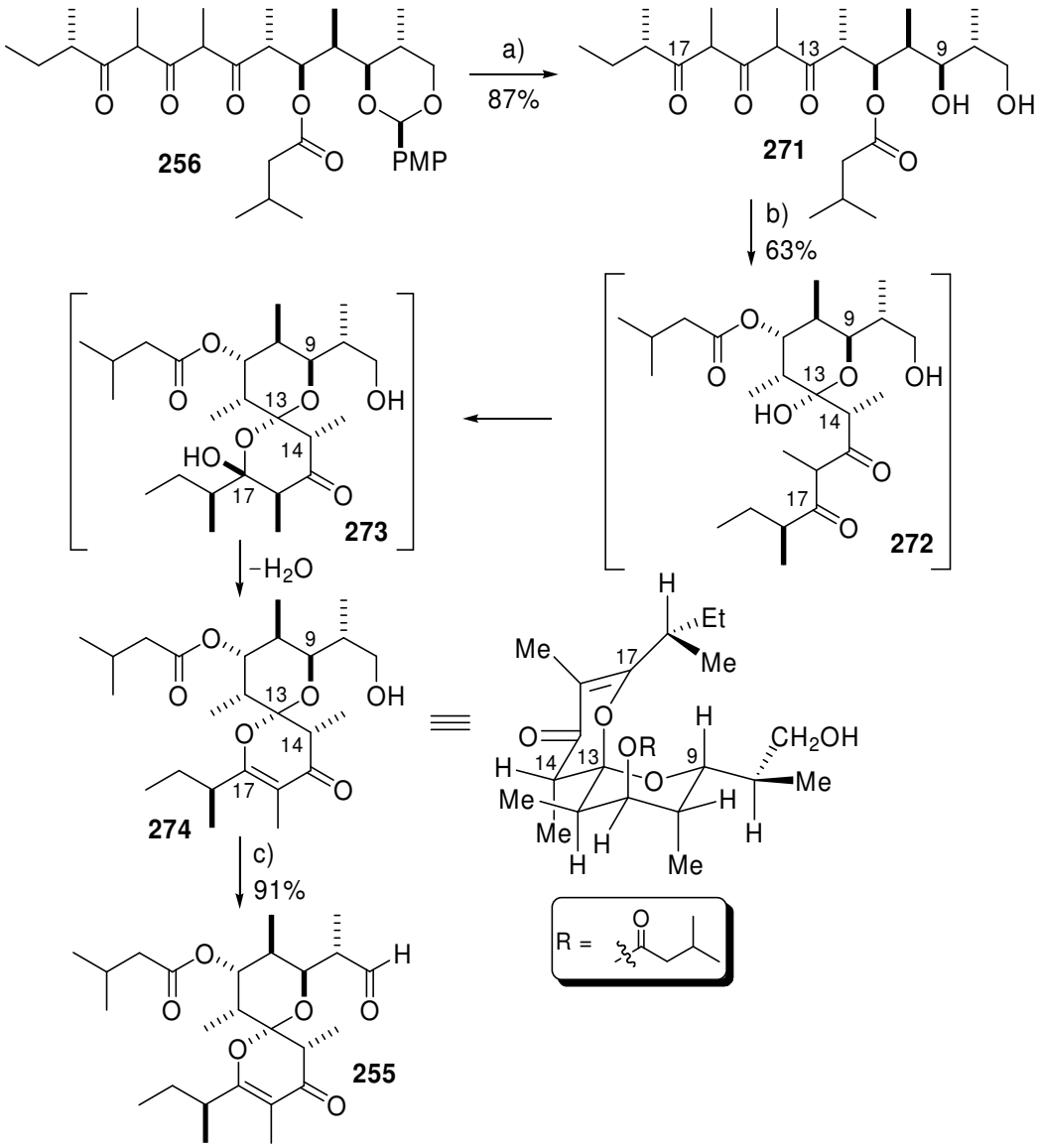
Finding use primarily as a desilylating agent, aqueous hydrofluoric acid (HF) has proved very useful in late stage deprotection/cyclisation reactions due to its mild acidity.[80] Despite not requiring the action of fluoride ion, it was hoped that the mild acidity of HF would be suitable to deprotect and cyclise/dehydrate β-triketide **256**,

whilst preserving the acyloxy functionality. In the event this proved to be a worthy assumption, as treatment of tricarbonyl **256** with 30% hydrofluoric acid in 2:2:1 $CH_3CN/THF/H_2O$[81,82] routinely afforded spiroacetal dihydropyrone **274**, albeit in a poor yield of 20% (not shown). It was clear that even these mildly acidic conditions were causing ester lysis and significant decomposition, presumably due to the long reaction time (24-28 h). The duration of the reaction could be significantly reduced (5 h) by removing the *p*-methoxybenzilidene acetal under hydrogenation conditions (H_2, Pd/C)[71] prior to reaction with HF. This resulted in yields of 30-35%, which despite the improvement, required further enhancement.

Further scouting, identified Amberlyst-15[83-85] resin as a potentially useful, mildly acidic reagent that was hoped could supersede HF. Indeed, under only slightly optimised conditions, the use of Amberlyst-15 lead to dramatically increased yields of spiroacetal **274** as shown in Scheme 4.32. In practice, exposure of β-triketide **256** to Pd/C under an atmosphere of hydrogen,[71] let to rapid cleavage (30 min) of the bis-hydroxyl protecting group and formation of a complex product mixture. An assortment of products was expected, due in part to the prevailing keto/enol distribution of the tricarbonyl system in **271**, but also from the potential for unprotected compound **271** to undergo partial cyclisation to give hemiacetal **272** and spiroacetal **273** intermediates (see Scheme 4.32). The product mixture was submitted to chromatographic purification to remove the by-product *p*-methoxytoluene, which results from hydrogenolysis of the *p*-methoxybenzilidene acetal (compared to *p*-anisaldehyde for acidic cleavage), but separation of the reaction products was not attempted. Instead, the product mixture was dissolved in CH_2Cl_2 and cooled to −50 °C, then treated with Amberlyst-15 for 30 minutes, before being warmed to 0 °C for 2 hours and finally, stirring at ambient temperature for an additional 2 hours. This sequence afforded, after chromatographic isolation, spiroacetal dihydropyrone **274** as a clear oil in 55% yield over 2 steps. The purified spiroacetal **274** contained ~ 7% of what appeared to be a stereoisomer (possibly the C14 epimer)[#]. This is an excellent result given that the spiroacetalisation reaction was performed without the use of

[#] This small impurity was unable to be removed by column chromatography in this and subsequent steps. As such, a small amount of isomeric material (~ 6%) was present in samples of synthetic auripyrone A and is evident in the ^{1}H NMR spectra displayed in section 4.8.6 and Appendix B.

any specific control elements (i.e. controlled oxidation states). Instead, the reaction was allowed to proceed under thermodynamic control, which was anticipated to direct the C14 methyl group (which was epimerisable due to its location between two carbonyl groups) to adopt the desired equatorial position, in addition to promoting the required facial attack of the nucleophilic hydroxyl groups on the C13 and C17 carbonyl groups.



Reagents and conditions: a. Pd/C (10% w/w), H_2, EtOH, rt, 30 min; **b.** Amberlyst-15, CH_2Cl_2, −50 °C, 30 min to 0 °C, 2 h to rt, 2 h; **c.** DMP (1.5 eq), CH_2Cl_2, rt 1 h.

Scheme 4.32: *Formation of the spiroacetal dihydropyrone core of auripyrone A.*

The seemingly modest yield of the spiroacetalisation reaction was impressive given the context of what was achieved. Namely, the cyclisation simultaneously forged two new bonds and introduced two new stereocentres to give a major diastereomer (> 93%) of a highly substituted, stereochemically rich spiroacetal, which exhibited a relatively labile acyloxy moiety at C11. The decision to install the ester functionality prior to spiroacetal formation has potentially contributed to the low yield in the cyclisation reaction, but it was hard to anticipate any alternative producing a higher overall yield. For instance, employing a more formal protecting group, such as a TBS ether, instead of the ester moiety to mask the C11 oxygen was considered. After similar spirocyclisation of such a substrate (which could be troublesome due to steric hindrance from to the bulky TBS ether), protection of the C7 primary alcohol, followed by removal of the installed silyl ether and esterification at C11, and finally cleavage of the C7 protecting group would be required to furnish the compound currently in hand. Hence, the decision to install the ester at such an early stage saved 4 steps in the overall sequence, and it could be argued a higher yield was realised than would be expected if the formal protection sequence had been employed.

Additionally, the PMP acetal has functioned remarkably well. Not only did its migration bestow differentiation on the diol system in **206** (Scheme 4.26) and its lysis provide the trigger for spirocyclisation, but its removal also simultaneously liberated the C7 primary alcohol, which could be immediately submitted for oxidation. Towards this end, alcohol **274** was treated with Dess-Martin reagent[47,48] in CH_2Cl_2 at room temperature for 1 hour to secure key aldehyde fragment **255** in excellent yield (91%) as depicted in Scheme 4.32.

The ^{1}H NMR (Figure 4.17) and ^{13}C NMR (Figure 4.18) spectral data for compound **274** showed excellent agreement with the data reported by Suenaga *et al.* for the corresponding spiroacetal dihydropyrone portion of auripyrone A (**78**). In particular, the acyloxymethine proton resonated as an apparent triplet at δ 4.93 (J = 3.6 Hz) [lit. δ 4.92 (t, J = 3.3 Hz)] and showed coupling to the methyl methine quartet of doublets at δ 1.87 (J = 7.2, 3.6 Hz) [lit. δ 1.83, m], the 2H multiplet at δ 1.81-1.73, which comprised the C10 methyl methine [lit. δ 1.81, m] and one of the C19 diastereotopic methylene protons [lit. δ 1.52, m]. The methyl methine signals at δ 1.87 and δ 1.81-

1.73 in turn showed coupling to the methyl doublets at δ 0.80 (*J* = 7.2 Hz) [lit. δ 0.77 (d, *J* = 7.0 Hz)] and δ 0.67 (*J* = 7.2 Hz) [lit. δ 0.63 (d, *J* = 7.0 Hz)], respectively. The methyl methine quartet at δ 2.43 (*J* = 6.6 Hz) [lit. δ 2.32 (q, *J* = 7.0 Hz)] coupled to the methyl doublet at δ 1.14 (J = 6.6 Hz) [lit. δ 1.12 (d, *J* = 7.0 Hz)] and was characteristic of a α-disubstituted dihydropyrone. The remaining signals due to the acyloxy and C18-C20 side chains were also consistent with the auripyrone A data. The C9 oxymethine proton resonated as a doublet of doublets at δ 3.83 (*J* = 10.2, 2.4 Hz) and showed coupling to the methyl methine multiplet at δ 1.61-1.55, which in turn coupled to the methyl doublet at δ 0.67 (*J* = 7.2 Hz) and the diastereotopic oxymethylene signals at δ 3.49 (dd, *J* = 10.8, 5.4 Hz) and δ 3.37-3.34 (dd, *J* = 10.8, 6.6 Hz). This grouping of signals was expectedly different to the reported auripyrone A data due to the absence of the γ-pyrone ring. Interestingly, the C27 vinyl methyl group resonated as a singlet at δ 1.89, which is considerably downfield of the resonance reported for the corresponding vinyl methyl group in auripyrone A [δ 1.65].[13] This anomaly will be discussed in section 4.8.6.

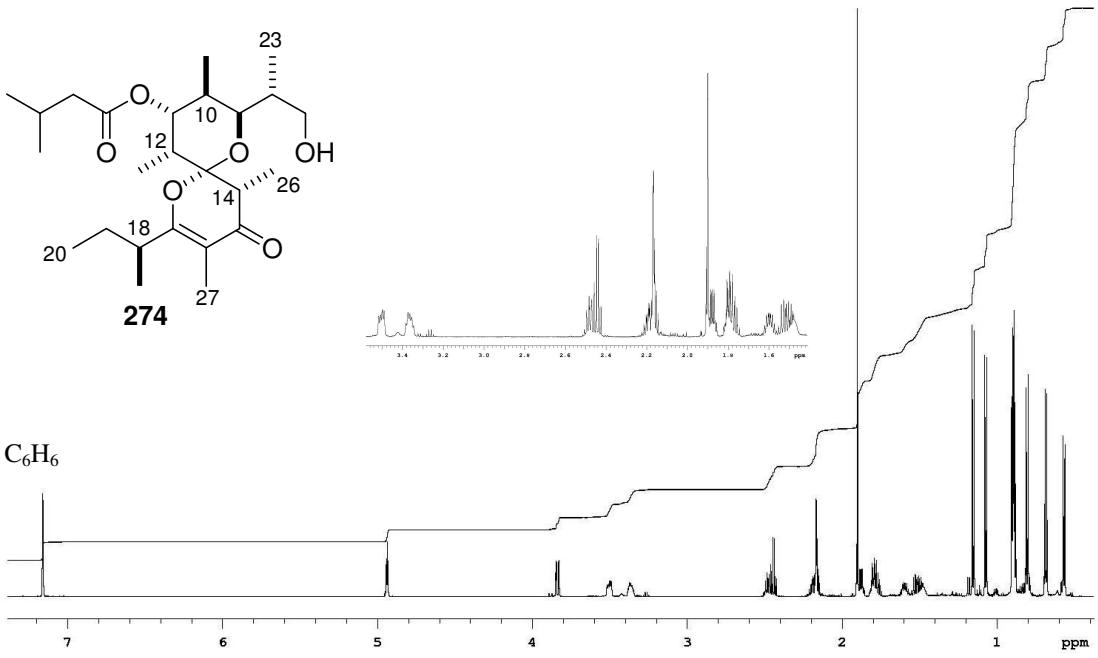


Figure 4.17: *600 MHz ^{1}H NMR spectrum of spiroacetal dihydropyrone* ***274*** *in C_6D_6*

The ^{13}C NMR spectrum showed similarly consistent resonances with those reported for the spiroacetal core of auripyrone A, with the most pertinent signals being the dihydropyrone and ester carbonyls at δ 192.8 [lit. δ 191.7] and δ 172.0 [lit. 172.0], the olefinic carbons at δ 167.3 [lit. δ 166.2] and δ 108.0 [lit. δ 107.8] and the dioxaspiro centre at δ 105.3 [lit. δ 105.0].

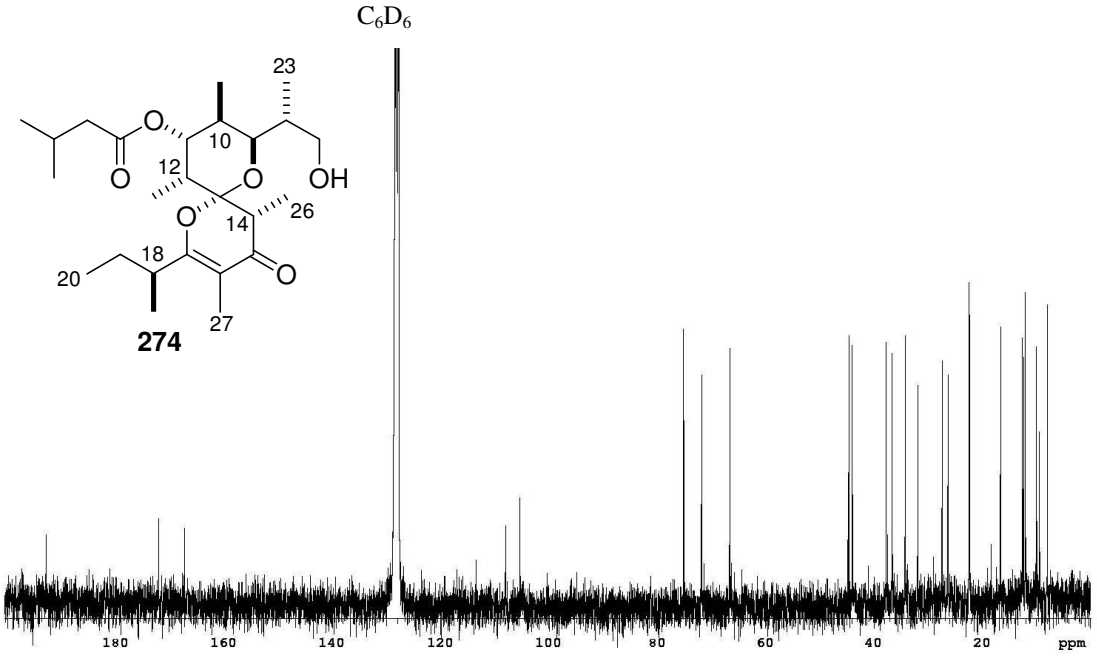


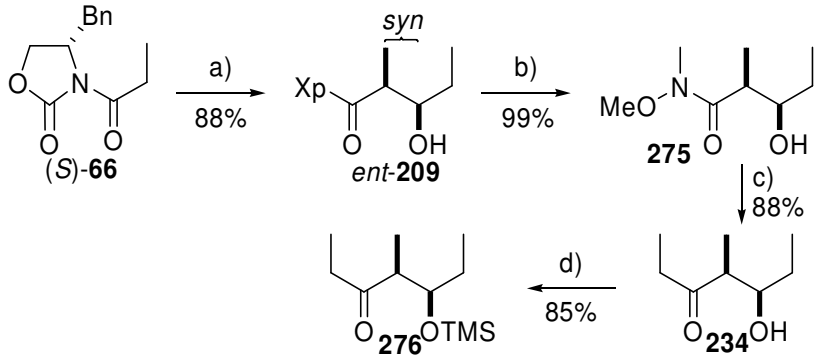
Figure 4.18: *75.5 MHz ^{13}C NMR spectrum of spiroacetal dihydropyrone* ***274*** *in C_6D_6*

Additionally, bands in the infrared spectrum at 3448, 1732, 1669 and 1624 cm^{-1}were consistent with hydroxyl, ester carbonyl, conjugated ketone carbonyl and alkene groups, respectively, while high resolution mass spectrometry confirmed the expected molecular formula of $C_{25}H_{42}O_6$.

4.8.5 Acquisition of β-Triketide 254

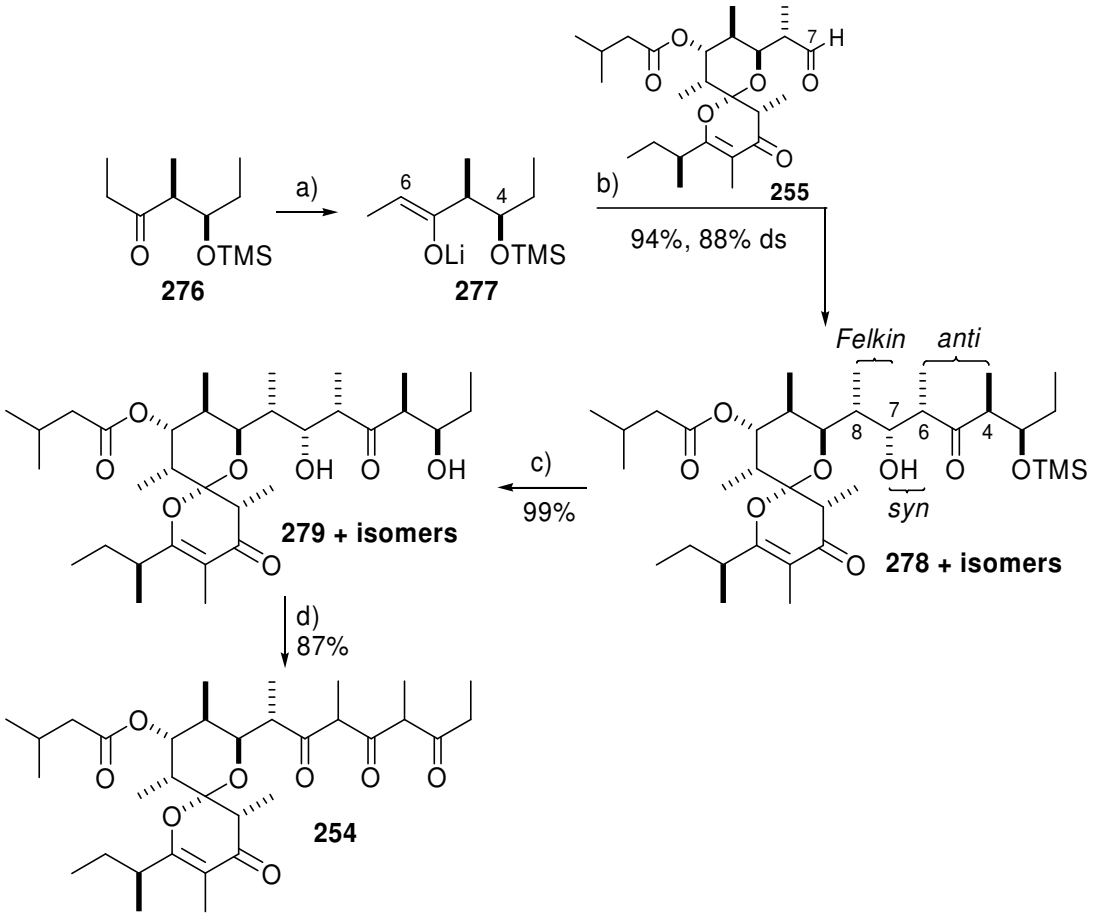
With the final C-C bond forming reaction at hand, the decision was taken to formulate the required aldol coupling partner to aldehyde **255**, as a single enantiomer. Although not specifically required, due to certain loss of the stereocentres in a future oxidation reaction, it was anticipated that use of an enantiopure ketone would enhance spectral analysis; an important concern given the growing complexity of the compounds. Additionally, it was hoped that careful choice

of stereochemistry for the ketone would enable replication of the excellent selectivity obtained for the previous aldol reaction (Scheme 4.31). As such, ketone **276** (Scheme 4.33) was chosen as it was anticipated to display the same sense of diastereofacial selectivity with aldehyde **255** as ketone **200** exhibited with aldehyde **257** (Scheme 4.31), and LiHMDS would again be employed to affect enolisation. Scheme 4.33 delineates the short synthesis of chiral ketone **276** using, Evans' oxazolidinone[19] technology. Starting from *N*-acyloxazolidinone (*S*)-**66** (synthesised in an identical manner to (*R*)-**66**),[19] enolisation with Bu_2BOTf and Et_3N followed by treatment with propanal (2.0 eq) afforded, after oxidative work-up, 3,4-*syn*-β-hydroxyimide *ent*-**209** as a single observable isomer.[19] Transamidation under Weinreb conditions (MeONH(Me)·HCl and $AlMe_3$)[86-88] and subsequent addition of an ethyl Grignard (EtMgBr)[88,89] to amide **275** delivered enantiomerically pure β-hydroxyketone **234** in excellent yield (87% over two steps). Amide substitution was critical in achieving mono-Grignard addition, as the excellent leaving group character of (*S*)-4-benzyl-2-oxazolidinone ((*S*)-**100**, Scheme 4.7) would result in destabilisation of the tetrahedral intermediate, leading to over addition. Finally, protection of the free alcohol as the TMS ether under mild conditions (to prevent silyl enol ether formation)[52] furnished β-silyloxyketone **276** as a single isomer in 65% yield over the four steps.



Reagents and conditions: a. i. Bu_2BOTf (1.2 eq), CH_2Cl_2, 0 °C, 30 min; ii. Et_3N (1.3 eq), 0 °C, 30 min; **c.** propanal, −78 °C, 30 min to 0 °C, 1 h; **b.** i. MeONH(Me)·HCl (2.0 eq), $AlMe_3$ (2.0 eq), CH_2Cl_2, 0 °C, 30 min; ii. imide (*S*)-**66**, CH_2Cl_2, −15 °C, 30 min to rt, o/n; **c.** EtMgBr (3.0 eq), Et_2O, 0 °C to rt, o/n; **d.** i. 2,6-lutidine (2.0 eq), CH_2Cl_2, −90 °C; ii. TMSOTf, (1.5 eq), −90 °C, 10 min.

Scheme 4.33: *Synthesis of chiral ketone* ***276*** *from N-acyl oxazolidinone(S)-****66****.*



Reagents and conditions: a. LiHMDS (1.1 eq), THF −78 °C, 30 min to −50 °C 30 min; **b.** aldehyde **255** (0.13 eq), THF, −78 °C, 1 h; **c.** HF·pyr/pyr, THF, rt, 45 min; **d.** i. DMP (3.0 eq), CH_2Cl_2, rt, 1 h.

Scheme 4.34: *Completion of carbon bond assembly and synthesis of β-triketide* ***254****.*

The final sequence of reactions towards the synthesis of β-triketide **254** proceeded as planned, beginning with the final aldol union, as shown in Scheme 4.34. Selective *cis*-enolisation of ethyl ketone **276** with LiHMDS[53-55] was followed by the addition of complex aldehyde **255** giving, after separation, two aldol adducts in excellent combined yield (94%) and high diastereoselectivity (88%). The major diastereomer was tentatively assigned as **278**, based again on the premise of dominating 4,6-*anti*-6,7-*syn*-7,8-Felkin selectivity exhibited by enolate **277**.[53,54] The elaborate aldol adduct **278** was subsequently treated with buffered HF/pyridine[49,79] at room temperature for 45 minutes to remove the C3 protecting group and afford β-dihydroxy ketone **279** in near quantitative yield. After initial spectroscopic

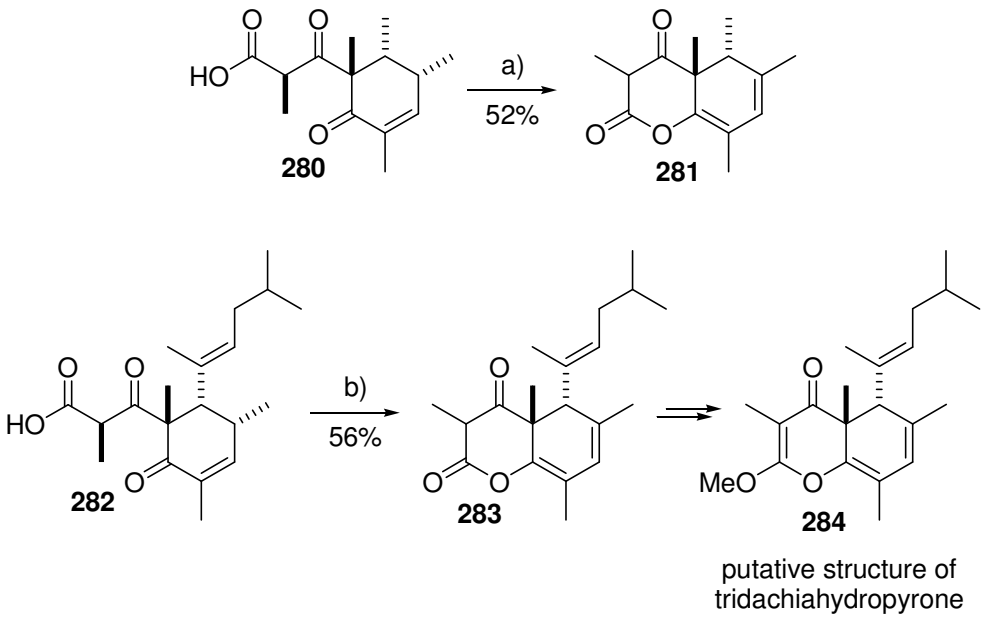
characterisation of the major diol **279**, desilylation was conducted on the mixed diastereomers and the resulting isomers were submitted as a mixture for oxidation. Dess-Martin periodinane[47,48] again dutifully facilitated conversion of diol **279** to coveted β-triketide **254** in good yield.

4.8.6 Completion of the Total Synthesis of Auripyrone A

The strategy towards auripyrone A, as outlined retro-synthetically in Scheme 4.25, had thus far proceeded exceptionally well, to provide access to significant quantities (~100 mg) of the precursor triketide **254**. With the final reaction at hand, attention once again turned to γ-pyrone formation and Yamamura's mild reaction conditions (Ph_3P/CCl_4 or DMSO/$(COCl)_2$, see discussion in Section 4.6.4).[61] To considerable dismay, neither set of conditions resulted in the formation of auripyrone A. Despite not fully characterising the reaction products (complex mixture), it was apparent from ^{1}H NMR spectral analysis that pyrone formation was occurring in almost all instances, but the spiroacetal dihydropyrone moiety was not present. This was evidenced from the ^{1}H NMR chemical shift of the hydrogen atom at the ester bearing C11 stereocentre. In all acyclic compounds featuring the acyloxy group at C11, the chemical shift (C_6D_6) of the C11 proton was always at ~ δ 5.5. However, after cyclisation had occurred, this same proton displayed and an upfield shift to ~ δ 4.9 which did not deviate for all subsequent cyclised products. All the products from the reactions of triketone **254** with Yamamura's reagents showed C11-H resonance in the ^{1}H NMR spectrum (C_6D_6) at ~ δ 5.5, which suggested that the acyloxy group was attached to an acylic substrate.

With the failure of the literature methods, a novel solution was sought. A recent synthesis from the Perkins laboratory of the putative structure of tridachiahyrdropyrone **284**, showed that β-ketopyrones **281** and **282**, could be formed in moderate yield from the appropriate β,δ-diketoacids **280** and **282**, respectively (Scheme 4.35).[90,91] These transformations were achieved by treatment of the tricarbonyl compounds with P_2O_5, either in the presence of methanesulfonic acid[90,92] or supported on celite[91,93] (Scheme 4.35). This reagent combination was derived from the documented use of Eaton's reagent (1:10 $P_2O_5/MeSO_3H$)[92] as a

mild medium for rearrangements,[92,94,95] where the active species is thought to be a mixed anhydride of P_2O_5 and $MeSO_3H$.[92] The advent of the celite support system[93] was due to the sensitivity of compound **282** to acid ($MeSO_3H$) and the desire to have a manageable way to handle the P_2O_5.



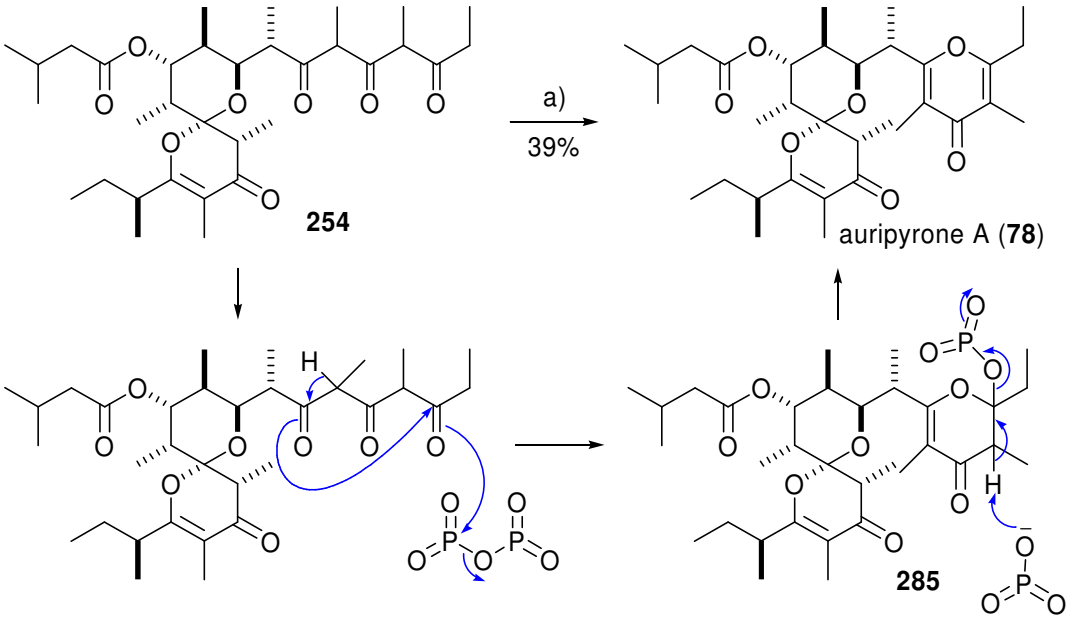
Reagents and conditions: a. 1:10 $P_2O_5/MeSO_3H$ (excess), CH_2Cl_2, rt, 1 h;
b. P_2O_5 (5.0 eq)-celite, CH_2Cl_2, rt, 1 h;.

Scheme 4.35: *The use of P_2O_5 to affect pyrone formation in Jeffery's attempted synthesis of putative tridachiahydropyrone.*

Despite the clear differences in the nature and arrangement of the respective tricarbonyl precursors to auripyrone A (**78**) and tridachiahyrdopyrone, it was anticipated that the use of celite supported P_2O_5[91] would provide a solution to the recalcitrant γ-pyrone ring.

Gratifyingly this conjecture proved correct, as addition of a solution of β-triketide **254** in CH_2Cl_2 to a stirred mixture of P_2O_5 and oven dried celite,[91] and subsequent stirring at room temperature for 5 hours, afforded 1 mg (10%) of synthetic auripyrone A (**78**). As shown in Scheme 4.36, the reaction was optimised by initially stirring tricarbonyl compound **254** with Amberlyst-15[83-85] resin for 5 minutes at −50 °C before the addition of the P_2O_5-celite mixture,[91] and then stirring at room

temperature for 24 hours. This slight modification resulted in significantly increased yields (39%), where addition of the acidic Amberlyst-15 was thought to aid the reaction by increasing the rate of tautomerisation of the β-triketone moiety. Scheme 4.36 depicts a proposed mechanism for the reaction, which suggests the P_2O_5 behaving in a similar manner to Yamamura's active species (Scheme 4.22).[61] Whilst the yield of this final reaction was moderate at best, it must be remembered that the current state-of-the-art γ-pyrone forming conditions failed to yield any product. Additionally, the complexity and sensitivity of the starting material triketide **254** is noteworthy. As such, this result was considered highly successful and the conditions developed may prove to be the mildest of those currently available for γ-pyrone formation from β-triketides.



Reagents and conditions: a. i. Amberlyst-15 (50% w/w), CH_2Cl_2, −50 °C, 5 min to rt; ii. P_2O_5 (4.0 eq)-celite, rt, 24 h.

Scheme 4.36: *Total synthesis of auripyrone A (**78**).*

Synthetic **78** exhibited identical spectral data (^{1}H and ^{13}C NMR, UV/Vis, IR, melting point, and MS) to those reported by Suenaga *et al.* for authentic auripyrone A.[13] Notably, the optical rotation of synthetic **78**, $[\alpha]^{20}_D$ = +33 (*c* 0.2, $CHCl_3$), was the same sign and essentially the same magnitude as that reported $[\alpha]^{20}_D$ = +28 (*c* 0.083,

$CHCl_3$),[13] thus establishing the absolute configuration of auripyrone A as that shown for **78**.

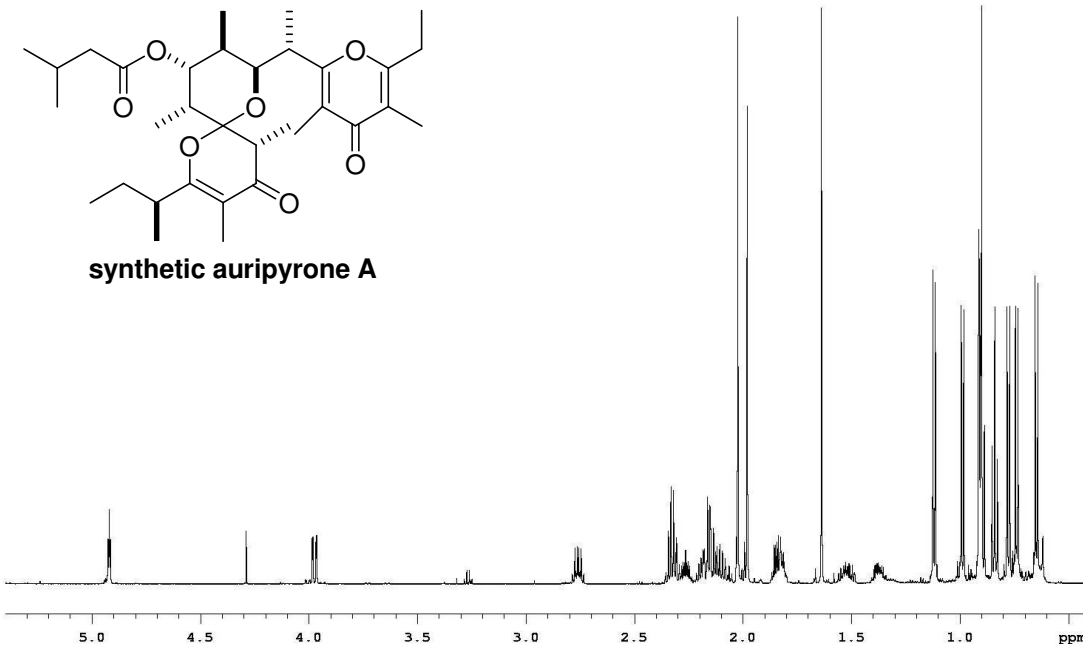


Figure 4.19: *600 MHz ^{1}H NMR spectrum of synthetic auripyrone A in C_6D_6*

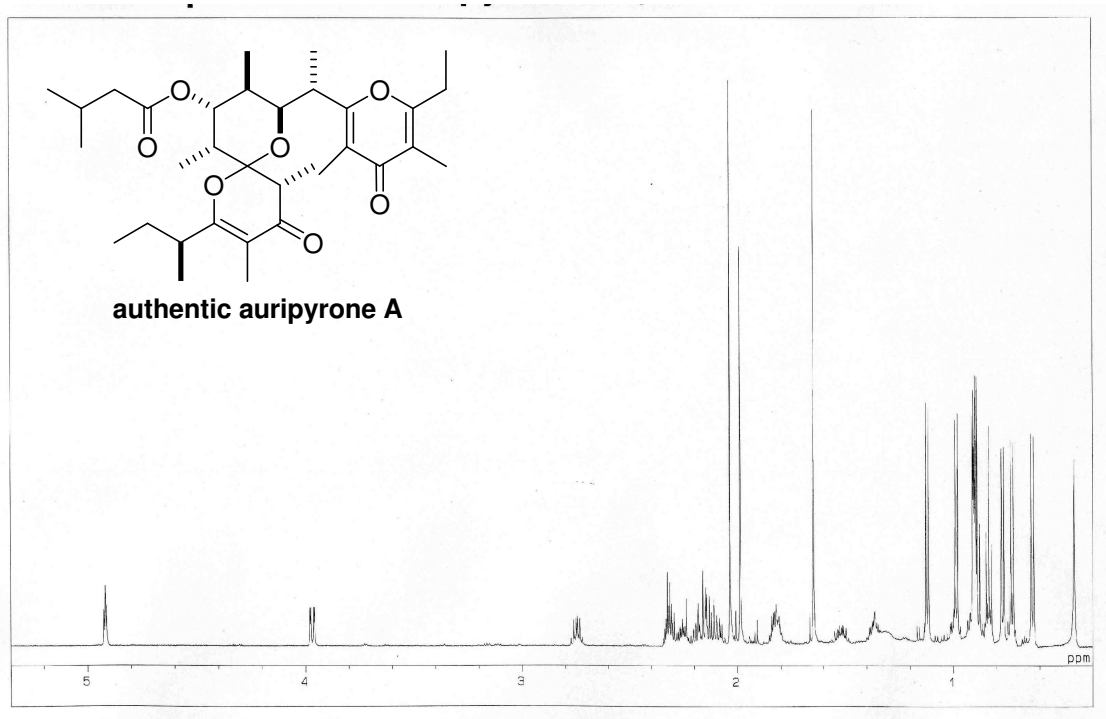


Figure 4.20: *600 MHz ^{1}H NMR spectrum of authentic auripyrone A in C_6D_6*

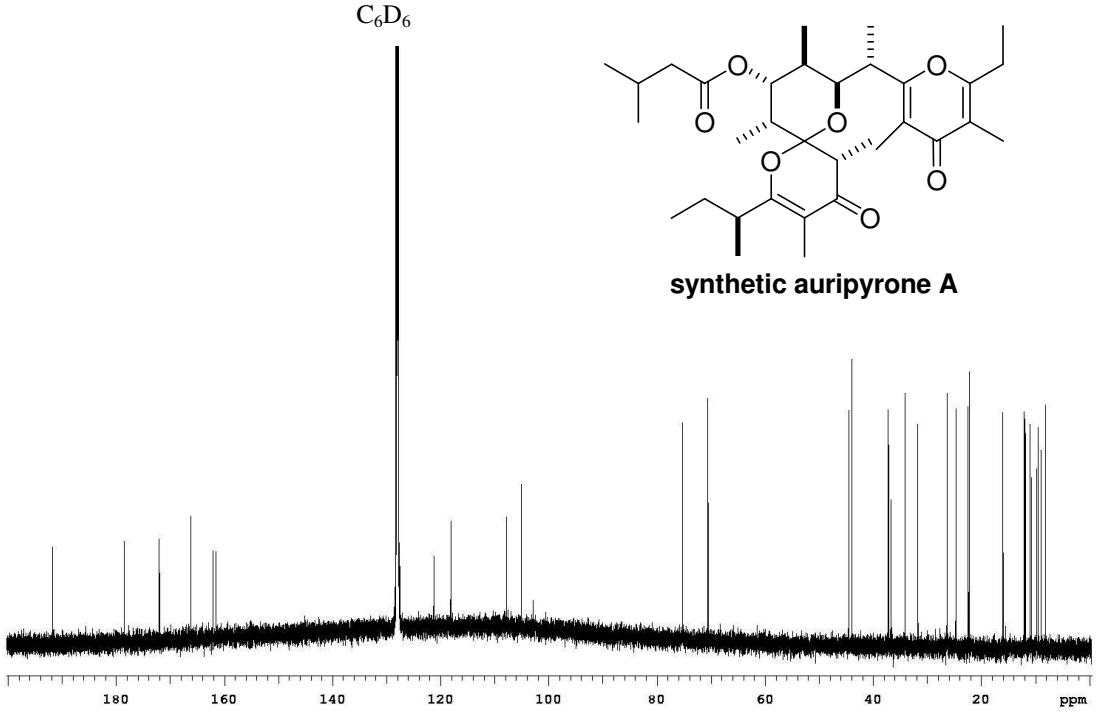


Figure 4.21: *151 MHz ^{13}C NMR spectrum of synthetic auripyrone A in C_6D_6*

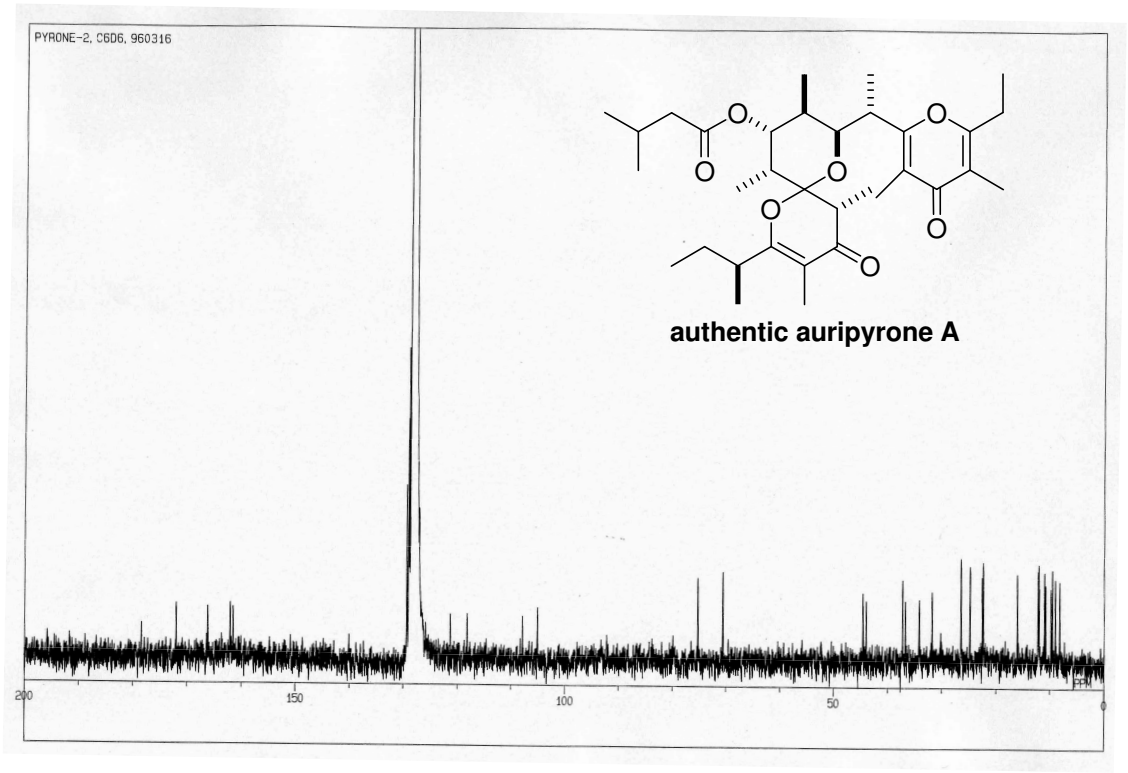


Figure 4.22: *151 MHz ^{13}C NMR spectrum of authentic auripyrone A in C_6D_6*

The ^{1}H NMR and ^{13}C NMR spectra for synthetic and authentic[ξ] auripyrone A are presented in Figures 4.19-4.22 and clearly show that the two compounds are identical. Much of the ^{1}H NMR spectrum for synthetic **78** is consistent with that discussed for compound **274** (Section 4.8.4, Figure 4.17), but some elements are noteworthy, namely the signals due to the γ-pyrone moiety. The vinyl methyl groups resonate as singlets at δ 2.03 and δ 1.98, while the diastereotopic allylic methylene protons appear as doublets of quartets at δ 2.31 (J = 15.0, 7.5 Hz) and δ 2.10 (J = 15.0, 7.5 Hz) and show coupling to the methyl triplet at δ 0.90 (J = 7.5 Hz). The C8 methyl methine now resonates as a doublet of quartets at δ 2.76 (J = 10.2, 7.2 Hz) which is significantly downfield of the resonance observed for C8 in compound **274** (Section 4.8.4, Figure 4.17).

Intriguingly, the spiroacetal dihydropyrone vinyl methyl in auripyrone A (**78**) resonates at δ 1.65, which is significantly upfield of its position in the ^{1}H NMR spectra of the other spiroacetal dihydropyrone containing compounds **255**, **274**, **278** and **279**, in which this group resonated at between δ 1.84-1.89. This can be explained by considering the structure depicted for auripyrone A in Figure 4.23. A full conformational search on the auripyrone A structure was conducted using Spartan® at the AM1 level. This calculation identified a low energy conformer which was subsequently submitted for geometry optimisation at the HF 6-31G(d) level, which returned the structure depicted below. The calculation predicts that the γ-pyrone moiety and the dihydropyrone ring of auripyrone A coordinate in a π-stacking arrangement, which potentially shields the dihydropyrone vinyl methyl, causing the observed upfield shift. Unfortunately, crystals of auripyrone A (**78**) suitable for X-ray crystallographic analysis, which hopefully would have supported the low energy conformer and the predicted π-stacking arrangement, were unable to be grown.

[ξ] Copies of the original ^{1}H NMR and ^{13}C NMR spectra recorded for auripyrone A (**78**) and B (**186**), including expansions (se Appendix B), were kindly provided by Prof. K. Suenaga and Prof. H. Kigoshi.

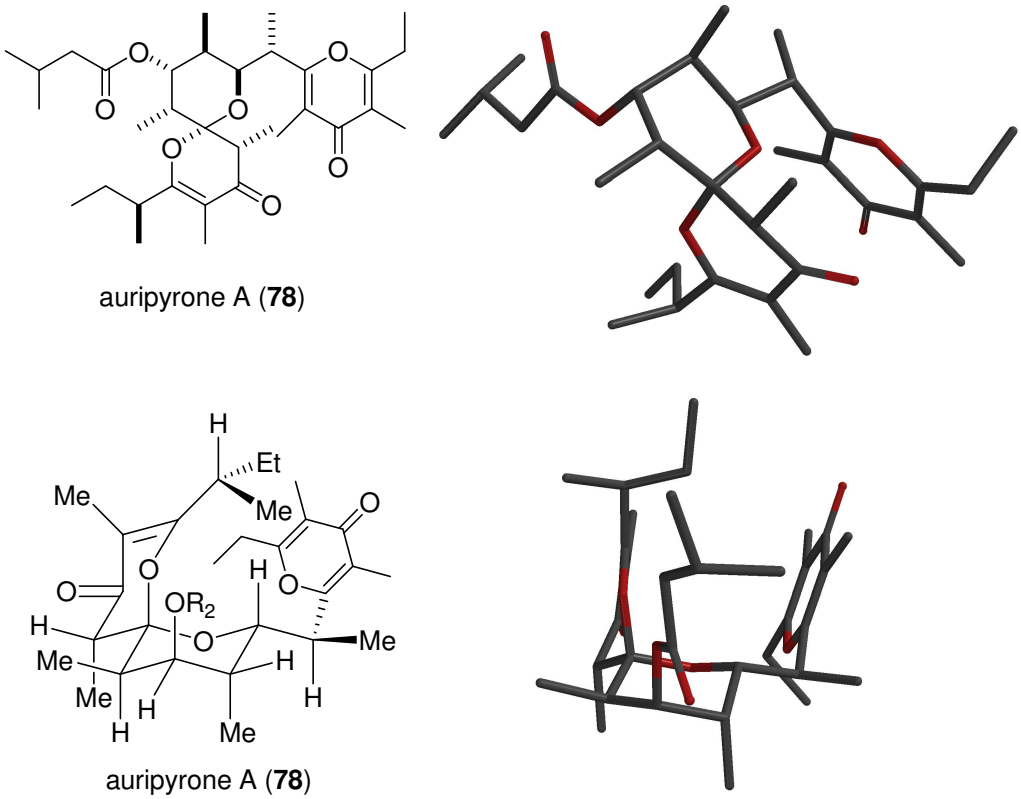


Figure 4.23: *Low energy structure of auripyrone A (**78**) as calculated on Spartan® at HF 6-31G.*

4.9 Conclusion

The work detailed above represents the first total synthesis of the cytotoxic marine polypropionate natural product auripyrone A and thus establishes the absolute configuration as that depicted for compound **78**. The strategy afforded synthetic auripyrone A (**78**) as a single isomer in just 16 linear steps from dipropionate **53** and 8.0% overall yield. Key reactions in the sequence involved double stereodifferentiating lithium aldol reactions of complex aldehydes **255** and **257** with ethyl ketones **276** and **200**, respectively, a high yielding cascade cyclisation/dehydration reaction to form the spiroacetal dihydropyrone core of auripyrone A and a novel γ-pyrone forming reaction that ultimately forged the natural product.

Significantly, the total synthesis presented in the preceding sections has demonstrated that complex, polyoxygenated natural products can be constructed with minimal protecting group manipulation. Indeed, no protecting groups were introduced within the linear sequence. In general, protecting groups are crucial to organic synthesis, often providing critical control elements. However, protecting group manipulations ultimately increase the number of synthetic operations within a sequence and can prove detrimental to a synthesis when unexpected stability (or instability) is encountered. This synthesis has shown that inherent structural functionality (if available) can serve admirably in a protecting group capacity.

4.10 References

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Chapter Five

Experimental Procedures for Chapters Two to Four

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Experimental Procedures for Chapters Two to Four

5.1 General Procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Mercury, Varian Gemini or Varian Inova spectrometer operating at 200, 300 or 600 MHz for proton and 50.3, 75.5 or 151 MHz for carbon nuclei, respectively. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in either deuterochloroform ($CDCl_3$) or dueterobenzene (C_6D_6) at ambient temperature, unless otherwise specified. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as internal reference, whilst those spectra recorded in C_6D_6, the peak due to residual C_6H_6 (δ 7.15) was used as internal reference. ^{1}H NMR spectral data were recorded as follows: chemical shift (δ), relative integral, multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, br = broad), coupling constant(s) *J* (Hz), assignment. For proton-decoupled ^{13}C NMR spectra recorded in $CDCl_3$, the central peak (δ 77.0) of the $CDCl_3$ triplet was used as the internal reference, whilst those recorded in C_6D_6, the central peak (δ 128.0) of the C_6D_6 triplet was used as internal reference and all data are given as chemical shift (δ). The assignments observed in various NMR spectra were confirmed by conducting homonuclear (^{1}H-^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (nOe) spectroscopy (NOESY), attached proton test (APT), heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HETCOR or HMQC) and long-range heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HMBC) experiments.

Optical rotations were recorded on a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20 °C, using the spectroscopic grade solvent specified and

at the concentration (*c*, g/100 mL) indicated. The measurements were carried out in a cell with a 1 dm path length

Infrared 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 (ν_{max}/cm^{-1}). 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.

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

Low and/or high resolution mass spectra were recorded on either a Bruker BioApex II 47e FTMS fitted with an Analytica electrospray source (EI or ESI) or Kartos 'Concept' high resolution double focussing mass spectrometer (EI or LSI). Mass spectral data are presented as follows: molecular formula, molecular ion ($[M]^+$, $[M+H]^+$ or $[M+Na]^+$), calculated mass and accurate mass; mass to charge ratio (m/z), intensity relative to base peak.

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 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. Silica gel was buffered by spinning 100 g of silica gel 60 (mesh size 0.040-0.063 mm) with 10 mL of pH 7 phosphate buffer on a rotary evaporator overnight at atmospheric pressure.

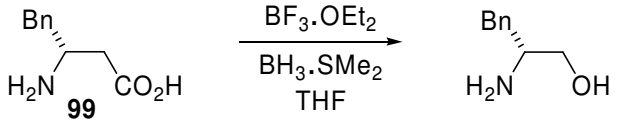
Many starting materials and reagents were available from the Sigma-Aldrich Chemical Company and were used as supplied, or dried and distilled using standard

procedures.[1] Triethylamine (Et_3N), dimethylethylamine (Me_2NEt) and pyridine were distilled from calcium hydride under an atmosphere of nitrogen prior to use and commercially available aldehydes, ketones and acid chlorides were distilled from calcium chloride under an atmosphere of nitrogen prior to use. Purchased organolithium reagents were freshly standardised by titration prior to use. Inorganic materials were used as received or purified according to standard procedures. All reactions were performed under an atmosphere of nitrogen or argon unless otherwise specified, in flame dried apparatus. Anhydrous reagents were handled under nitrogen using standard techniques.

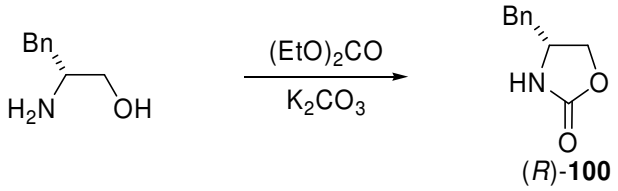
Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried using sodium metal wire and then distilled, as required, from sodium-benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under nitrogen as required. All other solvents required for use in reactions/extractions/chromatography were distilled prior to use.

Room temperature (rt) varied between 20-25 °C.

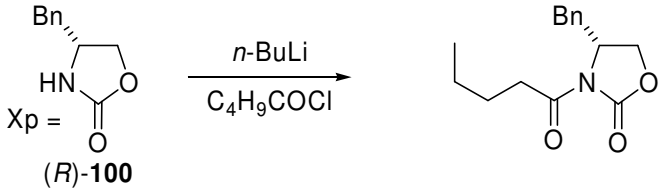
5.2 Experimental Procedures for Chapter Two



(*R*)-Phenylalanol.[2] (*R*)-Phenylalanol was synthesized according to the procedure of Evans and Gage.[2] To a slurry of (*R*)-phenylalanine **99** (10.0 g, 60.6 mmol) in THF (30 mL) was added $BF_3.OEt_2$ (7.67 mL, 60.6 mmol) dropwise over several minutes, and the resulting solution was heated under reflux for 2 hours. $BH_3.SMe_2$ (6.60 mL, 69.7 mmol) was then added carefully to the vigorously refluxing mixture over several minutes and the solution was then maintained at reflux for 6 hours. Once cool the mixture was treated with slow addition of a 1:1 THF/water solution (7.6 mL) followed by a 5 M solution of NaOH (45 mL) and the resulting two-phase mixture was heated at reflux for 12 hours. Upon cooling to ambient temperature the slurry was filtered and the solids were washed with THF (2 x 10 mL). The filtrate was concentrated *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (1 x 50 mL, 3 x 30 mL), the organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid. Recrystallisation from EtOAc gave the (*R*)-phenylalanol as white needles (7.0 g, 76%). **m.p.** 87-89 °C (lit. 88.5-91 °C)[2]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.20 (5H, m, Ar*H*), 3.65 (1H, dd, 10.8, 3,6 Hz, $CHCH_AH_BOH$), 3.42 (1H, dd, 10.8, 7.2 Hz, $CHCH_AH_BOH$), 3.17-3.09 (1H, m, CH_2CHNH_2), 2.81 (1H, dd, 13.5, 5.4 Hz, $CHCH_AH_BPh$), 2.64 (3H, br s, NH_2, O*H*), 2.54 (1H, dd, 13.5, 8.7 Hz, $CHCH_AH_BPh$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.6, 129.1, 128.5, 126.3, 65.8, 54.1, 40.4.



(4*R*)-4-(Phenylmethyl)-2-oxazolidinone [(*R*)-100].[2] (4*R*)-4-(Phenylmethyl)-2-oxazolidinone [(*R*)-100]was synthesized according to the procedure of Evans and Gage.[2] To round bottom flask fitted with a Vigreux column and a distillation head was added (*R*)-phenylalanol (6.8 g, 45.0 mmol), anhydrous K_2CO_3 (622 mg, 4.50 mmol) and diethyl carbonate (10.9 mL, 90.0 mmol). The mixture was lowered into an oil bath preheated to 135 °C and stirred until dissolution was achieved. The distillation receiver was cooled in an ice bath and ca. 5 mL of ethanol was collected from the reaction over several hours. The resulting yellow solution was cooled, diluted with CH_2Cl_2 (35 mL) and washed with H_2O (35 mL) and the organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to give a crystalline solid. The crude product was taken up in a hot 2:1 EtOAc-hexane solution and allowed to crystallise to give the oxazolidinone (*R*)-**100** (6.89 g, 86%) as white needles. **m.p.** 84-86 °C (lit. 84.5-86.5 °C)[2]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.17 (5H, m, Ar*H*), 5.18 (1H, br s, N*H*), 4.48 (1H, dd, 8.7, 7.8 Hz, CHCH_AH$_B$O), 4.18-4.04 (2H, m, CHCH$_A$$H_BO, CH_2$C*H*NH), 2.89-2.86 (2H, m, CHCH_2Ph); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.8, 136.0, 129.1, 129.0, 127.3, 69.7, 53.8, 41.6.

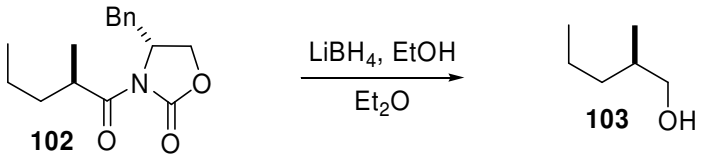


(4*R*)-3-(1-oxopentyl)-4-phenylmethyl-2-oxazolidinone. *N*-acylation was performed according to the procedure of Evans and Gage.[2] To a solution of the oxazolidinone (*R*)-**100** (10.0 g, 56.4 mmol) in dry THF (100 mL) at –78 °C was added *n*-BuLi (36.0 mL of a 1.6 M solution in hexanes, 57.5 mmol). The resulting yellow solution was treated immediately with valeryl chloride (7.36 mL, 62.1 mmol) and the mixture stirred at –78 °C for 30 minutes The reaction mixture was warmed to room

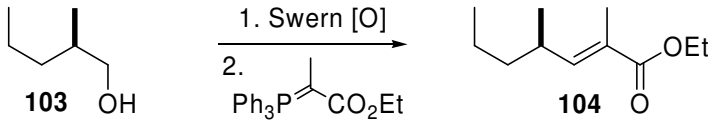
temperature over 30 minutes and stirred for an additional 30 minutes The reaction was quenched at room temperature by the slow addition of saturated aqueous NH_4Cl (100 mL) and the volatiles were removed *in vacuo.* The resulting slurry was extracted with CH_2Cl_2 (3 x 100 mL) with the combined organic extracts then washed with a 1 M solution of NaOH (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give *N*-valeryloxazolidinone (13.0 g, 88%) as a clear oil. ^1H and ^{13}C NMR indicated that the crude product comprised only one compound and thus purification was not required. **^{1}H NMR** (300 MHz, $CDCl_3$) 7.36-7.20 (5H, m, Ar*H*), 4.71-4.63 (1H, m, $CH_2CH(CH_2)N$), 4.23-4.15 (2H, m, $CHCH_AH_BO$), 3.32-3.27 (1H, dd, 13.2, 3.3 Hz, $CHCH_AH_BAr$), 3.04-2.84 (2H, m, $C(=O)CH_2CH_2$), 2.80-2.72 (1H, dd, 13.5, 9.6 Hz, $CHCH_AH_BAr$), 1.73-1.60 (2H, m, $CH_2CH_2CH_2$), 1.47-1.35 (2H, m, $CH_2CH_2CH_3$), 0.95 (3H, t, 7.2 Hz, CH_2CH_3).

(4*R*)-3-(1-oxo-2-methylpentyl)-4-phenylmethyl-2-oxazolidinone (102). To a solution of diisopropylamine (5.4 mL, 38.3 mmol) in THF (100 mL) at –78 °C was added *n*-BuLi (24 mL of a 1.6 M solution in hexanes, 38.3 mmol). The resulting mixture was warmed to 0 °C, stirred for 30 minutes, and then re-cooled to –78 °C. A solution of *N*-valeryloxazolidinone (5.00 g, 19.2 mmol) in THF (30 mL) was added *via* cannula and the resulting mixture stirred at –78 °C for 45 minutes. Methyl iodide (3.6 mL, 57.5 mmol) was added and the reaction mixture was stirred at –78 °C for 30 minutes, then at –30 °C for 2 hours and then allowed to sit in the freezer overnight. The reaction mixture was quenched at –5 °C by the slow addition of saturated aqueous NH_4Cl (70 mL), then the volatiles were removed *in vacuo*. The resulting slurry was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The product was purified by column chromatography (CH_2Cl_2) to give the oxazolidinone **102** (3.42 g, 65%) as a clear oil. $\mathbf{R}_f$ = 0.29 (CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$) 7.38-7.19 (5H, m, Ar*H*), 4.73-4.61 (1H, m, $CH_2CH(CH_2)N$), 4.20-4.16 (2H, m, $CHCH_AH_BO$), 3.81-3.64 (1H, m,

C(=O)C*H*(CH_3)CH_2), 3.31-3.23 (1H, dd, 13.4, 3.4 Hz, CHC$H_A$$H_B$Ar), 2.82-2.71 (1H, dd, 13.4, 9.6 Hz, CHC$H_A$$H_B$Ar), 1.79-1.57 (2H, m, CHC$H_2$$CH_2$), 1.44-1.31 (2H, m, CH_2C$H_2$$CH_3$), 1.22 (3H, d, 6.8 Hz, CH(CH_3)CH_2), 0.91 (3H, m, CH_2CH_3).

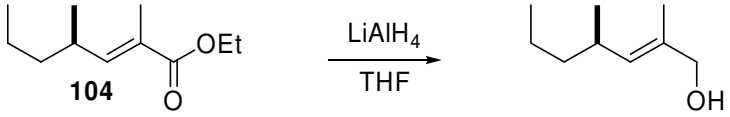


(2*R*)-2-methylpentanol (103). Auxiliary cleavage was peformed according to the procedure of Penning *et al*.[3] To a solution of oxazolidinone **102** (3.27 g, 11.9 mmol) in Et_2O (240 mL) at –10 °C was added anhydrous EtOH (1.66 mL, 28.5 mmol) and $LiBH_4$ (14.3 mL of a 2.0 M solution in THF, 28.5 mmol). The reaction mixture was stirred at -10 °C for 1.5 hours and then quenched by the addition of a 1 M solution of NaOH (60 mL). The resulting cloudy solution was stirred for 15 minutes at 0 °C, then poured into brine (200 mL). The mixture was extracted with Et_2O (4 x 100 mL), then the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/CH_2Cl_2) to give alcohol **103** (1.03 g, 85%) as a clear liquid. $\mathbf{R}_f$ = 0.33 (30% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) 3.52-3.36 (2H, m, CHC$H_A$$H_B$OH), 1.64-1.58 (2H, br m, CH_2CH_2CH(CH_3)), 1.41-1.24 (2H, br m, CH_3C$H_2$$CH_2$),1.11-1.03 (1H, m, CH_2C*H*(CH_3)CH_2), 0.90 (3H, d, 6.6 Hz, CH(CH_3)CH_2); **^{13}C NMR** (75.5 MHz, $CDCl_3$) 68.4, 35.4, 35.4, 20.0, 16.5, 14.3.

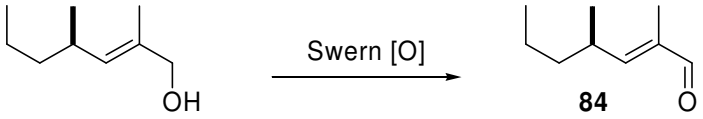


Ethyl (2*E*,4*R*)-2,4-dimethylheptenoate (104). Olefination was performed according to the procedure of Zelle *et al*.[4] To a solution of DMSO (3.26 mL, 46 mmol) in CH_2Cl_2 (80 mL) at –78 °C was added oxalyl chloride (11.5 mL of a 2 M solution in CH_2Cl_2, 23 mmol) over 10 minutes After 30 minutes, a solution of alcohol **103** (1.57 g, 15 mmol) in CH_2Cl_2 (50 mL) was added *via* cannula and the resulting mixture stirred at –78 °C for 45 minutes. Triethylamine (12.8 mL, 92 mmol) was added over

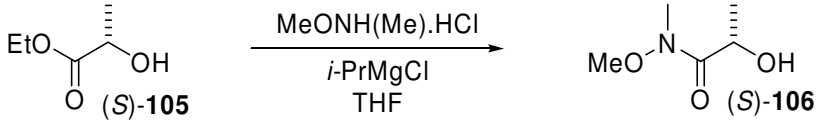
10 minutes and the resulting white solution was stirred at –78 °C for 30 minutes before being warmed to room temperature slowly. A solution of (carbethoxymethylene)triphenylphosphorane (6.66g, 18 mmol) in CH_2Cl_2 (30 mL) was added and the resulting solution was heated under reflux (60 °C) for 6 days. The solvent was removed *in vacuo* and the residue triturated with hexanes, filtered to remove the insoluble triphenylphosphine oxide and concentrated *in vacuo*. The resulting yellow liquid was purified by column chromatography (50% CH_2Cl_2/hexanes) to afford the geometrically pure *E*-ester **104** (2.43g, 86%) as a clear oil. $\mathbf{R}_f$ = 0.48 (50% CH_2Cl_2/hexanes); $\mathbf{[\alpha]^{20}_D}$ = –4.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.52 (1H, dd, 9.9, 1.2 Hz, C*H*=C(CH_3)), 4.18 (2H, q, 7.1 Hz, OC*H*$_2$CH$_3$), 2.54-2.33 (1H, m, $CH_2CH(CH_3)$), 1.82 (3H, *d*, 1.2 Hz, CH=C(C*H*$_3$)), 1.39-1.21 (4H, m, $CH_3CH_2CH_2$), 1.29 (3H, t, 7.1 Hz, OCH_2CH_3), 0.98 (3H, d, 6.6 Hz, $CH_2CH(CH_3)$), 0.87 (3H, t, 6.8 Hz, $CH_3CH_2CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 168.5, 148.1, 126.2, 60.4, 39.1, 33.0, 20.6, 20.0, 14.3, 14.1, 12.5.



(2*E*,4*R*)-2,4-dimethylheptenol. To a solution of $LiAlH_4$ (104 mg, 2.8 mmol) in THF (4.1 mL) cooled to 0 °C was added a solution of ester **104** (460 mg, 2.5 mmol) in THF (4.1 mL) *via* cannula. The reaction mixture was warmed to room temperature and stirred for 1.5 hours before being cooled to 0 °C and quenched *via* the dropwise addition of H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL) and H_2O (0.3 mL). The mixture was treated with $MgSO_4$, filtered (Et_2O) and concentrated *in vacuo* to give the crude alcohol in quantitative yield. $\mathbf{[\alpha]^{20}_D}$ = –14.6 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.14 (1H, dd, 9.5, 1.4 Hz, C*H*=C(CH_3)), 3.96 (2H, d, 0.9 Hz, C*H*$_2$OH), 2.41-2.31 (1H, m, $CH_2CH(CH_3)$), 1.85-1.76 (1H, m, O*H*), 1.64 (3H, d, 1.4 Hz, CH=C(C*H*$_3$)), 1.29-1.15 (4H, m, $CH_3CH_2CH_2$), 0.90 (3H, d, 6.9 Hz, $CH_2CH(CH_3)$), 0.85 (3H, t, 6.8 Hz, $CH_3CH_2CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 133.1, 132.9, 68.9, 39.8, 31.7, 20.9, 20.5, 14.1, 13.7.

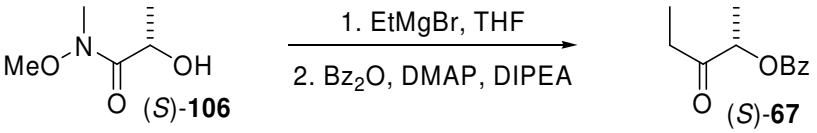


(2*E*,4*R*)-2,4-dimethylheptenal (84).[4] Oxidation was performed according to the procedure of Swern and Mancuso.[5] To a solution of DMSO (784 μL, 11 mmol) in CH_2Cl_2 (21 mL) at –78 °C was added oxalyl chloride (2.64 mL of a 2 M solution in CH_2Cl_2, 5.3 mmol) over 2 minutes. After 30 minutes, a solution of the crude alcohol (500 mg, 3.5 mmol) in CH_2Cl_2 (5 mL) was added *via* cannula and the resulting mixture stirred at –78 °C for 45 minutes. Triethylamine (2.94 mL, 21 mmol) was added over 2 minutes and the resulting white solution was stirred at –78 °C for 30 minutes then at 0 °C for 1 hour and finally at room temperature for 30 minutes. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (15 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) gave the volatile aldehyde **84** (424 mg, 86% from ester **104**) as a clear oil. $\mathbf{R}_f$ = 0.39 (CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.38 (1H, s, C*H*O), 6.25 (1H, dd, 9.9, 1.2 Hz, C*H*=C(CH_3)), 2.77-2.63 (1H, m, $CH_2CH(CH_3)$), 1.74 (3H, d, 1.2 Hz, CH=C(C*H*$_3$)), 1.52-1.21 (4H, m, $CH_3CH_2CH_2$), 1.05 (3H, d, 6.6 Hz, $CH_2CH(CH_3)$), 0.89 (3H, t, 7.1 Hz, $CH_3CH_2CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.6, 160.7, 137.9, 38.9, 33.3, 20.5, 19.8, 14.1, 9.3.

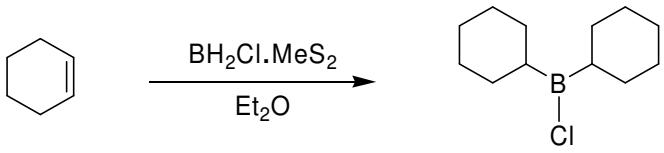


(2*S*)-2-Hydroxy-*N*-methoxy-*N*-methylpropionamide [(*S*)-106].[6,7] The amide was synthesized according to the procedure of Paterson *et al*.[6,7] To a mixture of ethyl (*S*)-lactate [(*S*)-**105**] (3.84 mL, 33.9 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (8.26 g, 84.7 mmol) in THF (50 mL) and Et_2O (50mL) at –20 °C was added ^{i}PrMgCl (85 mL of a 2 M solution in THF, 169 mmol) dropwise over 30 minutes. The reaction mixture was stirred at –20 C for 30 minutes and then at 0 °C

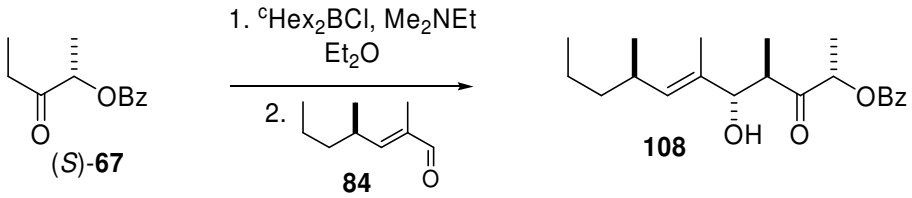
for a further 30 minutes before saturated aqueous NH_4Cl (300 mL) was added cautiously. The mixture was extracted with Et_2O (4 x 100 mL) and CH_2Cl_2 (4 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by distillation to give the amide (*S*)-**106** (4.45g, 99%) as a colourless oil. **b.p.** 64-65 °C @ 0.5 Torr (lit. 63-65 °C @ 0.5 Torr); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.42 (1H, qn, 6.6 Hz, C*H*(CH_3)OH), 3.65 (3H, s, OC*H*$_3$), 3.42 (1H, d, 6.6 Hz, O*H*), 3.17 (3H, s, NC*H*$_3$), 1.29 (3H, d, 6.6 Hz, CH(C*H*$_3$)OH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.5, 64.8, 61.2, 32.3, 20.8.



(2*S*)-2-Benzoyloxypentan-3-one (*S*)-67. [6,7] The ketone was synthesized according to the procedure of Paterson *et al*.[6,7] To a solution of the amide (*S*)-**106** (1.51 g, 11.3 mmol) in THF (45 mL) at 0 °C was added EtMgBr (36 mL of a 1 M solution in THF, 36.3 mmol) and the reaction mixture was allowed to warm to room temperature. After 1 hour, saturated aqueous NH_4Cl (60 mL) was carefully added and the mixture was extracted with Et_2O (30 mL) and CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to ca. 75 mL. To this solution was added benzoic anhydride (3.85 g, 17.0 mmol), DMAP (150 mg, 1.25 mmol) and ^{i}Pr$_2$NEt (3.8 mL, 27.7 mmol) and the resulting solution stirred at room temperature for 14 hours. Excess Bz_2O was removed by addition of ethylenediamine (842 μL, 12.6 mmol). H_2O (60 mL) was added and the mixture was extracted with Et_2O (4 x 30 mL), then the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude oil by column chromatography (20% EtOAc/hexanes) afforded the ketone (*S*)-**67** (1.64 g, 70%) as a colourless oil. **R$_f$** = 0.38 (20% EtOAc/hexanes); **$[\alpha]^{20}_D$** = +21.9 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (2H, dd, 6.9, 1.2 Hz, Ar*H*), 7.59 (1H, tt, 6.9, 1.2 Hz, Ar*H*), 7.46 (2H, t, 6.9 Hz, Ar*H*), 5.35 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 2.66 (1H, dq, 18.3, 7.2 Hz, $CH_3CH_AH_B$) 2.52 (1H, dq, 18.3, 7.2 Hz, $CH_3CH_AH_B$), 1.53 (3H, d, 7.0 Hz, BzOCH(C*H*$_3$)), 1.09 (3H, t, 7.2 Hz, C*H*$_3$CH$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.4, 165.8, 133.3, 129.7, 129.4, 128.4, 75.1, 31.4, 16.4, 7.1.

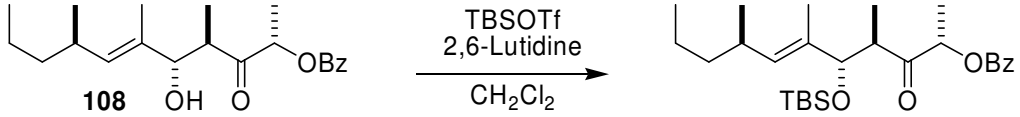


Dicyclohexylboron chloride.[8] Dicyclohexylboron chloride was synthesized according to the procedure of Brown *et al*.[8] To a solution of cyclohexene (21 mL, 207 mmol) in Et_2O (100 mL) at 0 °C was added monochloroborane-methyl sulfide complex (9.82 mL, 94.2 mmol) and the resulting mixture was warmed to ambient temperature and stirred for 2 hours. The solvent was removed in vacuo and the residue was distilled under reduced pressure to give pure dicyclohexylboron chloride (15.9 g, 80%) as a clear liquid. **b.p.** 76-86 °C @ 0.1-0.2 mm Hg.



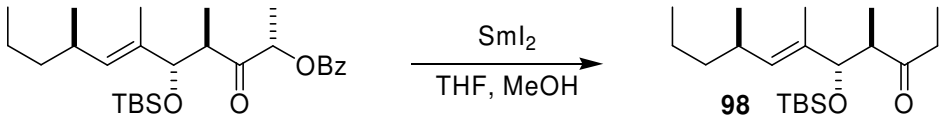
(2*S*,4*R*,5*S*,6*E*,8*R*)-2-benzoyloxy-4,6,8-trimethyl-5-hydroxyundec-6-en-3-one (108). The aldol addition was performed according to the procedure of Paterson *et al*.[6,7] To a solution of dicyclohexylboron chloride (2.2 mL, 10 mmol) in Et_2O (14 mL) at –78 °C was added Me_2NEt (1.3 mL, 12 mmol) followed by ketone (*S*)-**67** (1.38 g, 6.7 mmol) in Et_2O (14 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hours, before being re-cooled to –78 °C. The aldehyde **84** (493 mg, 3.5 mmol) in Et_2O (2+2+1 mL) was added *via* cannula and stirring continued at –78 °C for 2 hours then at –23 °C for 14 hours. The reaction was quenched at 0 °C with the addition of MeOH (14 mL), pH 7 buffer solution (14 mL) and 30% aqueous H_2O_2 (14 mL) and stirring maintained for 1 hour at room temperature. The mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give the adduct **108** (483 mg, 60%, >95% d.s.) as a white solid. **m.p.** 54-56 °C; $\mathbf{R}_f$ = 0.42 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +13.7 (*c* 2.3, $CHCl_3$); **IR** (FT, film) 3514, 1721, 1453, 1317, 1270, 1116, 1027, 997, 713 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11-8.07 (2H, m, Ar*H*), 7.60-7.55 (1H, m, Ar*H*), 7.49-7.42

(2H, m, Ar*H*), 5.45 (1H, q, 7.2 Hz, C*H*(CH_3)OBz), 5.19 (1H, d, 9.6 Hz, C*H*=C(CH_3)), 4.17 (1H, d, 7.5 Hz, C*H*OH), 3.04 (1H, dq, 9.6, 7.1 Hz, CH(OH)C*H*CH_3), 2.40-2.35 (1H, m, CH_2C*H*(CH_3)), 1.99 (1H, br s, O*H*), 1.60 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.57 (3H, d, 7.2Hz, CH(CH_3)OBz), 1.29-1.21 (4H, m, $CH_3CH_2CH_2$), 1.03 (3H, d, 6.9 Hz, CH(OH)CHCH_3), 0.90 (3H, d, 6.3 Hz, CH_2CH(CH_3)), 0.86 (3H, t, 6.6 Hz, C$H_3CH_2CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.1, 165.8, 136.6, 133.2, 132.6, 129.8, 129.6, 128.4, 80.2, 75.1, 45.6, 39.5, 31.8, 20.8, 20.5, 15.5, 14.5, 14.2, 10.8; **HRESIMS** calculated for $C_{21}H_{30}O_4Na^+$ $[M+Na]^+$: 369.2042; found 369.2034.

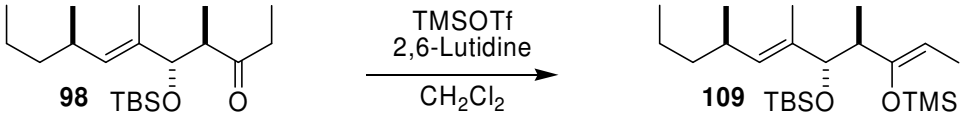


(2*S*,4*R*,5*S*,6*E*,8*R*)-2-benzoyloxy-5-*tert*-butyldimethylsilyloxy-4,6,8-trimethylundec-6-en-3-one. To a solution of the alcohol **108** (450 mg, 1.3 mmol) in CH_2Cl_2 (13 mL) at –78 °C was added 2,6-lutidine (303 μL, 2.6 mmol) followed by TBSOTf (450 μL, 2.0 mmol). After stirring for 30 minutes at –78 °C the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2) to give the protected adduct (602 mg, 94%) as a colourless oil. $\mathbf{R}_f$ = 0.73 (CH_2Cl_2); $[\alpha]^{20}_D$ = +2.7 (*c* 1.6, $CHCl_3$); **IR** (FT, film) 1724, 1268, 1116, 1070, 837, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar*H*), 7.56 (1H, tt, 7.4, 1.6 Hz, Ar*H*), 7.46-7.41 (2H, m, Ar*H*), 5.44 (1H, q, 7.2 Hz, C*H*(CH_3)OBz), 5.14 (1H, d, 9.3 Hz, C*H*=C(CH_3)), 4.20 (1H, d, 9.9 Hz, C*H*OTBS), 2.99 (1H, dq, 9.9, 7.0 Hz, CH(OTBS)C*H*CH_3), 2.42-2.32 (1H, m, CH_2C*H*(CH_3)), 1.56 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.54 (3H, d, 6.9Hz, CH(CH_3)OBz), 1.31-1.22 (4H, m, $CH_3CH_2CH_2$), 0.93 (3H, d, 6.9 Hz, CH(OTBS)CHCH_3), 0.89 (3H, d, 6.6 Hz, CH_2CH(CH_3)), 0.87 (3H, t, 6.6 Hz, C$H_3CH_2CH_2$), 0.82 (9H, s, SiC(CH_3)$_3$), -0.03 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.4, 165.7, 136.3, 133.1, 132.8, 129.8, 128.3, 81.3, 75.3, 46.3, 39.4, 31.6, 25.8, 20.8, 20.5, 18.0, 15.2, 14.6, 14.1, 10.5, –4.8, –5.1. (1 coincident

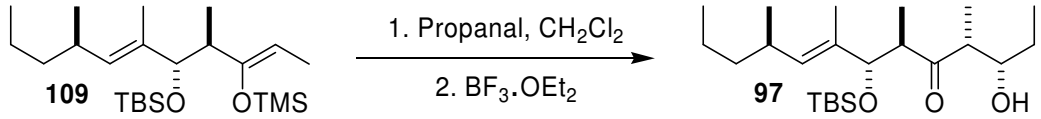
vinyl carbon); **HRESIMS** calculated for $C_{27}H_{44}O_4SiNa^+$ $[M+Na]^+$: 483.2907; found 483.2925.



(4*R*,5*S*,6*E*,8*R*)-5-*tert*-butyldimethylsilyloxy-4,6,8-trimethylundec-6-en-3-one (98). Reductive cleavage was performed according to the procedure of Paterson *et al*.[7] To a solution of the protected adduct (567 mg, 1.2 mmol) in THF (15 mL) and MeOH (7.4 mL) at 0 °C was added SmI_2 (~50 mL of a 0.1 M solution in THF, ~4.9 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0 °C with the addition of saturated aqueous K_2CO_3 (75 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% CH_2Cl_2/hexanes) afforded the ethyl ketone **98** (400 mg, 95%) as a colourless oil. $\mathbf{R}_f$ = 0.33 (30%CH_2Cl_2/hexanes); $\mathbf{[\alpha]^{20}_D}$ = –17.4 (*c* 1.9, $CHCl_3$); **IR** (FT, film) 1721, 1251, 1059, 837, 777 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.10 (1H, dd, 9.3, 1.2 Hz, C*H*=C(CH_3)), 4.03 (1H, d, 9.6 Hz, C*H*OTBS), 2.75 (1H, dq, 9.6, 6.9 Hz, CH(OTBS)C*H*CH_3), 2.56 (1H, dq, 18.6, 7.2 Hz, C(=O)C$H_A$$H_B$$CH_3$), 2.49 (1H, dq, 18.6, 7.2 Hz, C(=O)$CH_A$$H_B$$CH_3$), 2.41-2.31 (1H, m, CH_2C*H*(CH_3)), 1.54 (3H, d, 1.2 Hz, CH=C(C*H*$_3$)), 1.32-1.17 (4H, m, CH_3C*H*$_2$C*H*$_2$), 1.01 (3H, t, 7.2 Hz, C(=O)CH_2C*H*$_3$), 0.88 (3H, d, 6.9 Hz, CH_2CH(C*H*$_3$)), 0.86 (3H, t, 6.8 Hz, C*H*$_3$$CH_2$$CH_2$), 0.80 (9H, s, SiC(C*H*$_3$)$_3$), 0.75 (3H, d, 6.6 Hz, CH(OTBS)CHC*H*$_3$), –0.07 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 215.1, 135.9, 133.1, 82.3, 49.2, 39.5, 38.0, 31.7, 25.7, 20.9, 20.6, 18.0, 14.1, 13.9, 10.5, 7.2, –4.7, –5.5; **HRESIMS** calculated for $C_{20}H_{40}O_2SiNa^+$ $[M+Na]^+$: 363.2695; found 363.2692.

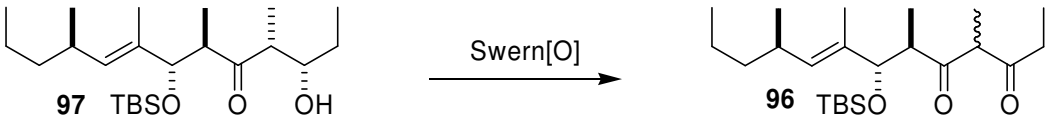


(2*Z*,4*R*,5*S*,6*E*,8*R*)-5-*tert*-butyldimethylsilyloxy-4,6,8-trimethyl-2-trimethylsilyloxyundec-2,6-diene (109). To a solution of the ethyl ketone **98** (250 mg, 0.73 mmol) in CH_2Cl_2 (6 mL) at –78 °C was added 2,6-lutidine (282 μL, 2.4 mmol) followed by TMSOTf (330 μL, 1.8 mmol). After stirring for 5 minutes at –78 °C the reaction mixture was warmed to room temperature and stirring continued for 14 hours. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (20 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (30% CH_2Cl_2/hexanes) to give the geometrically pure silylenol ether **109** (288 mg, 99%) as a colourless oil. $\mathbf{R}_f$ = 0.70 (30% CH_2Cl_2/hexanes); $[\alpha]^{20}_D$ = +8.4 (*c* 2.0, $CHCl_3$); **IR** (FT, film) 1677, 1461, 1253, 1197, 1069, 896, 838, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.99 (1H, d, 9.3 Hz, C*H*=C(CH_3)), 4.49 (1H, q, 6.7 Hz, C=C*H*(CH_3)), 3.84 (1H, d, 9.0 Hz, C*H*OTBS), 2.41-2.32 (1H, m, $CH_2CH(CH_3)$), 2.16 (1H, dq, 9.0, 7.2 Hz, CH(OTBS)C*H*CH_3), 1.54 (3H, d, 1.5 Hz, CH=C(C*H*$_3$)), 1.48 (3H, d, 6.7 Hz, C=CH(C*H*$_3$)), 1.35-1.19 (4H, m, $CH_3CH_2CH_2$), 0.88 (3H, d, 6.9 Hz, $CH_2CH(CH_3)$), 0.88 (3H, t, 6.9 Hz, $CH_3CH_2CH_2$), 0.83 (9H, s, SiC(C*H*$_3$)$_3$), 0.75 (3H, d, 6.9 Hz, CH(OTBS)CHC*H*$_3$), 0.21 (9H, s, Si(C*H*$_3$)$_3$), –0.02 (3H, s, SiC*H*$_3$), –0.05 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 153.1, 134.5, 134.2, 101.5, 80.7, 44.9, 39.7, 31.6, 25.8, 21.0, 20.6, 18.2, 15.7, 14.2, 11.2, 10.9, 1.0, –4.8, –5.3; **HRESIMS** calculated for $C_{23}H_{48}O_2Si_2Na^+$ $[M+Na]^+$: 435.3091; found 435.3097.



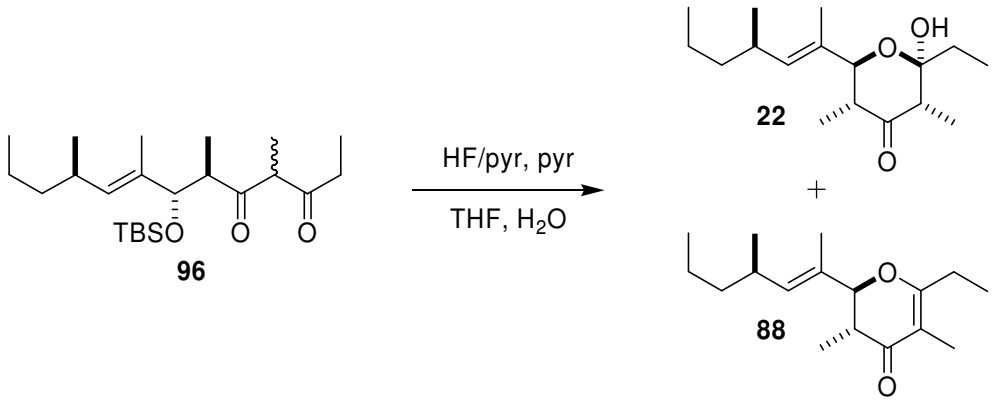
(3*S*,4*R*,6*R*,7*S*,8*E*,10*R*)-7-*tert*-butyldimethylsilyloxy-3-hydroxy-4,6,8,10-tetramethyltridec-8-en-5-one (97). Aldol addition was performed according to the procedure of Evans *et al*.[9] To a solution of silylenol ether **109** (227 mg, 0.55 mmol) and propanal (118 μL, 1.7 mmol) in CH_2Cl_2 (5.5 mL) at –78 °C was added BF_3•OEt_2

(105 μL, 0.83 mmol). The reaction mixture was stirred at –78 °C for 1.5 hours before being quenched with the addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (5% Et_2O/CH_2Cl_2) to give the adduct **97** (164 mg, 75%, 87% d.s.) as a colourless oil. $\mathbf{R}_f$ = 0.37 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +2.9 (*c* 2.1, $CHCl_3$); **IR** (FT, film) 3476, 1703, 1460, 1256, 1061, 837, 778 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.12 (1H, dd, 9.3, 1.2 Hz, C*H*=C(CH_3)), 4.15 (1H, d, 9.6 Hz, C*H*OTBS, 3.90-3.84 (1H, m, C*H*OH), 2.98 (1H, br s, O*H*), 2.96 (1H, dq, 9.8, 7.1 Hz, CH(OTBS)C*H*CH_3), 2.60 (1H, qd, 7.2, 2.6 Hz, C(=O)C*H*CH_3), 2.41-2.32 (1H, m, CH_2C*H*(CH_3)), 1.62-1.47 (1H, m, CHC$H_A$$H_B$$CH_3$), 1.56 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.44-1.32 (1H, m, CHC$H_A$$H_B$$CH_3$), 1.31-1.20 (4H, m, $CH_3C H_2CH_2$), 1.13 (3H, d, 7.2 Hz, C(=O)CHCH_3), 0.95 (3H, t, 7.5 Hz, $CHCH_2CH_3$), 0.88 (3H, d, 6.6 Hz, CH_2CH(CH_3)), 0.86 (3H, t, 6.9 Hz, $CH_3CH_2CH_2$), 0.81 (9H, s, SiC(CH_3)$_3$), 0.78 (3H, d, 6.9 Hz, CH(OTBS)CHCH_3), –0.03 (3H, s, SiCH_3), –0.04 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 218.5, 136.2, 132.8, 81.4, 72.5, 50.7, 48.1, 39.4, 31.7, 27.0, 25.7, 20.8, 20.5, 18.1, 14.7, 14.1, 10.6, 10.5, 8.0, –4.7, –5.0; **HRESIMS** calculated for $C_{23}H_{46}O_3SiNa^+$ $[M+Na]^+$: 421.3114; found 421.3115.



(6*R*,7*S*,8*E*,10*R*)-7-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyltridec-8-en-3,5-dione (96). Oxidation was performed according to Smith's modification of the Swern procedure.[10] To a solution of DMSO (64 μL, 0.90 mmol) in CH_2Cl_2 (1.3 mL) at –78 °C was added oxalyl chloride (226 μL of a 2 M solution in CH_2Cl_2, 0.46 mmol) dropwise. After 30 minutes, a solution of alcohol **97** (62.3 mg, 0.15 mmol) in CH_2Cl_2 (0.3 + 0.1 mL) was added *via* cannula and the resulting mixture stirred at –78 °C for 45 minutes. Triethylamine (189 μL, 1.4 mmol) was added dropwise and the resulting white solution was stirred at –78 °C for 30 minutes then at 0 °C for 1 hour. The reaction mixture (0 °C) was poured into a rapidly stirring 1 M solution of $NaHSO_4$ (1.5 mL), the layers were separated and the aqueous phase extracted with

Et_2O (3 x 20 mL). The combined organic extracts were concentrated *in vacuo* and the residue was diluted with Et_2O (20 mL), then washed successively with 1 M solution of $NaHSO_4$ (3 x 10 mL), H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (30% CH_2Cl_2/hexanes) to give compound **96** as a mixture of dione and enol forms (61.4 mg, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.12 (1H, m, C*H*=C(CH_3)), 4.14 (0.1H, d, 9.6 Hz, C*H*OTBS), 4.09 (0.3H, d, 9.6 Hz, C*H*OTBS), 3.99 (0.6H, d, 9.6 Hz, C*H*OTBS), 3.86 (0.6H, q, 7.1 Hz, C(=O)C*H*(CH_3)), 3.74 (0.1H, q, 7.1 Hz, C(=O)C*H*(CH_3)), 3.02-2.92 (0.4H, m, CHC*H*(CH_3)), 2.78 (0.6H, dq, 9.6, 6.9 Hz, CHC*H*(CH_3)), 2.53 (1.3H, qd, 7.2, 5.4 Hz, C(=O)C*H*$_2$$CH_3$), 2.48-2.30 (1.7H, m, C(=O)C*H*$_2$$CH_3$, CH_2C*H*(CH_3)CH), 1.88 (0.9H, s, C(C*H*$_3$)=COH), 1.58 (0.9H, d, 1.2 Hz, CH=C(C*H*$_3$)), 1.55-1.54 (2.1H, m, CH=C(C*H*$_3$)), 1.26 (2.1H, d, 7.2 Hz, CH(C*H*$_3$)C=O), 1.14-1.00 (4H, m, CH_3C*H*$_2$C*H*$_2$), 0.91-0.74 (21H, m, C*H*$_3$$CH_2CH_2$, CH_2CH(C*H*$_3$)CH, CHCH(C*H*$_3$), C(=O)CH_2C*H*$_3$, SiC(C*H*$_3$)$_3$), –0.03 (0.3H, s, SiC*H*$_3$), –0.03 (0.3H, s, SiC*H*$_3$), –0.06 (1.8H, s, SiC*H*$_3$), –0.08 (1.8H, s, SiC*H*$_3$), –0.09 (0.9H, s, SiC*H*$_3$), -0.11 (0.9H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.5, 209.1, 195.9, 193.7, 136.4, 136.3, 136.0, 133.4, 132.8, 105.4, 82.7, 82.3, 81.2, 62.5, 61.6, 49.6, 48.0, 41.2, 39.5, 39.4, 35.2, 34.9, 31.7, 29.8, 25.8, 25.8, 25.6, 20.9, 20.8, 20.5, 18.0, 14.8, 14.2, 14.1, 12.8, 12.2, 12.1, 10.4, 10.3, 9.2, 7.7, 7.5, –4.7, –4.8, –5.1, –5.3, –5.7.



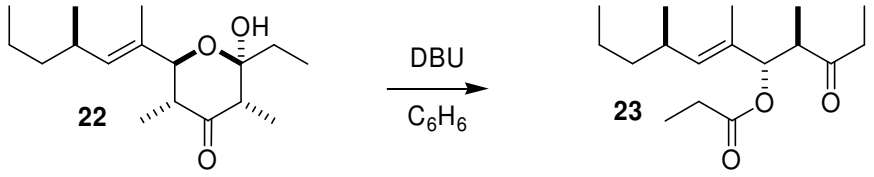
(2*S*,3*R*,5*R*,6*S*)-6[(1*E*,3*R*)-1,3-dimethylhex-1-enyl]-2-ethyl-2-hydroxy-3,5-dimethyltetrahydro-4H-pyran-4-one (22) and (2*S*,3*R*)-2-[(1*E*,3*R*)-1,3-dimethylhex-1-enyl)-6-ethyl-3,5-dimethyl-2,3-dihydro-4H-pyran-4-one (88).

Deprotection followed the procedure of Hoffmann *et al.*[11] To a Teflon cylinder containing the dione/enol **96** (61.4 mg, 0.16 mmol) was added buffered pyridinium hydrofluoride (0.5 mL) (stock solution prepared from dry THF (10 mL), pyridine (5 mL) and 30% pyridinium hydrofluoride (2.1 g)) and H_2O (20 μL). The resulting solution was stirred at room temperature for 6 days then diluted with Et_2O (10 mL) and partitioned with saturated aqueous $CuSO_4$ (8 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 10 mL), then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2, using buffered silica) to give the hemiacetal **22** (23.1 mg, 54%) as a white paste and dihydropyrone **88** (8.2 mg, 21%) as a colourless oil.

Hemiacetal 22: $\mathbf{R_f}$ = 0.38 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +27.1 (*c* 0.6, $CHCl_3$); **IR** (FT, film) 3468, 1719, 1457, 1169, 1033, 996 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.16 (1H, br d, 9.0 Hz, C*H*=C(CH_3)), 4.07 (1H, d, 10.2 Hz, C*H*(-O)CH(CH_3)), 2.68 (1H, br q, 6.8 Hz, C*H*(CH_3)COH), 2.48 (1H, dq, 10.2, 6.6, 1.2 Hz, CH(-O)C*H*(CH_3)), 2.45-2.38 (1H, m, CH_2C*H*(CH_3)CH), 1.93 (1H, d, 1.8 Hz, O*H*), 1.88-1.82 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.74-1.67 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.69 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.33-1.17 (4H, m, $CH_3CH_2CH_2$), 1.08 (3H, d, 6.6 Hz, CH(CH_3)COH), 1.03 (3H, t, 7.5 Hz, C(OH)CH_2CH_3), 0.92 (3H, d, 7.2 Hz, CH_2CH(CH_3)), 0.89 (3H, t, 6.6 Hz, C$H_3CH_2CH_2$), 0.86 (3H, d, 6.6 Hz, CH(-O)CH(CH_3)); **^{1}H NMR** (600 MHz, C_6D_6) δ 5.12 (1H, dd, 9.3, 0.9 Hz, C*H*=C(CH_3)), 4.15 (1H, d, 10.8 Hz, C*H*(-O)CH(CH_3)), 2.38-2.31 (1H, m, CH_2C*H*(CH_3)CH), 2.26 (1H, br q, 6.6 Hz, C*H*(CH_3)COH), 2.18 (1H, dqd, 10.8, 6.6, 1.2 Hz, CH(-O)C*H*(CH_3)), 1.65 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.54-1.45 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.39 (1H, d, 1.2 Hz, O*H*), 1.34-1.27 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.26-1.15 (4H, m, $CH_3CH_2CH_2$), 1.13 (3H, d, 6.6 Hz, CH(CH_3)COH), 1.01 (3H, d, 6.6 Hz, CH(-O)CH(CH_3)), 0.88 (3H, d, 6.6 Hz, CH_2CH(CH_3)), 0.85 (3H, t, 7.2 Hz, C$H_3CH_2CH_2$), 0.79 (3H, t, 7.5 Hz, C(OH)CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.8, 137.4, 131.1, 103.5, 83.2, 50.2, 47.1, 39.9, 33.5, 32.2, 21.0, 20.9, 14.6, 11.2, 10.0, 8.9, 8.5; **^{13}C NMR** (151 MHz, C_6D_6) δ 207.2, 136.6, 131.7, 102.8, 82.8, 49.9, 46.6, 39.9, 33.2, 32.2, 21.0, 21.0, 14.4, 11.0, 10.1, 8.9, 8.1; **HRESIMS** calculated for $C_{17}H_{30}O_3Na^+$ $[M+Na]^+$:

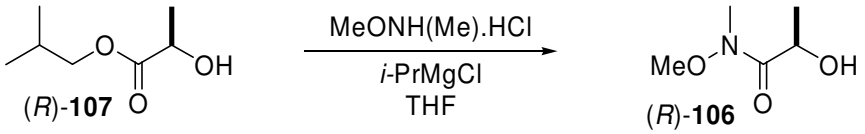
305.2093, found 305.2084; **EIMS** *m/z* (%): 264 (3), 193 (67), 153 (10), 137 (30), 123 (6), 109 (100), 95 (5), 82 (8), 67 (12), 57 (9).

Dihydropyrone 88: $\mathbf{R}_f$ = 0.63 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +38.9 (*c* 0.5, $CHCl_3$); **IR** (FT, film) 1665, 1618, 1458, 1392, 1365, 1179, 1063 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.24 (1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.15 (1H, d, 13.8 Hz, C*H*(-O)CH(CH_3)), 2.51 (1H, dq, 13.8, 6.9, Hz, CH(-O)C*H*(CH_3)), 2.55-2.41 (1H, m, CH_2C*H*(CH_3)), 2.33 (2H, q, 7.3 Hz, CC*H*$_2$$CH_3$), 1.72 (3H, s, C(C*H*$_3$)=C), 1.67 (3H, d, 1.2 Hz, CH=C(C*H*$_3$)), 1.34-1.21 (4H, m, CH_3C*H*$_2$C*H*$_2$), 1.12 (3H, t, 7.7 Hz, CCH_2C*H*$_3$), 0.94 (3H, d, 7.2 Hz, CH_2CH(C*H*$_3$)), 0.92 (3H, d, 6.9 Hz, CH(-O)CH(C*H*$_3$)), 0.89 (3H, t, 7.5 Hz, C*H*$_3$$CH_2CH_2$), **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.5, 173.3, 138.7, 129.7, 107.8, 89.8, 40.4, 39.5, 31.9, 25.7, 20.6, 20.6, 14.2, 11.2, 10.9, 10.3, 9.3; **HRESIMS** calculated for $C_{17}H_{28}O_2Na^+$ $[M+Na]^+$: 287.1987; found 287.1980; **EIMS** *m/z* (%): 226 (3), 209 (3), 152 (20), 137 (40), 123 (13), 109 (100), 57 (91).

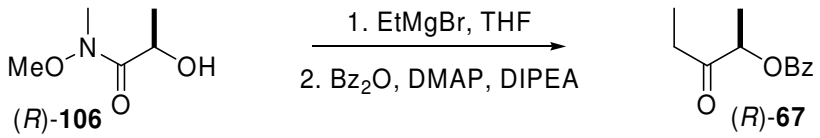


(4R,5S,6E,8R)-4,6,8-trimethyl-5-(1-oxopropoxy)-undec-6-en-3-one (23). Retro-Claisen rearrangement was performed according to the procedure of Faulkner and Hochlowski.[12] To a solution of the hemiacetal **22** (8.5 mg, 0.03 mmol) in benzene (10 mL) was added DBU (20μL) and the resulting mixture stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the residue immediately purified by column chromatography (5% Et_2O/CH_2Cl_2, using buffered silica) to give the ketol ester **23** and the starting hemiacetal **22** as an inseparable mixture (5.0 mg, 60%). $\mathbf{R}_f$ = 0.56 (5% Et_2O/CH_2Cl_2); By subtraction of the peaks due to hemiacetal **22** the spectra for ester **23** were recorded as follows. **^{1}HNMR** (300 MHz, $CDCl_3$) δ 5.33 (1H, d, 6.6 Hz, C*H*=C(CH_3)), 5.21 (1H, d, 10.5 Hz, C*H*(-O)CH(CH_3)), 2.91 (1H, dq, 10.5, 7.1 Hz, CH(-O)C*H*(CH_3)), 2.49 (2H, qd, 7.2, 1.2 Hz, C(=O)C*H*$_2$$CH_3$), 2.21 (1H, q, 7.5 Hz, CH_3C*H*$_2$$CO_2$), 1.57 (3H, d, 1.5 Hz,

CH=C(CH_3)), 1.25 (4H, m, $CH_3CH_2CH_2$), 1.07 (3H, t, 7.5 Hz, $CH_3CH_2CO_2$), 1.04 (1H, t, 7.2 Hz, C(=O)CH_2CH_3), 0.93 (3H, d, 6.9 Hz, CHCH(CH_3)), 0.90 (3H, d, 6.6 Hz, CH_2CH(CH_3)), 0.85 (3H, t, 6.6 Hz, $CH_3CH_2CH_2$); **^{1}HNMR** (300 MHz, C_6D_6) δ 5.52 (1H, d, 10.2 Hz, C*H*(-O)CH(CH_3)), 5.33 (1H, d, 9.9 Hz, C*H*=C(CH_3)), 2.76 (1H, dq, 10.2, 7.2 Hz, CHC*H*(CH_3)), 2.29-2.22 (1H, m, CH_2CH(CH_3)), 2.19 (2H, q, 7.2 Hz, C(=O)CH_2CH_3), 1.96 (2H, q, 7.5 Hz, $CH_3CH_2CO_2$), 1.51 (3H, d, 0.9 Hz, CH=C(CH_3)), 1.35-1.25 (1H, m, 1 of $CH_3CH_2CH_2$), 1.2-1.15 (3H, m, 3 of $CH_3CH_2CH_2$), 1.02 (3H, t, 7.5 Hz, $CH_3CH_2CO_2$), 0.88 (3H, t, 7.2 Hz, CH_2CH_3), 0.87 (3H, d, 7.0 Hz, CHCH(CH_3)), 0.84 (3H, d, 7.0 Hz, CHCH(CH_3)), 0.77 (3H, d, 7.2 Hz, CHCH(CH_3)); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 210.8, 172.1, 138.9, 129.2, 81.5, 47.7, 39.8, 35.3, 32.2, 27.7, 21.0, 20.9, 14.4, 13.7, 11.4, 9.3, 7.8;

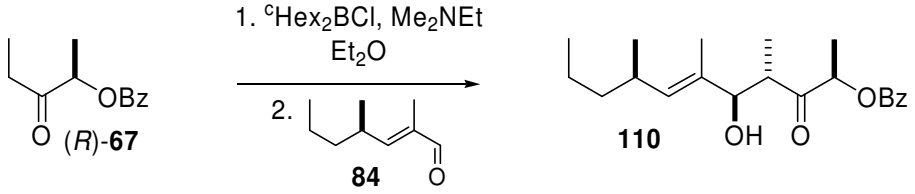


(2*R*)-2-Hydroxy-*N*-methoxy-*N*-methylpropionamide [(*R*)-106].[6,7] The previous procedure[6,7] used for the preparation of **106** was followed with isobutyl (*R*)-lactate (**107**) (4.12 mL, 27.4 mmol) *N,O*-dimethylhydroxylamine hydrochloride (6.67 g, 68.4 mmol) and ^{i}PrMgCl (68 mL of a 2 M solution in THF, 137 mmol). Standard work-up and purification by distillation (b.p. 64-65 °C @ 0.5 mm Hg) gave the amide (*R*)-**106** (3.51g, 96%) as a colourless oil. Spectroscopic data were identical to that reported for compound (*S*)-**106**, except for **$[\alpha]^{20}_D$** which had the opposite sign.

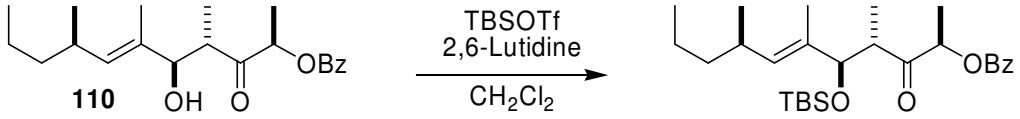


(2*R*)-2-Benzoyloxypentan-3-one [(*R*)-67]. [6,7] The previous procedure[6,7] used for the preparation of (*S*)-**67** was followed with amide (*R*)-**106** (3.5 g, 26.3 mmol), EtMgBr (84 mL of a 1 M solution in THF, 84.1 mmol), followed by benzoic anhydride (8.9 g, 39.4 mmol), DMAP (350 mg, 2.89 mmol) and $^{i}Pr_2NEt$ (8.75 mL, 50.2 mmol). Standard work-up and purification by column chromatography (20%

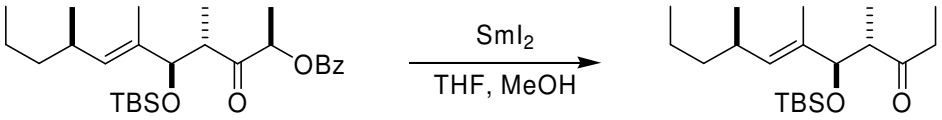
EtOAc/hexanes) afforded the ketone (*R*)-**67** (2.8 g, 52%) as a colourless oil. $\mathbf{R}_f$ = 0.38 (20% EtOAc/hexanes; Spectroscopic data were identical to that reported for compound (*S*)-**67**, except for $[\alpha]^{20}_{D}$ which had the opposite sign.



(2*R*,4*S*,5*R*,6*E*,8*R*)-2-benzoyloxy-4,6,8-trimethyl-5-hydroxyundec-6-en-3-one (110). The previous procedure[6,7] used for the preparation of **108** was followed with ketone (*R*)-**67** (1.38 g, 6.7 mmol), dicyclohexylboron chloride (2.2 mL, 10 mmol), Me_2NEt (1.3 mL, 12 mmol) and aldehyde **84** (493 mg, 3.5 mmol). Standard oxidative work-up and purification by column chromatography (5% Et_2O/CH_2Cl_2) gave adduct **110** (891 mg, 73%, >95% d.s.) as a white solid. **m.p.** 104-106 C; $\mathbf{R_f}$ = 0.35 (CH_2Cl_2); $[\alpha]^{20}_{D}$ = –38.7 (*c* 0.4, $CHCl_3$); **IR** (FT, film) 3537, 1730, 1718, 1285, 1267, 1118, 715 cm–1; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (2H, m, Ar*H*), 7.59 (1H, m, Ar*H*), 7.46 (2H, m, Ar*H*), 5.46 (1H, q, 7.0 Hz, C*H*(CH_3)OBz), 5.20 (1H, d, 9.6 Hz, C*H*=C(CH_3)), 4.18 (1H, dd, 9.5, 3.5 Hz, C*H*OH), 3.04 (1H, dq, 9.5, 7.1 Hz, CH(OH)C*H*CH_3), 2.43-2.33 (1H, m, CH_2C*H*(CH_3)), 1.90 (1H, d, 3.5 Hz, O*H*), 1.60 (3H, d, 1.2 Hz, CH=C(C*H*$_3$)), 1.58 (3H, d, 6.9 Hz, CH(C*H*$_3$)OBz), 1.29-1.14 (4H, m, $CH_3CH_2CH_2$), 1.04 (3H, d, 7.2 Hz, CH(OH)CHC*H*$_3$), 0.93 (3H, d, 6.6 Hz, CH_2CH(C*H*$_3$)), 0.86 (3H, t, 6.9 Hz, C*H*$_3$$CH_2CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.1, 165.9, 136.9, 133.2, 132.6, 129.8, 129.6, 128.4, 80.5, 75.1, 45.5, 39.7, 31.8, 20.8, 20.6, 15.6, 14.5, 14.1, 10.6; **HRESIMS** calculated for $C_{21}H_{30}O_4Na^+$ $[M+Na]^+$: 369.2042; found 369.2030; **EIMS** *m/z* (%): 177 (2), 162 (14), 149 (7), 105 (100), 77 (25), 57 (6), 51 (6).

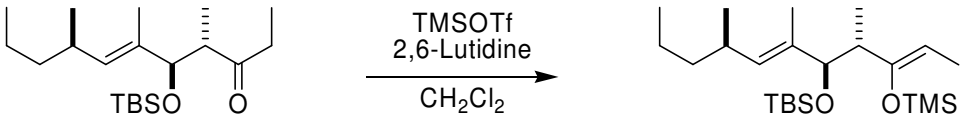


(2*R*,4*S*,5*R*,6*E*,8*R*)-2-benzoyloxy-5-*tert*-butyldimethylsilyloxy-4,6,8-trimethylundec-6-en-3-one. The previous procedure used was followed with alcohol **110** (688 mg, 2.0 mmol), 2,6-lutidine (463 μL, 4.0 mmol) and TBSOTf (684 mL, 3.0 mmol) followed by standard workup. Purification by column chromatography (CH_2Cl_2) gave the protected adduct (880 mg, 96%) as a colourless oil. $\mathbf{R}_f$ = 0.68 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = –16.9 (*c* 2.1, $CHCl_3$); **IR** (FT, film) 1724, 1267, 1116, 1070, 836, 778, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (2H, m, Ar*H*), 7.57 (1H, t, 7.5, Hz, Ar*H*), 7.44 (2H, m, Ar*H*), 5.44 (1H, q, 7.0 Hz, C*H*(CH_3)OBz), 5.10 (1H, dd, 9.6, 1.4 Hz, C*H*=C(CH_3)), 4.21 (1H, d, 9.9 Hz, C*H*OTBS), 3.01 (1H, dq, 9.9, 7.1 Hz, CH(OTBS)C*H*CH_3), 2.43-2.31 (1H, m, CH_2C*H*(CH_3)), 1.55 (3H, d, 1.4 Hz, CH=C(C*H*$_3$)), 1.53 (3H, d, 7.2 Hz, CH(C*H*$_3$)OBz), 1.28-1.12 (4H, m, CH_3C*H*$_2$C*H*$_2$), 0.94 (3H, d, 6.9 Hz, CH(OTBS)CHC*H*$_3$), 0.93 (3H, d, 6.9 Hz, CH_2CH(C*H*$_3$)), 0.85 (3H, t, 6.6 Hz, C*H*$_3$$CH_2$$CH_2$), 0.81 (9H, s, SiC(C*H*$_3$)$_3$), –0.03 (3H, s, SiC*H*$_3$) –0.03 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.5, 165.7, 136.5, 133.1, 132.7, 129.8, 128.4, 81.6, 75.3, 46.0, 39.7, 31.8, 25.8, 20.7, 20.4, 18.0, 15.2, 14.5, 14.1, 10.4, –4.7, –5.1. (1 coincident vinyl carbon); **HRESIMS** calculated for $C_{27}H_{44}O_4SiNa^+$ $[M+Na]^+$: 483.2907; found 483.2902; **EIMS** *m/z* (%): 403 (2), 263 (25), 255 (31), 221 (4), 179 (100), 105 (32), 73 (18).



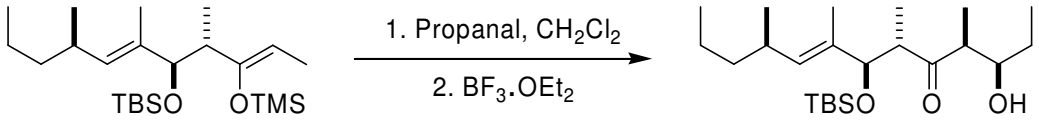
(4*S*,5*R*,6*E*,8*R*)-5-*tert*-butyldimethylsilyloxy-4,6,8-trimethylundec-6-en-3-one. The previous procedure[7] used for the preparation of **98** was followed with the protected adduct (600 mg, 1.3 mmol) and SmI_2 (~55 mL of a 0.1 M solution in THF, ~5.2 mmol) followed by standard workup. Purification by column chromatography (30% CH_2Cl_2/hexanes) afforded the protected hydroxy ketone (393 mg, 89%) as a colourless oil. $\mathbf{R}_f$ = 0.34 (30% CH_2Cl_2/hexanes); $\mathbf{[\alpha]^{20}_D}$ = +0.8 (*c* 2.5, $CHCl_3$); **IR** (FT, film) 1721, 1251, 1057, 836, 777 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.07

(1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.03 (1H, d, 9.9 Hz, C*H*OTBS), 2.77 (1H, dq, 9.9, 7.0 Hz, CH(OTBS)C*H*CH_3), 2.53 (2H, qd, 7.2, 6.9 Hz, C(=O)C$H_2$$CH_3$), 2.44-2.28 (1H, m, CH_2CH(CH_3)), 1.56 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.37-1.11 (4H, m, CH_3CH_2CH_2), 1.01 (3H, t, 7.2 Hz, C(=O)CH_2CH_3), 0.91 (3H, d, 6.9 Hz, CH_2CH(CH_3)), 0.84 (3H, t, 6.8 Hz, C$H_3$$CH_2$$CH_2$), 0.79 (9H, s, SiC(C$H_3$)$_3$), 0.77 (3H, d, 7.2 Hz, CH(OTBS)CHCH_3), –0.06 (3H, s, SiCH_3) –0.07 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 215.1, 136.1, 133.0, 82.7, 48.9, 39.7, 38.0, 31.8, 25.7, 20.7, 20.5, 18.0, 14.1, 13.9, 10.3, 7.2, –4.6, –5.5; **HRESIMS** calculated for $C_{20}H_{40}O_2SiNa^+$ $[M+Na]^+$: 363.2695; found 363.2691; **EIMS** *m/z* (%): 325 (2), 283 (100), 255 (52), 197 (69), 171 (20), 143 (56), 127 (14), 115 (9), 99 (5), 75 (67), 69 (7), 57 (14).

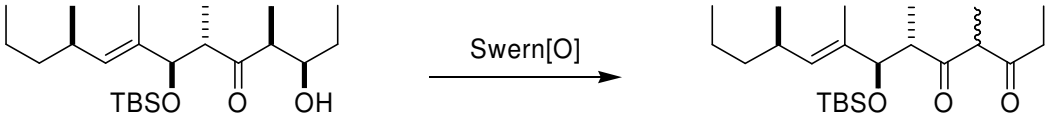


(2*Z*,4*S*,5*R*,6*E*,8*R*)-5-tert-butyldimethylsilyloxy-4,6,8-trimethyl-2-trimethylsilyloxyundec-2,6-diene. The previous procedure used for the preparation of **109** was followed with the protected hydroxy ketone (330 mg, 0.97 mmol), 2,6-lutidine (451 μL, 3.9 mmol) and TMSOTf (526 μL, 2.9 mmol) followed by standard workup. Purification by column chromatography (30% CH_2Cl_2/hexanes) gave the geometrically pure silylenol ether (386 mg, 97%) as a colourless oil. $\mathbf{R}_f$ = 0.67 (30% CH_2Cl_2/hexanes); $\mathbf{[\alpha]^{20}_D}$ = –28.1 (*c* 1.1, $CHCl_3$); **IR** (FT, film) 1677, 1459, 1253, 1197, 1068, 875, 838, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.97 (1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.49 (1H, q, 6.7 Hz, C=C*H*(CH_3)), 3.83 (1H, d, 9.3 Hz, C*H*OTBS), 2.44-2.30 (1H, m, CH_2C*H*(CH_3)), 2.17 (1H, dq, 9.3, 7.0 Hz, CH(OTBS)C*H*CH_3), 1.52 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.48 (3H, d, 6.9 Hz, C=CH(CH_3)), 1.29-1.15 (4H, m, CH_3CH_2CH_2), 0.92 (3H, d, 6.9 Hz, CH_2CH(CH_3)), 0.87 (3H, t, 6.9 Hz, C$H_3$$CH_2$$CH_2$), 0.83 (9H, s, SiC(C$H_3$)$_3$), 0.76 (3H, d, 6.9 Hz, CH(OTBS)CHCH_3), 0.21 (9H, s, Si(CH_3)$_3$), –0.02 (3H, s, SiCH_3), –0.06 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 153.2, 134.5, 134.5, 101.5, 81.1, 44.5, 39.9, 31.7, 25.8, 20.8, 20.7, 18.2, 15.8, 14.2, 11.2, 10.6, 1.0, –4.8, –5.3; **HRESIMS**

calculated for $C_{23}H_{46}O_2Si_2Na^+$ $[M+Na]^+$: 435.3091; found 435.3079; **EIMS** *m/z* (%): 355 (3), 287 (3), 255 (100), 185 (14), 147 (24), 127 (6), 115 (4), 73 (42).

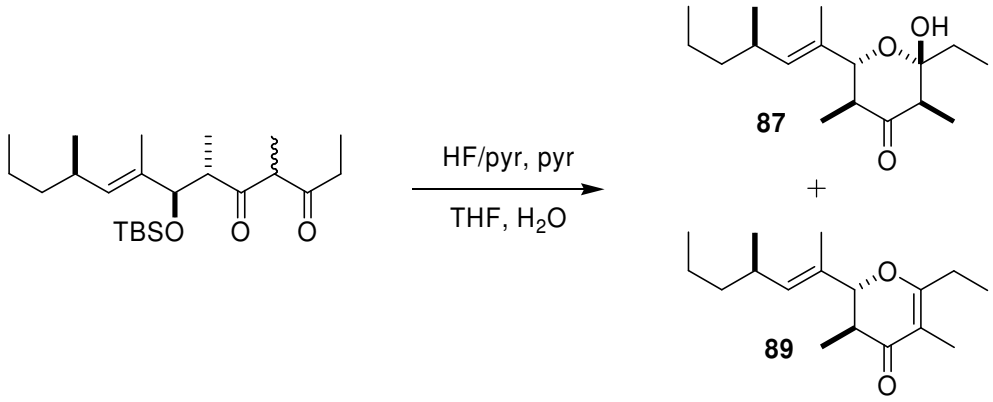


(3*S*,4*R*,6*S*,7*R*,8*E*,10*R*)-7-tert-butyldimethylsilyloxy-3-hydroxy-4,6,8,10-tetramethyltridec-8-en-5-one. The previous procedure[9] used for the preparation of **97** was followed with enol ether (366 mg, 0.89 mmol), propanal (191 μL, 2.7 mmol) and BF_3•OEt_2 (168 μL, 1.3 mmol), followed by standard workup. Purified by column chromatography (5% Et_2O/CH_2Cl_2) gave the adduct (235 mg, 67%, 85% d.s.) as a colourless oil. $\mathbf{R}_f$ = 0.37 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]_{20}^{D}}$ = –21.7 (*c* 1.1, $CHCl_3$); **IR** (FT, film) 3469, 1702, 1459, 1255, 1060, 998, 877, 836, 777 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.09 (1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.16 (1H, d, 9.9 Hz, C*H*OTBS), 3.90-3.84 (1H, m, C*H*OH), 2.98 (1H, dq, 9.8, 7.1 Hz, CH(OTBS)C*H*CH_3), 2.97 (1H, d, 3.9 Hz, O*H*), 2.60 (1H, qd, 7.2, 2.6 Hz, C(=O)C*H*(CH_3)), 2.44-2.30 (1H, m, CH_2C*H*(CH_3)), 1.62-1.47 (1H, m, CHC$H_A$$H_B$$CH_3$), 1.55 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.45-1.33 (1H, m, CHC$H_A$$H_B$$CH_3$), 1.27-1.17 (4H, m, $CH_3CH_2CH_2$), 1.13 (3H, d, 7.2 Hz, C(=O)CH(CH_3)), 0.95 (3H, t, 7.4 Hz, $CHCH_2CH_3$), 0.92 (3H, d, 6.6 Hz, CH_2CH(CH_3)), 0.84 (3H, t, 7.1 Hz, $CH_3CH_2CH_2$), 0.80 (9H, s, SiC(CH_3)$_3$), 0.80 (3H, d, 7.0 Hz, CH(OTBS)CHCH_3), –0.04 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 218.5, 136.4, 132.7, 81.7, 72.6, 50.8, 47.8, 39.7, 31.8, 27.0, 25.8, 20.7, 20.4, 18.1, 14.6, 14.1, 10.5, 10.5, 8.0, –4.6, –5.0; **HRESIMS** calculated for $C_{23}H_{46}O_3SiNa^+$ $[M+Na]^+$: 421.3114; found 421.3114; **EIMS** *m/z* (%): 355 (2), 283 (100), 255 (53), 197 (72), 171 (21), 143 (61), 127 (16), 75 (78), 57 (16).



(4*R*,6*S*,7*R*,8*E*,10*R*)-7-tert-butyldimethylsilyloxy-4,6,8,10-tetramethyltridec-8-en-3,5-dione. The previous procedure[10] used for the preparation of **96** was followed with DMSO (107 μL, 1.5 mmol), oxalyl chloride (376 μL of a 2 M solution in

CH_2Cl_2, 0.75 mmol), the alcohol (100 mg, 0.25 mmol) and triethylamine (315 μL, 2.3 mmol), followed by standard workup. Purification by column chromatography (30% CH_2Cl_2/hexanes) gave the product as a mixture of dione and enol forms (99 mg, 99%). **^{1}H NMR** (300 MHz; $CDCl_3$) δ 5.08 (1H, m, C*H*=C(CH_3)), 4.14 (0.2H, d, 9.6 Hz, C*H*OTBS), 4.09 (0.3H, d, 9.6 Hz, C*H*OTBS), 3.99 (0.5H, d, 9.6 Hz, C*H*OTBS), 3.86 (0.5H, q, 7.1 Hz, C(=O)C*H*(CH_3)), 3.75 (0.2H, q, 7.1 Hz, C(=O)C*H*(CH_3)), 3.05-2.94 (0.5H, m, CHC*H*(CH_3)), 2.80 (0.5H, dq, 9.6, 6.9 Hz, CHC*H*(CH_3)), 2.54 (1.3H, qd, 7.2, 5.4 Hz, C(=O)C$H_2$$CH_3$), 2.49-2.30 (1.7H, m, C(=O)C$H_2$$CH_3$, CH_2C*H*(CH_3)CH), 1.87 (0.9H, s, C(CH_3)=COH), 1.57 (0.6H, d, 1.2 Hz, CH=C(CH_3)), 1.55-1.54 (2.4H, m, CH=C(CH_3)), 1.26 (2.1H, d, 7.2 Hz, CH(CH_3)C=O), 1.14-1.00 (4H, m, CH_3CH_2CH_2), 0.93-0.74 (21H, m, C$H_3$$CH_2$$CH_2$, CH_2CH(CH_3)CH, CHCH(CH_3), C(=O)CH_2CH_3, SiC(CH_3)$_3$), –0.03 (1.5H, s, SiCH_3), –0.06 (1.5H, s, SiCH_3), –0.08 (1.8H, s, SiCH_3), –0.10 (0.6H, s, SiCH_3), –0.11 (0.6H, s, SiCH_3); **^{13}C NMR** (75.5 MHz; $CDCl_3$) δ 210.5, 209.1, 207.4, 195.9, 193.8, 136.6, 136.5, 136.1, 133.4, 132.7, 105.0, 83.1, 82.6, 81.6, 62.5, 61.6, 49.2, 47.7, 40.9, 39.7, 39.6, 35.2, 34.9, 31.8, 29.8, 25.8, 25.8, 25.5, 20.6, 20.6, 20.4, 18.0, 14.7, 14.1, 12.8, 12.2, 12.1, 10.5, 10.3, 10.2, 9.2, 7.7, 7.5, –4.5, –4.6, –4.7, –5.0, –5.2, –5.7.



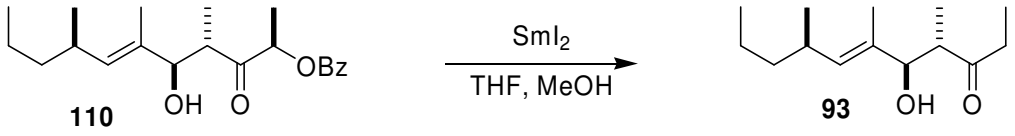
(2*R*,3*S*,5*S*,6*R*)-6[(1E,3*R*)-1,3-dimethylhex-1-enyl]-2-ethyl-2-hydroxy-3,5-dimethyltetrahydro-4H-pyran-4-one (87) and **(2*R*,3*S*)-2-[(1E,3*R*)-1,3-dimethylhex-1-enyl)-6-ethyl-3,5-dimethyl-2,3-dihydro-4H-pyran-4-one (89).** The previous procedure[11] used for the preparation of **22** was followed with the dione/enols (99 mg, 0.25 mmol), buffered pyridinium hydrofluoride (1.0 mL) and H_2O (40 μL), followed by standard workup. Purification by column chromatography

(5% Et_2O/CH_2Cl_2, using buffered silica) gave the hemiacetal **87** (29.8 mg, 43%) as a white paste and dihydropyrone **89** (11.2 mg, 17%) as a colourless oil.

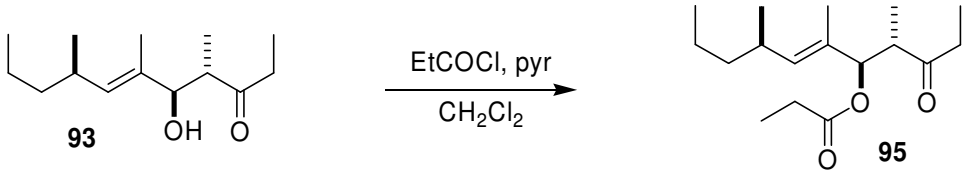
Hemiacetal 87: $\mathbf{R_f}$ = 0.43 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = –65.9 (*c* 2.0, $CHCl_3$); **IR** (FT, film) 3357, 1718, 1457, 1173, 1042, 953 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.16 (1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.08 (1H, d, 10.2 Hz, C*H*(-O)CH(CH_3)), 2.69 (1H, br q, 6.6, C*H*(CH_3)COH), 2.50 (1H, dqd, 10.2, 6.6, 1.2 Hz, CH(-O)C*H*(CH_3)), 2.45-2.40 (1H, m, CH_2C*H*(CH_3)), 1.92 (1H, d, 1.8 Hz, O*H*), 1.88-1.82 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.73-1.70 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.70 (3H, d, 1.2 Hz, CH=C(CH_3)), 1.29-1.16 (4H, m, $CH_3CH_2CH_2$), 1.08 (3H, d, 6.6 Hz, CH(CH_3)COH), 1.03 (3H, t, 7.2 Hz, C(OH)CH_2CH_3), 0.96 (3H, d, 7.2 Hz, CH_2CH(CH_3)), 0.88 (3H, d, 6.6 Hz, CH(-O)CH(CH_3)), 0.87 (3H, t, 7.2 Hz, C$H_3CH_2CH_2$); **^{1}H NMR** (600 MHz, C_6D_6) δ 5.12 (1H, dd, 9.6, 1.2 Hz, C*H*=C(CH_3)), 4.15 (1H, d, 10.2 Hz, C*H*(-O)CH(CH_3)), 2.38-2.30 (1H, m, CH_2C*H*(CH_3)CH), 2.27 (1H, br q, 6.6 Hz, C*H*(CH_3)COH), 2.19 (1H, dqd, 10.2, 6.6, 1.2 Hz, CH(-O)C*H*(CH_3)), 1.66 (3H, d, 1.8 Hz, CH=C(CH_3)), 1.53-1.47 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.47 (1H, d, 1.2 Hz, O*H*), 1.39-1.29 (1H, m, C(OH)C$H_A$$H_B$$CH_3$), 1.28-1.12 (4H, m, $CH_3CH_2CH_2$), 1.13 (3H, d, 6.6 Hz, CH(CH_3)COH), 1.02 (3H, d, 6.6 Hz, CH(-O)CH(CH_3)), 0.93 (3H, d, 7.2 Hz, CH_2CH(CH_3)), 0.86 (3H, t, 7.2 Hz, C$H_3CH_2CH_2$), 0.80 (3H, t, 7.5 Hz, C(OH)CH_2CH_3);**^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.5, 137.1, 131.0, 103.1, 83.0, 49.7, 46.5, 39.7, 33.2, 31.8, 20.7, 20.6, 14.1, 10.7, 9.6, 8.5, 8.2; **^{13}C NMR** (151 MHz, C_6D_6) δ 207.3, 136.7, 131.7, 102.8, 82.9, 49.8, 46.4, 40.0, 33.2, 32.1, 21.0, 21.0, 14.3, 11.0, 10.1, 8.9, 8.2; **HRESIMS** calculated for $C_{17}H_{30}O_3Na^+$ $[M+Na]^+$: 305.2093; found 305.2082; **EIMS** *m/z* (%): 264 (4), 207 (3), 193 (68), 153 (10), 137 (29), 123 (7), 109 (100), 95 (5), 82 (8), 67 (12), 57 (9).

Dihydropyrone 89: $\mathbf{R_f}$ = 0.63 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = –57.6 (*c* 0.75, $CHCl_3$); **IR** (FT, film) 1666, 1618, 1456, 1390, 1366, 1179, 1063 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.23 (1H, dd, 9.6, 0.9 Hz, C*H*=C(CH_3)), 4.16 (1H, d, 13.2 Hz, C*H*(-O)CH(CH_3)), 2.52 (1H, dq, 13.2, 6.9, Hz, CH(-O)C*H*(CH_3)), 2.44 (1H, m, CH_2C*H*(CH_3)), 2.33 (2H, q, 7.5 Hz, CCH_2CH_3), 1.72 (3H, s, C(CH_3)=C), 1.68 (3H, d, 1.5 Hz, CH=C(CH_3)), 1.31-1.17 (4H, m, $CH_3CH_2CH_2$), 1.12 (3H, t, 7.7 Hz,

CCH_2CH_3), 0.98 (3H, d, 6.6 Hz, $CH_2CH(CH_3)$), 0.95 (3H, d, 6.9 Hz, CH(=O)$CH(CH_3)$), 0.87 (3H, t, 6.9 Hz, $CH_3CH_2CH_2$), **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.5, 173.3, 138.9, 129.8, 107.9, 90.0, 40.2, 39.6, 31.9, 25.8, 20.7, 20.6, 14.1, 11.2, 11.0, 10.3, 9.3; **HRESIMS** calculated for $C_{17}H_{28}O_2Na^+$ $[M+Na]^+$: 287.1987; found 287.1983; **EIMS** *m/z* (%): 226 (2), 209 (3), 179 (2), 169 (3), 165 (3), 152 (19), 141 (10), 137 (42), 123 (13), 109 (100), 99 (4), 95 (8), 91 (3), 86 (7), 82 (7), 77 (3), 69 (10), 57 (91).

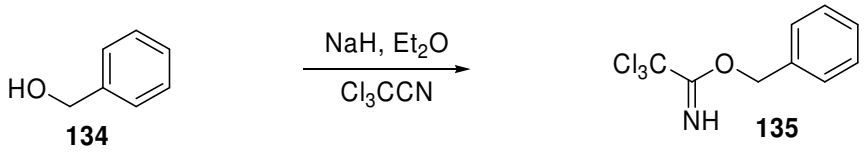


(4S,5R,6E,8R)-5-hydroxy-4,6,8-trimethylundec-6-en-3-one (93). Reductive cleavage was performed according to the procedure of Paterson *et al*.[7] To a solution of the unprotected adduct **110** (100 mg, 0.22 mmol) in THF (2.6 mL) and MeOH (1.3 mL) at 0 °C was added SmI_2 (~9 mL of a 0.1 M solution in THF, ~0.87 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0 °C with the addition of saturated aqueous K_2CO_3 (13 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 15 mL), the combined organic extracts were dried (MgSO4) and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O/CH_2Cl_2) afforded the β-hydroxy ketone **93** with an indeterminate amount of benzoyloxy derived contaminant. $\mathbf{R}_f$ = 0.39 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.17 (1H, d, 9.6, Hz, C*H*=C(CH_3)), 4.09 (1H, d, 9.3 Hz, C*H*OH), 3.99 (1H, s, O*H*), 2.78 (1H, dq, 9.3, 7.2 Hz, CH(OH)C*H*CH_3), 2.59 (1H, dq, 18.6, 7.2 Hz, C(=O)C$H_A$$H_B$$CH_3$), 2.51 (1H, dq, 18.6, 7.2 Hz, C(=O)C$H_A$$H_B$$CH_3$), 2.37 (1H, m, $CH_2CH(CH_3)$), 1.61 (3H, d, 1.5 Hz, CH=C(CH_3)), 1.25 (4H, m, $CH_3CH_2CH_2$), 1.05 (3H, t, 7.2 Hz, C(=O)CH_2CH_3), 0.93 (6H, d, 6.9 Hz, $CH_2CH(CH_3)$, CH(OH)CHCH_3), 0.86 (3H, t, 6.8 Hz, $CH_3CH_2CH_2$);

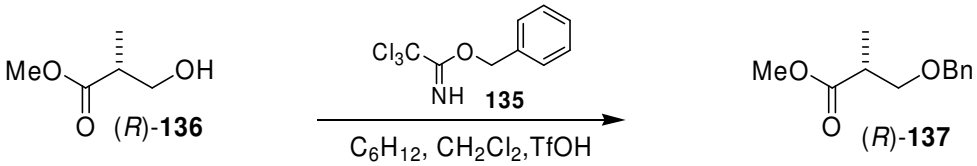


(4*S*,5*R*,6*E*,8*R*)-4,6,8-trimethyl-5-(1-oxopropoxy)-undec-6-en-3-one (95). To a solution of the β-hydroxy ketone **93** (11 mg, 0.04 mmol) in CH_2Cl_2 (284 μL) was added pyridine (17 μL, 0.21 mmol) followed by propionyl chloride (17 μL, 0.20 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with a 2 M solution of HCl (4 mL) and saturated aqueous $NaHCO_3$ (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) gave the ester **95** (7.5 mg, 18% over 2 steps) as a colourless oil. $\mathbf{R_f}$ = 0.34 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = –6.0 (*c* 0.5, $CHCl_3$); **IR** (FT, film) 1741, 1718, 1458, 1376, 1181, 1004 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.33 (1H, dd, 9.6, 1.5 Hz, C*H*=C(CH_3)), 5.22 (1H, d, 10.2 Hz, C*H*(O_2Et)CH), 2.91 (1H, dq, 10.2, 7.1 Hz, CH(O-)C*H*CH_3), 2.49 (2H, qd, 7.2, 1.5 Hz, C(=O)C*H*$_2$$CH_3$), 2.34 (1H, m, CH_2C*H*(CH_3)), 2.21 (2H, q, 7.5 Hz, CH_3C*H*$_2$$CO_2$), 1.57 (3H, d, 1.5 Hz, CH=C(C*H*$_3$)), 1.27-1.11 (4H, m, CH_3C*H*$_2$C*H*$_2$), 1.07 (3H, t, 7.7, Hz, C*H*$_3$$CH_2CO_2$), 1.03 (3H, t, 7.4 Hz, C(=O)CH_2C*H*$_3$), 0.94 (3H, d, 7.2 Hz, CH(O-)CHC*H*$_3$), 0.92 (3H, d, 6.6 Hz, CH_2CH(C*H*$_3$)), 0.85 (3H, t, 6.7 Hz, C*H*$_3$$CH_2CH_2$); **^{1}H NMR** (300 MHz, C_6D_6) δ 5.54 (1H, d, 10.5 Hz, C*H*(-O)CH(CH_3)), 5.33 (1H, d, 9.6 Hz, C*H*=C(CH_3)), 2.75 (1H, dq, 10.5, 7.1 Hz, CH(O-)C*H*CH_3), 2.29-2.15 (1H, m, CH_2C*H*(CH_3)), 2.18 (2H, q, 7.1 Hz, C(=O)C*H*$_2$$CH_3$), 1.96 (2H, q, 7.3 Hz, CH_3C*H*$_2$$CO_2$), 1.52 (3H, d, 1.5 Hz, CH=C(C*H*$_3$)), 1.34-1.05 (4H, m, CH_3C*H*$_2$C*H*$_2$), 1.01 (3H, t, 7.1 Hz, C*H*$_3$$CH_2CO_2$), 0.89 (3H, d, 6.6 Hz, CH_2CH(C*H*$_3$)CH), 0.88 (3H, t, 7.3 Hz, C*H*$_3$$CH_2CO_2$), 0.83 (3H, t, 6.6 Hz, C*H*$_3$$CH_2CH_2$), 0.77 (3H, d, 6.9 Hz, CH(O-)CHC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.8, 172.7, 138.7, 128.7, 81.3, 47.6, 39.6, 35.3, 31.9, 27.7, 20.6, 20.6, 14.1, 13.7, 11.5, 9.1, 7.6; **^{13}C NMR** (75.5 MHz, C_6D_6) δ 210.7, 172.1, 138.7, 129.4, 81.4, 47.7, 39.8, 35.3, 32.2, 27.7, 21.0, 20.8, 14.3, 13.7, 11.6, 9.2, 7.8; **HRESIMS** calculated for $C_{17}H_{30}O_3Na^+$ $[M+Na]^+$: 305.2093; found 305.2084; **EIMS** *m/z* (%): 226 (2), 209 (3), 169 (3), 165 (3), 152 (21), 141 (11), 137 (40), 123 (13), 109 (100), 99 (4), 95 (8), 91 (3), 86 (5), 82 (7), 77 (2), 71 (6), 67 (6), 57 (80).

5.3 Experimental Procedures for Chapter Three

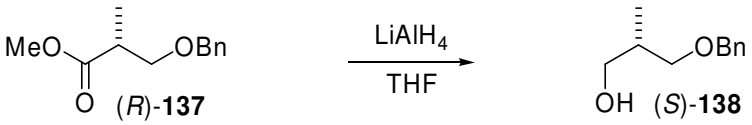


Benzyl-2,2,2-trichloroacetimidate (135).[13] The trichloroacetimidate was synthesized according to the procedure of Iverson and Bundle.[13] To a solution of sodium hydride (210 mg, 5.25 mmol) in dry Et_2O (20 mL) was added benzyl alcohol (**134**) (5.44 mL, 52.5 mmol) dropwise with stirring. After stirring at room temperature for 15 minutes, the mixture was cooled to 0 °C and trichloroacetonitrile (5.25 mL, 52.5 mmol) was added slowly. The resulting mixture was stirred at room temperature for 1 hour. Excess Et_2O was removed *in vacuo* and the residue diluted with pentane (70 mL) and MeOH (3 mL) and the mixture shaken vigorously for several minutes. The resulting solution was decanted and the filtrate concentrated in vacuo to afford the imidate **135** as a yellow oil (13.2 g, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (1H, br s, N*H*), 7.49-7.31 (5H, m, Ar*H*), 5.36 (2H, s, CH_2Ph); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 207.3, 162.5, 135.4, 128.5, 128.2, 127.7, 70.7.

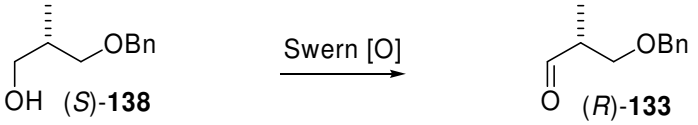


(2*R*)-Methyl-3-benzyloxy-2-methylpropionate [(*R*)-137].[14] Protection of the hydroxy ester was performed according to the procedure oe Wessel *et al.*[14] To a stirring solution of imidate **135** (3.23 g, 12.5 mmol) in cyclohexane (20 mL) was added a solution of (*R*)-(−)-methyl-3-hydroxy-2-methylpropionate [(*R*)-**136]** (1.0 g, 8.47 mmol) in CH_2Cl_2 (10 mL) *via* cannula. Trifluoromethanesulfonic acid (168 μL) was then added dropwise, giving a white precipitate, and the resulting mixture was stirred at room temperature for 18 hours. The crystalline residue was triturated with hexane (3 x 20 mL) and removed by gravity filtration. The filtrate was washed with

saturated aqueous $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/hexanes) to give the ester (*R*)-**137** (1.67 g, 95%) as a clear oil. $\mathbf{R}_f$ = 0.35 (15% EtOAc/hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.26 (5H, m, Ar*H*), 4.52 (2H, s, CH_2Ph), 3.70 (3H, s, OCH_3), 3.66 (1H, dd, 9.0, 7.4 Hz, CH_AH$_B$OBn), 3.50 (1H, dd, 9.0, 6.0 Hz, CH$_A$$H_B$OBn), 2.79 (1H, dqd, 7.4, 7.2, 6.0 Hz, C*H*(CH$_3$)CH$_2$OBn), 1.18 (3H, d, 7.2 Hz, CH(CH_3)CH$_2$OBn); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.3, 138.1, 128.3, 127.6, 127.5, 73.1, 71.9, 51.7, 40.2, 14.0.

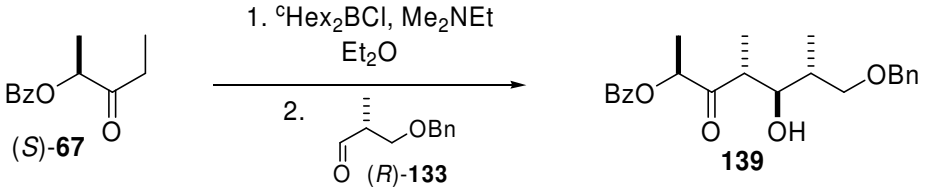


(2*S*)-3-Benzyloxy-2-methylpropan-1-ol [(*S*)-138]. A solution of ester (*R*)-**137** (1.63 g, 7.83 mmol) in THF (16 mL) was added *via* cannula to a stirring solution of $LiAlH_4$ (335 mg, 8.83 mmol) in THF (12 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 30 minutes, then re-cooled to 0 °C and H_2O (1 mL), 15% aqueous NaOH (1 mL) and H_2O (2 mL) was added dropwise. The mixture was then dried ($MgSO_4$), filtered (Et_2O), concentrated *in vacuo* and purified by column chromatography (30% Et_2O/CH_2Cl_2) to give alcohol (*S*)-**138** (1.29 g, 91%) as a clear oil. $\mathbf{R}_f$ = 0.39 (30% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.26 (5H, m, Ar*H*), 4.52 (2H, s, CH_2Ph), 3.60 (2H, br d, 6.9 Hz, CH_2OH), 3.54 (1H, dd, 9.0, 4.8 Hz, CH_AH$_B$OBn), 3.42 (1H, dd, 9.0, 8.1 Hz, CH$_A$$H_B$OBn), 2.74 (1H, br s, O*H*), 2.13-2.01 (1H, m, C*H*(CH$_3$)CH$_2$OBn), 0.88 (3H, d, 6.9 Hz, CH(CH_3)CH$_2$OBn); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.0, 128.4, 127.7, 127.6, 75.3, 73.3, 67.6, 35.5, 13.4.



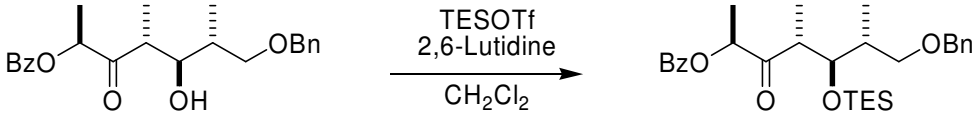
(2*R*)-3-Benzyloxy-2-methylpropan-1-al [(*R*)-133].[15] Oxidation was performed according to Smith's modification of the Swern procedure.[10] To a solution of DMSO

(1.77 mL, 25.0 mmol) in CH_2Cl_2 (35 mL) at −78 °C was added oxalyl chloride (6.24 mL of a 2 M in CH_2Cl_2, 12.5 mmol) over 5 mins. After 30 minutes, alcohol (*S*)-**138** (1.50 mg, 8.32 mmol) in CH_2Cl_2 (5 mL) was added *via* cannula and the resulting mixture stirred at −78 °C for 45 minutes. Triethylamine (6.96 mL, 49.9 mmol) was added over 5 minutes and the resulting white solution was stirred at −78 °C for 30 minutes then at 0 °C for 30 minutes. The reaction was quenched by pouring into a rapidly stirring 1 M aqueous solution of $NaHSO_4$ (50 mL), then the layers were separated and the aqueous phase extracted with Et_2O (3 x 40 mL). The combined organic extracts were concentrated *in vacuo* and the residue diluted with Et_2O (60 mL), then washed successively with 1 M aqueous solution of $NaHSO_4$ (3 x 25 mL), H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2, buffered silica) to give the aldehyde (*R*)-**133** (1.49 mg, 99%) as a clear oil. $\mathbf{R}_f$ = 0.43 (CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.73 (1H, d, 1.8 Hz, C*H*O), 7.38-7.27 (5H, m, Ar*H*), 4.53 (2H, s, CH_2Ph), 3.69 (1H, dd, 9.3, 6.6 Hz, CH_AH$_B$OBn), 3.65 (1H, dd, 9.3, 5.3 Hz, CH$_A$$H_B$OBn), 2.73 (1H, m, C*H*(CH$_3$)CH$_2$OBn), 1.14 (3H, d, 6.9 Hz, CH(CH_3)CH$_2$OBn); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 203.9, 137.8, 128.4, 127.7, 127.5, 73.2, 70.0, 46.7, 10.7.



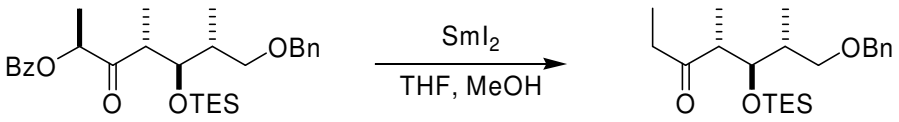
(2*S*,4*R*,5*R*,6*S*)-2-Benzoyloxy-7-benzyloxy-5-hydroxy-4,6-dimethylheptan-3-one (139).[7] The aldol addition was performed according to the procedure of Paterson *et al.*[6,7] To a solution of dicyclohexylboron chloride (1.07 mL, 4.95 mmol) in Et_2O (13 mL) at −78 °C was added Me_2NEt (643 μL, 5.94 mmol) followed by ketone (*S*)-**67** (680 mg, 3.30 mmol) in Et_2O (13 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hours, before being re-cooled to −78 °C. The aldehyde (*R*)-**133** (850 mg, 4.77 mmol) in Et_2O (2 mL) was added *via* cannula and stirring continued at −78 °C for 2 hours then at −23 °C for 14 hours. The reaction was quenched at 0 °C with the addition of MeOH (13 mL), pH 7 buffer solution (13 mL) and 30% aqueous H_2O_2

(13 mL) and stirring maintained for 1 hour at room temperature. The mixture was partitioned between H_2O (60 mL) and CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (50% Et_2O/hexanes) to give the adduct **139** (1.26 g, 99%, >99% d.s.) as a colourless oil. $\mathbf{R}_f$ = 0.34 (50% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = +1.3 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3503, 1718, 1453, 1269, 1116, 1072, 1027, 1002, 989, 713 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (2H, d, 7.2 Hz, Ar*H*), 7.58 (1H, t, 7.2 Hz, Ar*H*), 7.45 (2H, t, 7.2 Hz, Ar*H*), 7.36-7.28 (5H, m, Ar*H*), 5.44 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 4.46 (2H, s, OCH_2Ph), 3.70 (1H, dd, 7.8, 4.4 Hz, C*H*OH), 3.56 (2H, d, 4.8 Hz, CHCH_2OBn), 3.13 (1H, qn, 7.2 Hz, C*H*(CH_3)CHOH), 1.97 (1H, m, C*H*(CH_3)CH_2OBn), 1.53 (3H, d, 7.0 Hz, BzOCH(CH_3)), 1.22 (3H, d, 7.2 Hz, CH(CH_3)CHOH), 1.08 (3H, d, 6.9 Hz, CH(CH_3)CH_2OBn); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.5, 165.8, 138.0, 133.3, 129.8, 129.5, 128.4, 128.4, 127.7, 127.6, 77.1, 75.0, 73.4, 72.0, 46.2, 35.1, 15.8, 15.6, 14.4.



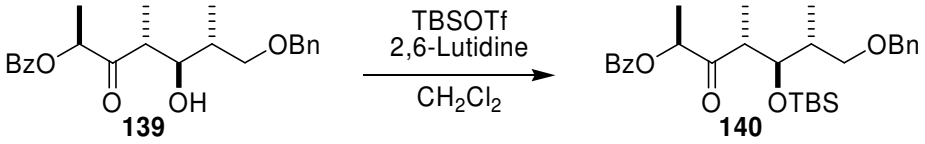
(2*S*,4*R*,5*R*,6*S*)-2-Benzoyloxy-7-benzyloxy-5-triethylsilyloxy-4,6-dimethylheptan-3-one. To a solution of the alcohol **139** (370 mg, 0.93 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added 2,6-lutidine (242 μL, 1.93 mmol) followed by TESOTf (326 μL, 1.45 mmol). After stirring for 30 mins at −78 °C, the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL) and then extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (50% Et_2O/hexanes) to give the protected adduct (460 mg, 99%) as a colourless oil. $\mathbf{R}_f$ = 0.64 (50% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −1.6 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1723, 1454, 1268, 1116, 1072, 1010, 712, 698 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (2H, d, 7.2 Hz, Ar*H*), 7.54 (1H, t, 7.2 Hz, Ar*H*), 7.40 (2H, t, 7.2 Hz, Ar*H*), 7.31-7.20 (5H, m, Ar*H*), 5.39 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 4.41 (2H, s, OCH_2Ph), 3.99 (1H, dd, 9.0, 2.1 Hz, C*H*OTES), 3.57 (1H, dd, 9.3, 6.3 Hz, CHC$H_A$$H_B$OBn), 3.21 (1H, dd, 9.3, 6.9 Hz, CHC$H_A$$H_B$OBn), 3.21 (1H, dq, 9.0, 6.9 Hz, C*H*(CH_3)CHOTES), 2.04

(1H, m, C*H*(CH_3)CH_2OBn), 1.46 (3H, d, 7.0 Hz, BzOCH(C*H*$_3$)), 1.09 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTES), 0.97 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH_2OBn), 0.88 (9H, t, 7.8 Hz, Si(CH_2CH_3)$_3$), 0.53 (6H, q, 7.8 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.4, 165.7, 138.6, 133.2, 129.8, 129.4, 128.3, 127.7, 127.4, 127.4, 76.7, 75.0, 73.0, 71.2, 46.4, 36.6, 15.6, 15.4, 14.3, 7.0, 5.2; **HRESIMS** calculated for $C_{29}H_{42}O_5SiNa^+$ $[M+Na]^+$: 521.2699; found 521.2690; **EIMS** *m/z* (%): 469 (1), 451 (8), 349 (12), 321 (6), 241 (80), 227 (30), 207 (100), 199 (32), 187 (16), 173 (14), 159 (6), 143 (9), 139 (19), 115 (16), 105 (86), 91 (98), 77 (27), 59 (11).

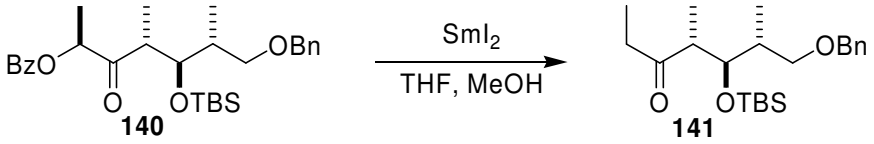


(4*R*,5*R*,6*S*)-7-benzyloxy-5-triethylsilyloxy-4,6-dimethylheptan-3-one. The Reductive cleavage was performed according to the procedure of Paterson *et al.*[7]To a solution of the protected adduct (470 mg, 0.94 mmol) in THF (11 mL) and MeOH (5.7 mL) at 0 °C was added SmI_2 (~38 mL of a 0.1 M solution in THF, ~3.77 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0 °C with the addition of saturated aqueous K_2CO_3 (57 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 80 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/hexanes) afforded the protected hydroxy ketone (180 mg, 54%) as a colourless oil. $\mathbf{R}_f$ = 0.45 (20% Et_2O/hexanes); $[\alpha]^{20}_D$ = −14.0 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1719, 1456, 1377, 1241, 1050, 1009, 736, 698 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar*H*), 4.50 (2H, s, OC*H*$_2$Ph), 3.96 (1H, dd, 8.1, 3.3 Hz, C*H*OTES), 3.60 (1H, dd, 9.3, 5.9 Hz, CHC*H*$_A$H$_B$OBn), 3.28 (1H, dd, 9.3, 7.2 Hz, CHCH$_A$*H*$_B$OBn), 2.86 (1H, qn, 7.2 Hz, C*H*(CH_3)CHOTES), 2.53 (1H, dq, 18.6, 7.2 Hz, CH_3C*H*$_A$H$_B$), 2.42 (1H, dq, 18.2, 7.2 Hz, CH_3CH$_A$*H*$_B$), 2.01 (1H, m, C*H*(CH_3)CH_2OBn), 61.02 (3H, t, 7.2 Hz, C*H*$_3$$CH_2$), 0.98 (6H, d, 7.2 Hz, CH(C*H*$_3$)CHOTES, CH(C*H*$_3$)CH_2OBn), 0.92 (9H, t, 7.9 Hz, Si(CH_2C*H*$_3$)$_3$), 0.56 (6H, q, 7.9 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.3, 138.7, 128.3, 127.4, 127.4, 76.8, 73.0, 71.8, 50.0, 39.8, 36.6, 15.2, 13.7, 7.3, 7.0, 5.2; **HRESIMS** calculated for $C_{22}H_{38}O_3SiNa^+$ $[M+Na]^+$:

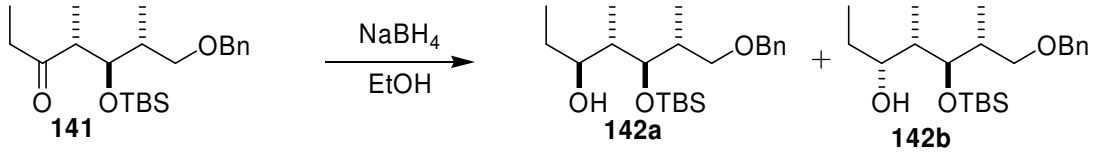
401.2488; found 401.2477; **EIMS** *m/z* (%): 243 (6), 201 (21), 173 (9), 159 (5), 149 (9), 123 (10), 105 (17), 91 (100), 75 (18), 57 (30).



(2*S*,4*R*,5*R*,6*S*)-2-Benzoyloxy-7-benzyloxy-5-tert-butyldimethylsilyloxy-4,6-dimethylheptan-3-one (140).[7] To a solution of the alcohol **139** (1.50 g, 3.93 mmol) in CH_2Cl_2 (39 mL) at −78 °C was added 2,6-lutidine (915 μL, 7.86 mmol) followed by TBSOTf (1.35 mL, 5.89 mmol). The resulting mixture was stirred at −78 °C for 1 hour before being quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 40 mL) and then the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give the protected adduct **140** (1.83 g, 94%) as a colourless oil. $\mathbf{R}_f$ = 0.55 (CH_2Cl_2); $[\alpha]^{20}_{D}$ = −2.1 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1723, 1454, 1268, 1117, 1072, 1048, 836, 778, 712 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (2H, d, 7.5 Hz, Ar*H*), 7.58 (1H, t, 7.5 Hz, Ar*H*), 7.44 (2H, t, 7.5 Hz, Ar*H*), 7.34-7.22 (5H, m, Ar*H*), 5.46 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 4.46 (2H, s, OCH_2Ph), 4.06 (1H, dd, 9.0, 2.4 Hz, C*H*OTBS), 3.60 (1H, dd, 9.6, 6.6 Hz, CHCH_AH$_B$OBn), 3.27 (1H, dd, 9.6, 6.6 Hz, CHCH$_A$$H_B$OBn), 3.23 (1H, dq, 9.0, 6.9 Hz, C*H*(CH_3)CHOTBS), 2.01 (1H, m, C*H*(CH_3)CH_2OBn), 1.51 (3H, d, 7.0 Hz, BzOCH(CH_3)), 1.13 (3H, d, 6.9 Hz, CH(CH_3)CHOTBS), 1.00 (3H, d, 7.2 Hz, CH(CH_3)CH_2OBn), 0.83 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3), −0.06 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.0, 165.6, 138.5, 133.2, 129.8, 128.4, 128.3, 127.5, 127.4, 127.4, 76.0, 74.9, 73.0, 71.8, 46.3, 37.2, 26.2, 18.4, 15.5, 14.9, 14.2, −3.9, −4.9; **HRESIMS** calculated for $C_{29}H_{42}O_5SiNa^+$ $[M+Na]^+$: 521.2699; found 521.2692; **EIMS** *m/z* (%): 423 (4), 349 (5), 319 (3), 293 (4), 213 (25), 199 (8), 179 (36), 157 (5), 145 (8), 105 (54), 91 (100), 75 (13), 57 (2).



(4*R*,5*R*,6*S*)-7-benzyloxy-5-tert-butyldimethylsilyloxy-4,6-dimethylheptan-3-one (141). Reductive cleavage was performed according to the procedure of Paterson *et al.*[7] To a solution of the protected adduct **140** (950 mg, 1.91 mmol) in THF (23 mL) and MeOH (12 mL) at 0 °C was added SmI_2 (~76 mL of a 0.1 M solution in THF, ~7.62 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0 °C with the addition of saturated aqueous K_2CO_3 (120 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/hexanes) afforded the ethyl ketone **141** (714 mg, 99%) as a colourless oil. $\mathbf{R}_f$ = 0.46 (20% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −28.2 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1719, 1473, 1458, 1377, 1253, 1102, 1047, 836, 777, 697, 668 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m, Ar*H*), 4.49 (2H, s, OCH_2Ph), 3.98 (1H, dd, 7.4, 3.5 Hz, C*H*OTBS), 3.58 (1H, dd, 9.2, 5.9 Hz, CHCH_AH$_B$OBn), 3.30 (1H, dd, 9.2, 7.1 Hz, CHCH$_A$$H_B$OBn), 2.83 (1H, qn, 7.2 Hz, C*H*(CH_3)CHOTBS), 2.54 (1H, dq, 18.3, 7.2 Hz, CH_3CH_AH$_B$), 2.44 (1H, dq, 18.3, 7.2 Hz, CH_3CH$_A$$H_B$), 2.07-1.99 (1H, m, C*H*(CH_3)CH_2OBn), 1.01 (3H, t, 7.2 Hz, C$H_3$$CH_2$), 0.99 (3H, d, 7.2 Hz, CH(CH_3)CHOTBS), 0.96 (3H, d, 6.9 Hz, CH(CH_3)CH_2OBn), 0.84 (9H, SiC(CH_3)$_3$), 0.05 (3H, s, SiCH_3), −0.05 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.1, 138.6, 128.3, 127.5, 127.4, 76.2, 73.0, 71.9, 50.1, 37.3, 36.6, 26.1, 18.3, 14.7, 13.6, 7.4, −4.4, −4.6; **HRESIMS** calculated for $C_{22}H_{38}O_3SiNa^+$ $[M+Na]^+$: 401.2488; found 401.2487; **EIMS** *m/z* (%): 229 (8), 215 (11), 173 (31), 145 (6), 115 (5), 91 (100), 75 (8), 57 (14).

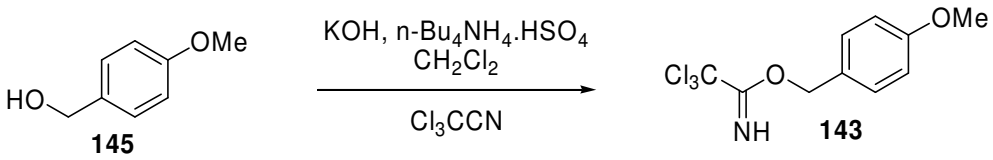


(3R/S,4*R*,5*R*,6*S*)-7-benzyloxy-5-tert-butyldimethylsilyloxy-4,6-dimethylheptan-3-ol (142a and 142b). To a solution of the ketone **141** (1.40 g, 3.70 mmol) in EtOH (19 mL) at 0 °C was added $NaBH_4$ (280 mg, 7.40 mmol) and the resulting mixture was warmed to room temperature. After 5 hours H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (25% Et_2O/hexanes) to give first the *anti*-Felkin isomer, alcohol **142b** (282 mg, 20%) followed by the Felkin isomer, alcohol **142a** (1.13 g, 80%) both as clear oils.

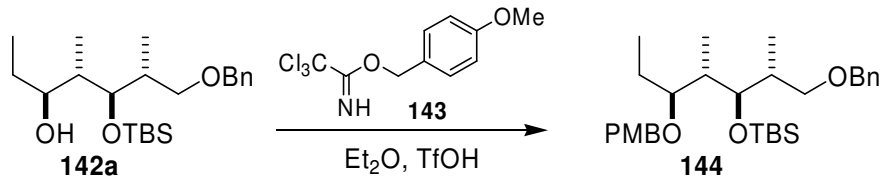
***anti*-Felkin isomer 142b**: $\mathbf{R}_f$ = 0.30 (25% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = + 3.4 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3509, 1462, 1255, 1095, 1041, 1002, 837, 776, 735 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.28 (5H, m, Ar*H*), 4.54 (1H, d, 12.0 Hz, OCH_AH$_B$Ph), 4.44 (1H, d, 12.0 Hz, OCH$_A$$H_B$Ph), 3.99-3.94 (1H, m, C*H*OH), 3.77 (1H, dd, 7.7, 2.3 Hz, C*H*OTBS), 3.50 (1H, dd, 9.0, 5.1 Hz, CHCH_AH$_B$OBn), 3.38 (1H, dd, 9.0, 6.5 Hz, CHCH$_A$$H_B$OBn), 2.20-2.11 (1H, m, C*H*(CH$_3$)CH$_2$OBn), 1.73-1.66 (1H, m, C*H*(CH$_3$)CHOTBS), 1.62-1.48 (1H, m, CH$_3$CH_AH$_B$), 1.39-1.25 (1H, m, CH$_3$CH$_A$$H_B$), 1.00 (3H, d, 6.9 Hz, CH(CH_3)CH$_2$OBn), 0.99 (3H, d, 7.2 Hz, CH(CH_3)CHOTBS), 0.90 (9H, s, SiC(CH_3)$_3$), 0.89 (3H, t, 7.5 Hz, CH_3CH$_2$), 0.12 (3H, SiCH_3), 0.08 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.5, 128.3, 127.6, 127.5, 80.3, 73.0, 72.6 x2, 38.5, 36.6, 27.5, 26.1, 18.2, 14.4, 11.9, 10.5, –3.7, –4.4; **HRESIMS** calculated for $C_{22}H_{40}O_3SiNa^+$ [M+Na] $^+$: 403.2639; found 403.2632.

Felkin isomer142a: $\mathbf{R}_f$ = 0.25 (25% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = –1.2 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3459, 1461, 1362, 1254, 1095, 1040, 1005, 837, 775, 735 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.26 (5H, m, Ar*H*), 4.48 (2H, s, OCH_2Ph), 3.73 (1H, t, 5.0 Hz, C*H*OTBS), 3.52 (1H, dd, 9.3, 6.0 Hz, CHCH_AH$_B$OBn), 3.47 (1H, dt, 8.4, 3.0 Hz, C*H*OH), 3.29 (1H, dd, 9.3, 7.2 Hz, CHCH$_A$$H_B$OBn), 3.08 (1H, br s,

O*H*), 2.13-2.05 (1H, m, C*H*(CH_3)CH_2OBn), 1.78-1.69 (1H, m, C*H*(CH_3)CHOTBS), 1.66-1.55 (1H, m, $CH_3CH_AH_B$), 1.38-1.26 (1H, m, $CH_3CH_AH_B$), 1.00 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH_2OBn), 0.96 (3H, t, 7.4 Hz, C*H*$_3$$CH_2$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.82 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTBS), 0.11 (3H, SiC*H*$_3$), 0.09 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.6, 128.3, 127.5, 127.4, 79.2, 74.6, 72.9, 72.4, 40.6, 39.5, 26.7, 26.0, 18.1, 15.7, 13.9, 9.4, –4.3, –4.5.



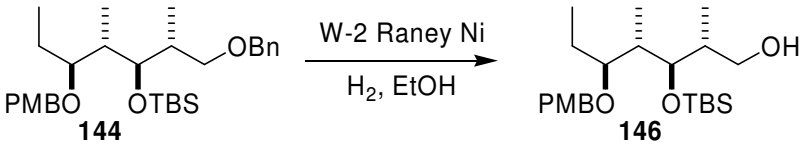
***p*-methoxy-benzyl-2,2,2-trichloroacetimidate (143).** The trichloroacetimidate was synthesized according to the procedure of Patil.[16] To a solution of *p*-methoxy benzyl alcohol (**145**) (4.51 mL, 36.2 mmol) in CH_2Cl_2 (50 mL) at –15 °C was added 50% aqueous KOH (50 mL) followed by tetrabutylammonium hydrogen sulphate (75 mg) and the resulting mixture was stirred vigorously. After 5 minutes trichloroacetonitrile (4.35 mL, 43.4 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 30 minutes then allowed to warm to ambient temperature over an additional 30 minutes. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to approximately 1/3 volume, then filtered through celite (CH_2Cl_2). Finally concentration of the solvent in vacuo gave the imidate **143** (10.1 g, 99%) as a clear yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.36 (1H, br s, N*H*), 7.38 (2H, d, 8.7 Hz, Ar*H*), 6.91 (2H, d, 8.7 Hz, Ar*H*), 5.28 (2H, s, OC*H*$_2$PMP), 3.82 (3H, s, OC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 207.3, 162.6, 159.7, 129.7, 127.5, 113.9, 70.7, 55.2.



(3S,4*R*,5*R*,6*S*)-7-benzyloxy-5-tert-butyldimethylsilyloxy-3-*p*-methoxy-benzyloxy-4,6-dimethylheptane (144). The alcohol was protected employing Paterson's modified procedure.[17] To a solution of the alcohol **142a** (1.00 g, 2.63 mmol) in Et_2O (38 mL) at 0 °C was added *via* cannula PMB imidate **143** (1.49 g, 5.25 mmol) in Et_2O (7.5 mL). The solution was then treated with trifluoromethanesulfonic acid (0.5 μL, 5.25 μmol) and the resulting yellow solution was warmed to room temperature and stirred for 1h. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (30 mL) and the mixture was extracted with Et_2O (3 x 45 mL). The combined organic extracts were washed with brine (45 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to give a solid which was triturated with hexanes to give a yellow oil. Purification of the crude product by column chromatography (80% CH_2Cl_2/ hexanes) gave the PMB ether **144** (1.10 g, 84%) as a colourless oil. $\mathbf{R}_f$ = 0.40 (80% CH_2Cl_2/hexanes); $\mathbf{[\alpha]^{20}_D}$ = +5.9 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1614, 1514, 1464, 1249, 1095, 1038, 835, 774 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.25 (7H, m, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.50 (2H, s, OCH_2PMP), 4.41 (2H, d, 2.4 Hz, OCH_2Ph), 3.80 (3H, s, OCH_3), 3.76 (1H, dd, 6.0, 3.6 Hz, C*H*OTBS), 3.66 (1H, dd, 9.0, 4.5 Hz, CHCH_AH$_B$OBn), 3.49 (1H, ddd, 8.1, 6.6, 3.3 Hz, C*H*OPMB), 3.32 (1H, dd, 9.0, 8.4 Hz, CHCH$_A$$H_B$OBn), 2.17-2.04 (2H, m, C*H*(CH_3)CHOTBS, C*H*(CH_3)CH_2OBn), 1.66-1.56 (1H, m, CH_3CH_AH$_B$), 1.51-1.39 (1H, m, CH_3CH$_A$$H_B$), 1.05 (3H, d, 6.9 Hz, CH(CH_3)CH_2OBn), 0.95 (3H, t, 7.2 Hz, C$H_3$$CH_2$), 0.91 (9H, s, SiC(C$H_3$)$_3$), 0.89 (3H, d, 7.2 Hz, CH(CH_3)CHOTBS), 0.07 (3H, SiCH_3), 0.05 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 158.9, 138.8, 131.3, 129.2, 129.1, 128.2, 127.5, 113.6, 80.5, 75.9, 72.9, 72.7, 70.5, 55.2, 39.8, 37.0, 26.1, 22.3, 18.3, 15.9, 11.0, 9.3, –4.1, –4.2; **HRESIMS** calculated for $C_{30}H_{48}O_4SiNa^+$ $[M+Na]^+$: 523.3214; found 523.3204.

$$NiAl_2 + 6NaOH \xrightarrow{H_2O} \text{W-2 Raney Ni} + 2Na_3AlO_3 + 3H_2$$

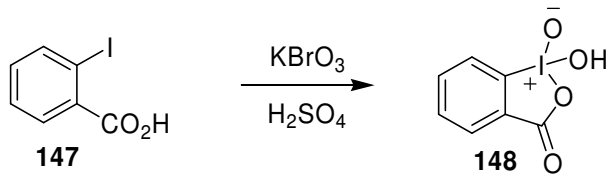
W-2 Raney Nickel. W-2 Raney Ni was synthesized according to the procedure of Mozingo.[18] To a solution of 25% aqueous NaOH (50 mL) at 10 °C was added $NiAl_2$ (10 g) at such a rate as to maintain the temperature below 25 °C. After the addition was complete the reaction was allowed to come to ambient temperature and once hydrogen evolution had become slow the mixture was heated on a steam bath until the evolution of hydrogen had once again become slow. Once cool most of the liquid was decanted and the nickel was then resuspended in water, allowed to settle and again decanted. The nickel was then suspended in a 10% solution of NaOH (17 mL), allowed to settle and then decanted. Finally, the nickel was washed by suspension and decantation with water until the washings were neutral to litmus, then ten times more to remove the alkali completely. The process was repeated 3 times with 95% ethanol and 3 times with absolute ethanol and the catalyst was stored under absolute ethanol in a tightly sealed bottle.



144 **146**

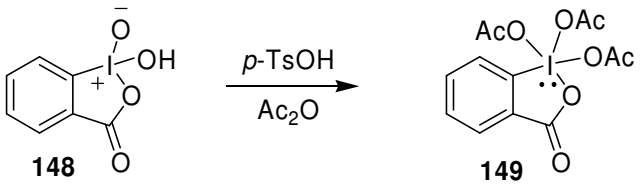
(2*S*,3*R*,4*R*,5*S*)-3-tert-butyldimethylsilyloxy-5-*p*-methoxy-benzyloxy-2,4-dimethylheptan-1-ol (146). Deprotection was performed according to the procedure of Yonemitsu et al.[19] To a suspension of W-2 Raney nickel in EtOH (10 mL) at room temperature was added a solution of the benzyl ether **144** (1.00 g, 2.00 mmol). The reaction vessel was flushed with H_2 three times and then maintained under an atmosphere of H_2 for 6 hours. The mixture was filtered through celite (EtOH) and then concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (5% Et_2O/CH_2Cl_2) gave the alcohol **146** (677 mg, 87%) as a clear oil. $\mathbf{R}_f$ = 0.38 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +6.8 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3447, 1615, 1515, 1465, 1250, 1085, 1037, 836, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.45 (1H, d, 11.1 Hz, OCH_AH_BPMP), 4.31 (1H, d, 11.1, OCH_AH_BPMP), 3.96 (1H, dd, 5.4, 3.9 Hz,

C*H*OTBS), 3.80 (3H, s, OCH_3), 3.73 (1H, dd, 10.8, 3.9 Hz, CHCH_AH$_B$OH), 3.57 (1H, dd, 10.8, 5.4 Hz, CHCH$_A$$H_B$OH), 3.39 (1H, ddd, 7.2, 6.0, 3.9 Hz, C*H*OPMB), 2.37 (1H, br s, O*H*), 2.08 (1H, qdd, 7.2, 6.0, 5.4 Hz, C*H*(CH$_3$)CHOTBS), 1.94-1.83 (1H, m, C*H*(CH$_3$)CH$_2$OH), 1.70 (1H, dqd, 14.7, 7.2, 3.9 Hz, CH$_3$CH_AH$_B$), 1.48 (1H, dqd, 14.7, 7.2, 7.2 Hz, CH$_3$CH$_A$$H_B$), 0.99 (3H, d, 7.2 Hz, CH(CH_3)CH$_2$OH), 0.94-0.90 (15H, m, CH_3CH$_2$, SiC(CH_3)$_3$, CH(CH_3)CHOTBS), 0.11 (3H, SiCH_3), 0.07 (3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.0, 131.1, 128.9, 113.7, 80.2, 78.1, 70.1, 66.4, 55.3, 41.2, 36.0, 26.0, 22.1, 18.1, 16.8, 10.7, 8.2, –4.3, –4.4.



147 **148**

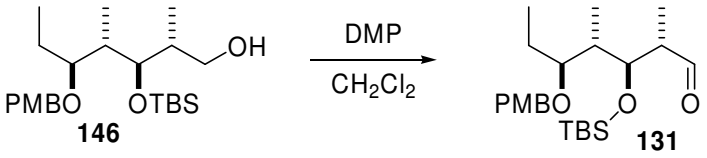
2-Iodoxybenzoic acid (148). Iodobenzoic acid was synthesized according to the procedure of Dess and Martin.[20] To a slurry of 2-iodobenzoic acid (**147**) (45.88 g, 0.185 mol) in a 0.7 M solution of H_2SO_4 (370 mL) at 55 °C was added $KBrO_3$ (40.2 g, 0.240 mol) in small portions over 30 minutes. The resulting mixture was stirred at 68 °C for 3.6 hours then cooled on ice and filtered at the pump with washing H_2O (500 mL) and EtOH (2 x 25 mL). The product was dried on a high vacuum pump, giving the title compound **148** (45.7 g, 88%) as a white solid, **m.p.** 232-234 °C (lit. mp 233 °C)[20].



148 **149**

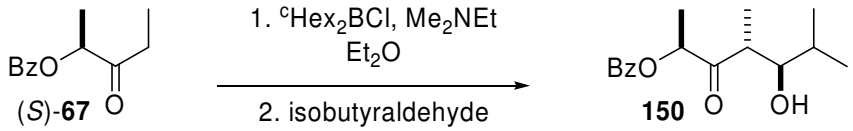
1,1,1-Triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1*H*)-one (149).[20] The acetylation was performed according to the procedure of Ireland *et al.*[21] To a solution of *p*-TsOH·H_2O (229 mg) in acetic anhydride (183 mL) in a flask fitted with a drying tube at ambient temperature was added 2-iodoxybenzoic acid (**148**) (45.7 g, 0.160 mol) and the resulting mixture was emmersed in an 80 °C bath and stirred for 2 hours. The

reaction mixture was then cooled on ice and filtered with rinsing (anhydrous Et_2O, 5 x 50 mL) and then dried on a high vacuum pump to give Dess-Martin Periodinane **149** (51.9 g, 75%) as a white solid, **m.p.** 133 °C (lit. 132-134 °C).[20] The solid was transferred to an amber glass bottle under a stream of nitrogen and stored in the freezer.

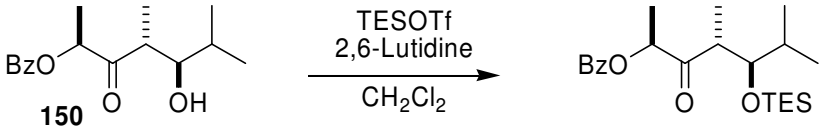


(2*S*,3*S*,4*S*,5*S*)-3-tert-butyldimethylsilyloxy-5-*p*-methoxy-benzyloxy-2,4-dimethylheptan-1-al (131). Oxidation was performed according to the procedure of Dess and Martin.[22] To a solution of the alcohol **146** (345 mg, 0.84 mmol) in CH_2Cl_2 (8.5 mL) at room temperature was added Dess-Martin Periodinane (535 mg, 1.26 mmol) and the resulting suspension was stirred in darkness for 1 hour. The reaction was diluted with Et_2O (20 mL) then quenched with the addition of a solution of $Na_2S_2O_3$ (2.14 g) in saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) gave the aldehyde **134** (330 mg, 96%) as a clear oil. $\mathbf{R}_f$ = 0.59 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +30.8 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1722, 1614, 1587, 1515, 1464, 1303, 1250, 1174, 1097, 1038, 837, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.81 (1H, d, 2.7 Hz, C*H*O), 7.28 (2H, d, 8.7 Hz, Ar*H*), 6.90 (2H, d, 8.7 Hz, Ar*H*), 4.49 (1H, d, 11.1 Hz, OCH_AH_BPMP), 4.36 (1H, d, 11.1, OCH_AH_BPMP), 4.14 (1H, dd, 5.4, 2.7 Hz, C*H*OTBS), 3.83 (3H, s, OCH_3), 3.42 (1H, td, 6.9, 3.6 Hz, C*H*OPMB), 2.52 (1H, qdd, 6.9, 5.4, 2.7 Hz, $CH(CH_3)CHO$), 2.07 (1H, qdd, 6.9, 3.5, 2.7 Hz, $CH(CH_3)CHOTBS$), 1.70 (1H, dqd, 14.7, 7.2, 3.6 Hz, $CH_3CH_AH_B$), 1.49 (1H, dqn, 14.7, 7.2 Hz, $CH_3CH_AH_B$), 1.11 (3H, d, 6.9 Hz, $CH(CH_3)CHO$), 0.96 (3H, t, 7.2 Hz, CH_3CH_2), 0.93 (9H, s, $SiC(CH_3)_3$), 0.84 (3H, d, 6.9 Hz, $CH(CH_3)CHOTBS$), 0.11 (3H, $SiCH_3$), 0.09 (3H, s, $SiCH_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.3, 159.0, 130.9, 129.1, 113.7, 80.2, 75.2, 70.5, 55.2, 49.3, 40.8, 25.8, 22.1, 18.1, 12.2, 10.9, 8.5, –4.4, –4.7; **HRESIMS** calculated for

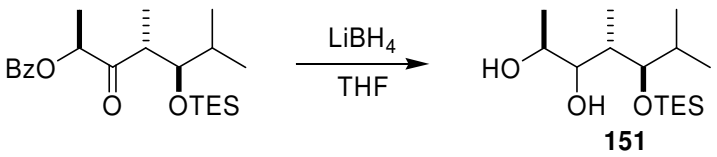
$C_{23}H_{40}O_4SiNa^+$ $[M+Na]^+$: 431.2594; found 431.2589; **EIMS** *m/z* (%): 241 (4), 137 (4), 121 (100), 99 (2), 85 (5), 75 (8), 57 (10).



(2*S*,4*R*,5*R*)-2-Benzoyloxy-5-hydroxy-4,6-dimethylheptan-3-one (150).[6,7] The aldol addition was performed according to the procedure of Paterson *et al*.[6,7] To a solution of dicyclohexylboron chloride (1.58 mL, 7.27 mmol) in Et_2O (20 mL) at −78 °C was added Me_2NEt (946 μL, 8.73 mmol) followed by ketone (*S*)-**67** (1.00 g, 4.85 mmol) in Et_2O (20 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hours, before being re-cooled to −78 °C. Isobutyraldehyde (1.76 mL, 19.4 mmol) was added and stirring continued at −78 °C for 2 hours then at −23 °C for 14 hours. The reaction was quenched at 0 °C with the addition of MeOH (20 mL), pH 7 buffer solution (20 mL) and 3% aqueous H_2O_2 (20 mL) and stirring maintained for 1 hour at room temperature. The mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (60% Et_2O/hexanes) to give the adduct **150** (1.34 g, 99%, >95% d.s.) as a white solid. **m.p.** 94-95 °C (lit. 93-94 °C)[7]; $\mathbf{R_f}$ = 0.44 (60% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = +46.1 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3547, 1731, 1699, 1455, 1318, 1307, 1295, 1277, 1127, 993, 713 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (2H, d, 7.8 Hz, Ar*H*), 7.58 (1H, t, 7.4 Hz, Ar*H*), 7.46 (2H, dd, 7.8, 7.4 Hz, Ar*H*), 5.46 (1H, q, 7.1 Hz, BzOC*H*(CH_3)), 3.58 (1H, dd, 7.7, 4.1 Hz, C*H*OH), 3.01 (1H, qn, 7.2 Hz, C*H*(CH_3)CHOH), 2.25 (1H, br s, O*H*), 1.78 (1H, septet, d, 6.9, 4.1 Hz, C*H*(CH_3)$_2$), 1.57 (3H, d, 7.1 Hz, BzOCH(C*H*$_3$)), 1.23 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOH), 0.96 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH$_3$), 0.89 (3H, d, 6.9 Hz, CH(CH$_3$)C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.0, 165.9, 133.3, 129.8, 129.5, 128.4, 77.7, 74.7, 45.4, 29.8, 20.0, 15.9, 15.2, 14.4; **HRESIMS** calculated for $C_{16}H_{22}O_4Na^+$ $[M+Na]^+$: 301.1416; found 301.1416; **EIMS** *m/z* (%): 279 (2), 235 (7), 206 (3), 177 (5), 150 (56), 129 (18), 113 (13), 105 (100), 77 (31), 57 (14), 43 (9).

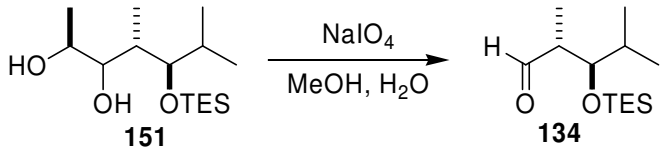


(2*S*,4*R*,5*R*)-2-Benzoyloxy-5-triethylsilyloxy-4,6-dimethylheptan-3-one. To a solution of the alcohol **150** (1.01 g, 3.59 mmol) in CH_2Cl_2 (36 mL) at −78 °C was added 2,6-lutidine (837 μL, 7.19 mmol) followed by TESOTf (1.22 mL, 5.39 mmol). After stirring for 30 mins at −78 °C the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ (100 mL) and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (20% Et_2O/hexanes) to give the TES protected adduct (1.43 g, 99%) as a colourless oil. $\mathbf{R}_f$ = 0.42 (20% Et_2O/hexanes); $[\alpha]^{20}_D$ = −0.62 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1723, 1268, 1116, 1052, 1009, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (2H, d, 8.4 Hz, Ar*H*), 7.58 (1H, t, 7.4 Hz, Ar*H*), 7.45 (2H, dd, 8.4, 7.4 Hz, Ar*H*), 5.44 (1H, q, 6.9 Hz, BzOC*H*(CH_3)), 3.89 (1H, dd, 8.9, 2.3 Hz, C*H*OTES), 3.04 (1H, dq, 8.9, 7.2 Hz, C*H*(CH_3)CHOTES), 1.78 (1H, septet, d, 6.9, 2.3 Hz, C*H*(CH_3)$_2$), 1.52 (3H, d, 6.9 Hz, BzOCH(C*H*$_3$)), 1.10 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTES), 0.96 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.93 (9H, t, 7.8 Hz, Si(CH_2C*H*$_3$)$_3$), 0.85 (3H, d, 6.9 Hz, CH(CH_3)C*H*$_3$), 0.57 (6H, q, 7.8 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.4, 165.7, 133.2, 129.8, 129.8, 128.4, 77.9, 75.0, 46.6, 30.5, 19.9, 15.6, 15.4, 14.3, 7.0, 5.3; **HRESIMS** calculated for $C_{22}H_{36}O_4SiNa^+$ $[M+Na]^+$: 415.2281; found 415.2273; **EIMS** *m/z* (%): 369 (2), 349 (2), 291 (4), 241 (15), 207 (100), 199 (9), 187 (4), 177 (2), 159 (4), 149 (1), 135 (2), 115 (9), 105 (28), 87 (9), 77 (9), 59 (5).



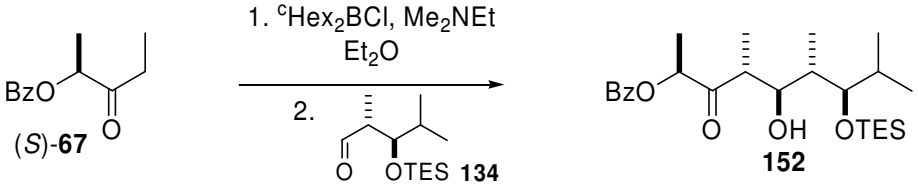
(2*S*,3*R*,4*S*,5*R*)-5-triethylsilyloxy-4,6-dimethylheptan-2,3-diol (151). The reduction was performed according to the procedure of Paterson *et al.*[6,7] To a solution of the TES protected adduct (1.43 g, 3.64 mmol) in THF (36 mL) at −78 °C was added $LiBH_4$ (36 mL of a 2 M solution in THF, 72.9 mmol). The reaction mixture was

warmed to room temperature slowly and stirred for 24 hours, then cooled to 0 °C and carefully quenched with the addition of H_2O. The mixture was partitioned between H_2O (100 mL) and Et_2O (4 x 120 mL) and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (50% Et_2O/hexanes) to give the diol **151** and benzyl alcohol as an inseparable mixture (1.43 g, 99% by NMR). A small amount of diol was separated to allow characterisation but ultimately the mixture was used unseparated in the next step. $\mathbf{R}_f$ = 0.12 (50% Et_2O/hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.76 (1H, qd, 6.4, 3.9 Hz, C*H*(CH_3)OH), 3.63 (1H, dd, 8.6, 3.9 Hz, C*H*OH), 3.45 (1H, t, 5.3 Hz, C*H*OTES), 1.85 (1H, m, CH(OH)C*H*(CH_3)CH), 1.75 (1H, m, C*H*(CH_3)$_2$), 1.16 (3H, d, 6.4 Hz, CH(C*H*$_3$)OH), 0.99 (9H, t, 8.0 Hz, Si(CH_2CH_3)$_3$), 0.93 (3H, d, 6.6 Hz, CH(OH)CH(C*H*$_3$)CH), 0.90 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.85 (3H, d, 7.2 Hz, CH(CH_3)C*H*$_3$), 0.67 (6H, q, 8.0 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 83.2, 76.3, 67.6, 38.4, 33.2, 19.0, 18.3, 16.4, 15.2, 6.9, 5.2.



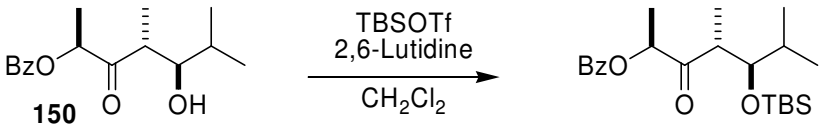
(2*R*,3*R*)-3-triethylsilyloxy-2,4-dimethylpentanal (134). The oxidation was performed according to the procedure of Paterson *et al*.[6,7] To a stirred solution of the 1,2-diol **151** (333 mg, 1.15 mmol) in MeOH (11.5 mL) and H_2O (5.7 mL) at room temperature was added $NaIO_4$ (1.47 g, 6.88 mmol) and the resulting white suspension was stirred for 10 minutes. The reaction mixture was diluted with H_2O (36 mL) and extracted with Et_2O (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography (10% Et_2O/hexanes) to give the aldehyde **134** (263 mg, 94%) as clear oil. $\mathbf{R}_f$ = 0.43 (10% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −37.5 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1727, 1459, 1241, 1094, 1056, 1041, 1010, 819, 740, 728 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.77 (1H, d, 2.7 Hz, C*H*O), 3.68 (1H, t, 4.8 Hz, C*H*OTES), 2.52 (1H, m, C*H*(CH_3)CHOTES), 1.82 (1H, m, C*H*(CH_3)$_2$), 1.08 (3H, d, 6.9 Hz,

CH(CH_3)CHOTES), 0.95 (9H, t, 8.1 Hz, Si(CH$_2$CH_3)$_3$), 0.92 (3H, d, 6.6 Hz, CH(CH_3)CH$_3$), 0.90 (3H, d, 6.9 Hz, CH(CH$_3$)CH_3), 0.61 (6H, q, 8.1 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 205.2, 79.4, 50.0, 32.6, 19.0, 17.9, 11.8, 6.9, 5.2.

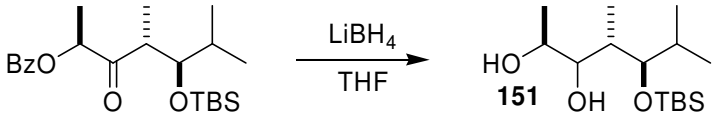


(2*S*,4*R*,5*R*,6*S*,7*R*)-2-Benzoyloxy-5-hydroxy-7-triethylsilyloxy-4,6,8-trimethylnon-3-one (152). The aldol addition was performed according to the procedure of Paterson *et al*.[6,7] To a solution of dicyclohexylboron chloride (772 μL, 3.56 mmol) in Et$_2$O (5 mL) at −78 °C was added Me$_2$NEt (452 μL, 417 mmol) followed by ketone (*S*)-**67** (481 mg, 2.33 mmol) in Et$_2$O (5 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hours, before being re-cooled to −78 °C. A solution of aldehyde **134** (300 mg, 1.23 mmol) in Et$_2$O (1 mL) was added *via* cannula and stirring continued at −78 °C for 2 hours then at −23 °C for 14 hours. The reaction was quenched at 0 °C with the addition of MeOH (5 mL), pH 7 buffer solution (5 mL) and 30% aqueous H$_2$O$_2$ (5 mL) and stirring maintained for 1 hour at room temperature. The mixture was partitioned between H$_2$O (60 mL) and CH$_2$Cl$_2$ (3 x 60 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (50% Et$_2$O/hexanes) to give the adduct **152** (149 mg, 27%, >95% d.s.) as a colourless oil. **R$_f$** = 0.55 (50% Et$_2$O/hexanes); **[α]$^{20}_D$** = +25.3 (*c* 1.5, CHCl$_3$); **IR** (CHCl$_3$, FT, film) 3475, 1724, 1454, 1270, 1178, 1119, 1058, 1006, 713 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 8.08 (2H, d, 7.8 Hz, Ar*H*), 7.58 (1H, t, 7.8 Hz, Ar*H*), 7.45 (2H, d, 7.8 Hz, Ar*H*), 5.49 (1H, q, 6.9 Hz, BzOC*H*(CH$_3$)), 3.69 (1H, m, C*H*OTES), 3.63-3.56 (2H, m, C*H*OH, O*H*), 3.10 (1H, qd, 7.1, 4.4 Hz, C*H*(CH$_3$)CHOH), 2.00-1.81 (2H, m, C*H*(CH$_3$)CHOTES, C*H*(CH$_3$)$_2$), 1.55 (3H, d, 6.9 Hz, BzOCH(CH_3)), 1.36 (3H, d, 7.2 Hz, CH(CH_3)CHOH), 0.93 (9H, t, 7.8 Hz, Si(CH$_2$CH_3)$_3$), 0.89 (6H, d, 6.6 Hz, CH(CH_3)$_3$), 0.85 (3H, d, 6.9 Hz, CH(CH_3)CHOTES), 0.59 (6H, q, 7.8 Hz, Si(CH_2CH$_3$)$_3$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 212.2, 165.7, 133.3, 129.8, 129.5,

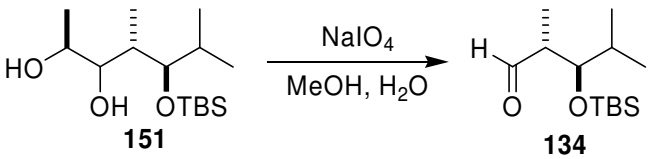
128.4, 80.4, 77.3, 74.7, 45.3, 41.1, 31.6, 20.5, 18.5, 16.2, 15.3, 14.9, 6.9, 5.2; **HRESIMS** calculated for $C_{25}H_{42}O_5SiNa^+$ $[M+Na]^+$: 473.2699; found 473.2705; **EIMS** *m/z* (%): 215 (14), 187 (15), 177 (12), 159 (9), 143 (9), 115 (22), 105 (100), 84 (25), 77 (27), 57 (11), 51 (15).



(2*S*,4*R*,5*R*)-2-Benzoyloxy-5-tert-butyldimethylsilyloxy-4,6-dimethylheptan-3-one.[6,7] To a solution of the alcohol **150** (1.35 g, 4.85 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added 2,6-lutidine (1.13 mL, 9.70 mmol) followed by TBSOTf (2.07 mL, 9.01 mmol). After stirring for 1 hour at −78 °C the reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (100 mL) and the mixture extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (20% Et_2O/hexanes) to give the protected adduct (1.89 g, 99%) as a colourless oil. $\mathbf{R}_f$ = 0.53 (20% Et_2O/hexanes); $[\alpha]^{20}_D$ = −7.9 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1722, 1452, 1267, 1117, 1048, 838, 776, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (2H, d, 7.4 Hz, Ar*H*), 7.58 (1H, t, 7.4 Hz, Ar*H*), 7.46 (2H, d, 7.4 Hz, Ar*H*), 5.47 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 3.89 (1H, dd, 8.6, 2.3 Hz, C*H*OTBS), 3.07 (1H, dq, 8.7, 6.9 Hz, C*H*(CH_3)CHOTBS), 1.80 (1H, sep d, 6.9, 2.4 Hz, C*H*(CH_3)$_2$), 1.53 (3H, d, 6.9 Hz, BzOCH(C*H*$_3$)), 1.11 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTBS), 0.95 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.88 (3H, d, 6.9 Hz, CH(CH_3)C*H*$_3$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.05 (3H, s, SiC*H*$_3$), −0.07 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.1, 165.7, 133.2, 129.8, 129.8, 128.4, 77.5, 74.9, 46.5, 31.0, 26.2, 19.7, 18.5, 16.0, 15.5, 14.3, −3.7, −4.7.

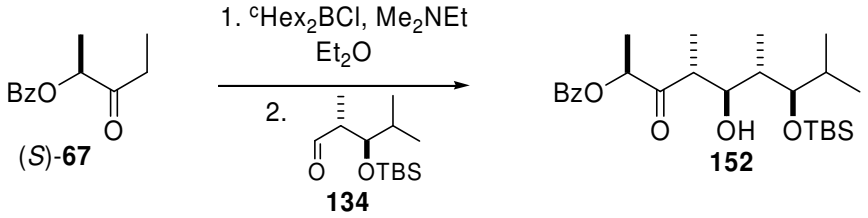


(2*S*,3*R*,4*S*,5*R*)-5-tert-butyldimethylsilyloxy-4,6-dimethylheptan-2,3-diol (151).[6,7] The reduction was performed according to the procedure of Paterson *et al.*[6,7] To a solution of the protected adduct (1.88 g, 4.79 mmol) in THF (50 mL) at −78 °C was added $LiBH_4$ (50 mL of a 2 M solution in THF, 95.8 mmol). The reaction mixture was warmed to room temperature slowly and stirred for 24 hours, then cooled to 0 °C and carefully quenched with the addition of H_2O. The mixture was partitioned between H_2O (150 mL) and Et_2O (4 x 150 mL) and the combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (50% Et_2O/hexanes) to give the diol **151** and benzyl alcohol as an inseparable mixture (1.87 g, 99% by NMR). A small amount of diol was separated to allow characterisation but ultimately the mixture was used unseparated in the next step. $\mathbf{R}_f$ = 0.22 (50% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −7.6 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3424, 1466, 1387, 1254, 1112, 1052, 837, 774 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.80-3.71 (1H, m, C*H*(CH_3)OH), 3.64 (1H, dd, 9.3, 3.3 Hz, C*H*OH), 3.46 (1H, t, 4.8 Hz, C*H*OTBS), 1.97-1.78 (1H, m, C*H*(CH_3)CHOH), 1.75-1.66 (1H, m, C*H*(CH_3)$_2$), 1.15 (3H, d, 6.3 Hz, CH(C*H*$_3$)OH), 0.93 (9H, s, SiC(C*H*$_3$)$_3$), 0.93 (3H, d, 6.6 Hz, CH(C*H*$_3$)CHOH), 0.90 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.84 (3H, d, 7.2 Hz, CH(CH_3)C*H*$_3$), 0.13 (3H, SiC*H*$_3$), 0.10 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 82.5, 76.2, 67.9, 38.2, 33.6, 26.0, 19.0, 18.3, 18.2, 15.9, 15.5, −4.0, −4.3.



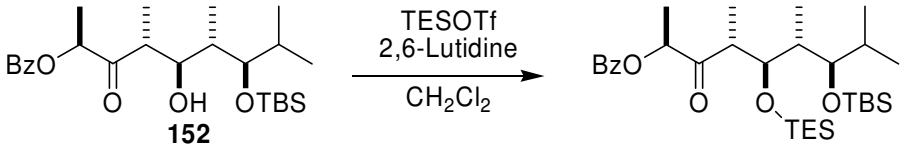
(2*R*,3*R*)-3-tert-butyldimethylsilyloxy-2,4-dimethylpentanal (134).[6,7] The oxidation was performed according to the procedure of Paterson *et al.*[6,7] To a stirred solution of the 1,2-diol **151** (553 mg, 1.90 mmol) in MeOH (19 mL) and H_2O (9.5 mL) at room temperature was added $NaIO_4$ (2.44 g, 11.4 mmol) and the resulting

white suspension was stirred for 10 minutes. The reaction mixture was diluted with H_2O (80 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (10% Et_2O/hexanes) to give the aldehyde **134** (462 mg, 94%) as clear oil. $\mathbf{R}_f$ = 0.45 (10% Et_2O/hexanes); $[\alpha]^{20}_D$ = −40.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1726, 1467, 1389, 1255, 1091, 1043, 841, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.77 (1H, d, 2.7 Hz, C*H*O), 3.67 (1H, dd, 5.1, 3.9 Hz, C*H*OTBS), 2.52 (1H, m, C*H*(CH_3)CHOTBS), 1.83 (1H, m, C*H*(CH_3)$_2$), 1.09 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.92 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.89 (3H, d, 6.6 Hz, CH(CH_3)C*H*$_3$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.1, 79.2, 49.9, 32.9, 25.9, 18.8, 18.2 (x 2), 12.0, −4.1, −4.3.



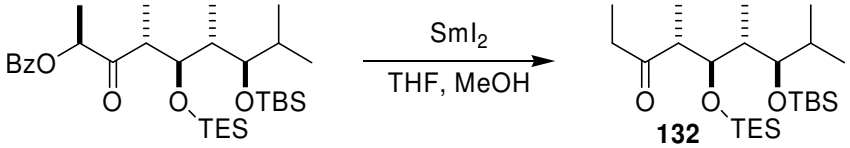
(2*S*,4*R*,5*R*,6*R*,7*R*)-2-Benzoyloxy-7-tert-butyldimethylsilyloxy-5-hydroxy-4,6,8-trimethylnon-3-one (152). The aldol addition was performed according to the procedure of Paterson *et al*.[6,7] To a solution of dicyclohexylboron chloride (316 μL, 1.46 mmol) in Et_2O (3.9 mL) at −78 °C was added Me_2NEt (189 μL, 1.75 mmol) followed by ketone (*S*)-**67** (200 mg, 0.97 mmol) in Et_2O (3.9 mL). The reaction mixture was warmed to 0 °C and stirred for 2 hours, before being re-cooled to −78 °C. A solution of aldehyde **134** (356 mg, 1.46 mmol) in Et_2O (0.5 mL) was added *via* cannula and stirring continued at −78 °C for 2 hours then at −23 °C for 14 hours. The reaction was quenched at 0 °C with the addition of MeOH (3.9 mL), pH 7 buffer solution (3.9 mL) and 30% aqueous H_2O_2 (3.9 mL) and stirring maintained for 1 hour at room temperature. The mixture was partitioned between H_2O (30 mL) and CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (CH_2Cl_2) to give the adduct **152** (338 mg, 77%, >95% d.s.) as a colourless oil. $\mathbf{R}_f$ =

0.25 (CH_2Cl_2); $[\alpha]^{20}_D$ = +29.1 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3504, 1722, 1263, 1116, 1050, 839, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 (2H, d, 7.5 Hz, Ar*H*), 7.58 (1H, t, 7.5 Hz, Ar*H*), 7.45 (2H, d, 7.5 Hz, Ar*H*), 5.48 (1H, q, 6.9 Hz, BzOC*H*(CH_3)), 3.69 (1H, 4.2, C*H*OTBS), 3.54 (1H, dd, 6.3, 3.6 Hz, C*H*OH), 3.50 (1H, br s, O*H*), 3.09 (1H, qd, 7.2, 3.6 Hz, C*H*(CH_3)CHOH), 1.92-1.82 (2H, m, C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$), 1.55 (3H, d, 6.9 Hz, BzOCH(C*H*$_3$)), 1.40 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOH), 0.91-0.84 (18H, m, SiC(C*H*$_3$)$_3$, CH(C*H*$_3$)CHOTBS, CH(C*H*$_3$)CH$_3$, CH(CH$_3$)C*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.5, 165.7, 133.4, 129.8, 129.4, 128.4, 78.8, 77.3, 74.6, 44.9, 42.1, 31.1, 26.0, 21.0, 18.5, 18.2, 16.2, 15.1, 14.2, –4.1, –4.5; **HRESIMS** calculated for $C_{25}H_{42}O_5SiNa^+$ $[M+Na]^+$: 473.2699; found 473.2699; **EIMS** *m/z* (%): 453 (1), 389 (2), 334 (6), 301 (7), 267 (16), 257 (15), 199 (16), 187 (47), 179 (25), 177 (21), 131 (75), 105 (100).



(2*S*,4*R*,5*R*,6*R*,7*R*)-2-Benzoyloxy-7-tert-butyldimethylsilyloxy-5-triethylsilyloxy-4,6,8-trimethylnon-3-one. To a solution of the alcohol **152** (65.0 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C was added 2,6-lutidine (34 μL, 0.29 mmol) followed by TESOTf (49.0 μL, 0.22 mmol). After stirring for 1 hour at −78 °C the reaction mixture was warmed to room temperature and stirred for 10 minutes. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (5 mL) and the mixture partitioned between water (5 mL) and CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (50% CH_2Cl_2/hexanes) to give the protected adduct (78 mg, 96%) as a colourless oil. $\mathbf{R}_f$ = 0.49 (50% CH_2Cl_2/hexanes); $[\alpha]^{20}_D$ = –4.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1723, 1266, 1116, 1048, 1005, 835, 774, 711 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (2H, d, 7.4 Hz, Ar*H*), 7.57 (1H, t, 7.4 Hz, Ar*H*), 7.45 (2H, t, 7.4 Hz, Ar*H*), 5.46 (1H, q, 7.0 Hz, BzOC*H*(CH_3)), 4.32 (1H, dd, 8.4, 3.5 Hz, C*H*OTES), 3.62 (1H, dd, 8.0, 2.3 Hz, C*H*OTBS), 3.11 (1H, dq, 8.4,

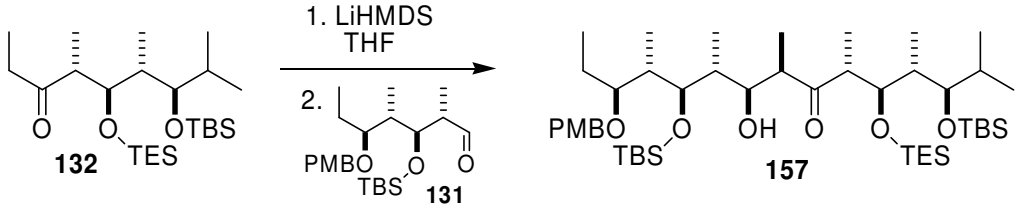
6.9 Hz, C*H*(CH_3)CHOTES), 1.88 (2H, m, C*H*(CH_3)CHOTBS, C*H*(CH_3)CH_3), 1.52 (3H, d, 7.0 Hz, BzOC*H*(CH_3)), 1.18 (3H, d, 6.9 Hz, CH(CH_3)CHOTES), 0.94-0.88 (24H, m, CH(CH_3)CH_3, CH(CH_3)CHOTBS, SiC(CH_3)$_3$, Si(CH_2CH_3)$_3$), 0.86 (3H, d, 6.9 Hz, CH(CH_3)CH_3), 0.57 (6H, q, 8.1 Hz, Si(C$H_2$$CH_3$)$_3$), 0.16 (3H, s, SiC$H_3$), 0.04 (3H, s, SiC$H_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.8, 165.7, 133.2, 129.8, 129.8, 128.4, 77.2, 74.8, 74.1, 46.6, 43.8, 31.2, 26.3, 20.5, 18.6, 16.3, 15.5, 13.7, 11.0, 6.9, 5.1, −4.1, −4.5; **HRESIMS** calculated for $C_{31}H_{56}O_5Si_2Na^+$ $[M+Na]^+$: 587.3564; found 587.3569; **EIMS** *m/z* (%): 389 (1), 267 (7), 263 (15), 257 (9), 227 (27), 207 (44), 187 (99), 179 (100), 131 (84), 105 (39).



132

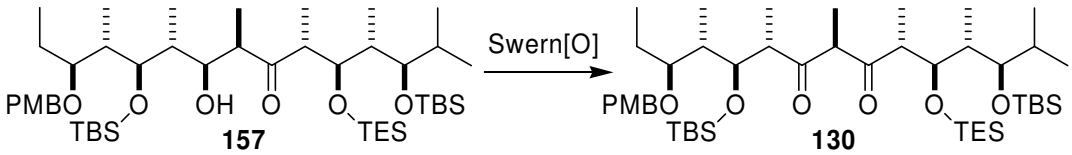
(4*R*,5*R*,6*R*,7*R*)-7-tert-butyldimethylsilyloxy-5-triethylsilyloxy-4,6,8-trimethylnon-3-one (132). The reductive cleavage was performed according to the procedure of Paterson *et al*.[6,7] To a solution of the protected adduct (540 mg, 0.96 mmol) in THF (12 mL) and MeOH (6 mL) at 0 °C was added SmI_2 (~38 mL of a 0.1 M solution in THF, ~3.82 mmol) until a deep green colour persisted in the reaction mixture. The reaction was quenched at 0 °C with the addition of saturated aqueous K_2CO_3 (60 mL) and allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (3 x 70 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (50% CH_2Cl_2/hexanes) afforded the ethyl ketone **132** (400 mg, 94%) as a colourless oil. $\mathbf{R}_f$ = 0.37 (50% CH_2Cl_2/hexanes); $[\alpha]^{20}_D$ = −8.7 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1721, 1463, 1251, 1107, 1086, 1051, 1006, 970, 869, 835, 773, 741 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.19 (1H, dd, 6.2, 5.3 Hz, C*H*OTES), 3.66 (1H, dd, 6.8, 2.6 Hz, C*H*OTBS), 2.73 (1H, qn, 6.8 Hz, C*H*(CH_3)CHOTES), 2.56 (1H, dq, 18.5, 7.2 Hz, $CH_3CH_AH_B$), 2.47 (1H, dq, 18.5, 7.2 Hz, $CH_3CH_AH_B$), 1.92-1.77 (2H, m, C*H*(CH_3)CHOTBS, C*H*(CH_3)CH_3), 1.07 (3H, d, 7.2 Hz, CH(CH_3)CHOTES), 1.02 (3H, t, 7.2 Hz, C$H_3$$CH_2$), 0.97-0.92 (12H, m, CH(CH_3)CH_3, Si(CH_2CH_3)$_3$), 0.91 (3H, s, SiC(CH_3)$_3$), 0.86 (3H, d, 6.9 Hz, CH(CH_3)CH_3), 0.80 (3H, d, 7.2 Hz, CH(CH_3)CHOTBS), 0.59 (6H, q, 8.0 Hz, Si(C$H_2$$CH_3$)$_3$), 0.11 (3H, s, SiC$H_3$), 0.05

(3H, s, SiCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.0, 76.9, 75.1, 50.7, 43.7, 35.7, 31.0, 26.2, 20.9, 18.5, 17.0, 12.8, 11.0, 7.5, 7.0, 5.2, −3.4, −4.4; **HRESIMS** calculated for $C_{24}H_{52}O_3Si_2Na^+$ $[M+Na]^+$: 467.3353; found 473.3348; **EIMS** *m/z* (%): 350 (19), 334 (100), 319 (33), 287 (13), 275 (6), 267 (6), 257 (6), 215 (10), 199 (9), 187 (40), 131 (68), 105 (50).



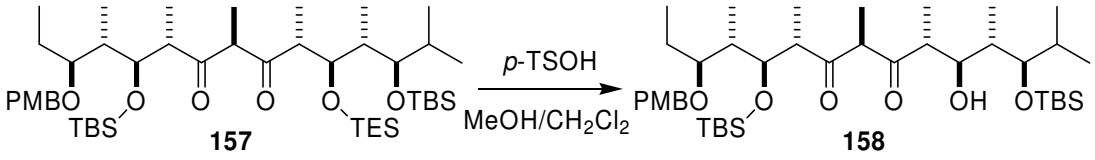
(3*R*,4*R*,5*R*,6*R*,8*R*,9*S*,10*S*,11*S*,12*S*,13*S*)-3,11-bis-[tert-butyldimethylsilyloxy]-5-triethylsilyloxy-9-hydroxy-2,4,6,8,10,12,-hexamethyl-13-[4-methoxy-benzyloxy]-pentadec-7-one (157). To a solution of the ketone **132** (30.4 mg, 68.3 μmol) in THF (140 μL) at −78 °C was added LiHMDS (82 μL of a 1.0 M solution in THF, 82.0 μmol) dropwise and the resulting yellow solution was stirred at −78 °C for 30 minutes and then at −50 °C for a further 30 minutes. The reaction was re-cooled to −78 °C and the aldehyde **131** (42 mg, 102.5 μmol) as a solution in THF (100 μL) was added *via* cannula. After 2 hours the reaction was diluted with Et_2O (10 mL) and quenched with the addition of saturated aqueous $NaHCO_3$ (3 mL) then allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification of the crude product by column chromatography (20% Et_2O/hexanes) gave the adduct **157** (45.7 mg, 78%, > 85% ds) as a clear oil. $\mathbf{R}_f$ = 0.38 (20% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −16.8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3505, 1717, 1615, 1515, 1472, 1464, 1384, 1251, 1045, 1006, 871, 835, 775, 743 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.42 (1H. d. 11.1 Hz, OCH_AH$_B$PMP), 4.35 (1H, d, 11.1 Hz, OCH$_A$$H_B$PMP), 4.19 (1H, dd, 8.4, 3.6 Hz, C*H*OTES), 4.08-4.04 (2H, m, C*H*OH, C*H*(OTBS)CH(CH$_3$)CHOH), 3.80 (3H, s, OCH_3), 3.65 (1H, dd, 8.1, 2.1 Hz, C*H*(OTBS)CH(CH$_3$)$_2$), 3.56 (1H, br s, O*H*), 3.43 (1H, td, 6.6, 3.0 Hz, C*H*OPMB), 3.08 (1H, dq, 8.1, 6.9 Hz, C*H*(CH-

$_3$)CHOTES), 2.73 (1H, qd, 6.9, 2.1 Hz, CH(OH)C*H*(CH_3)C=O), 2.08 (1H, dqn, 6.9, 6.9 Hz, CH(OPMB)C*H*(CH_3)CHOTBS), 1.95-1.80 (3H, m, CH(OTBS)C*H*(CH_3)CHOH, CH(OTES)C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$), 1.67 (1H, dqd, 14.4, 7.2, 3.0 Hz, $CH_3CH_AH_B$), 1.46 (1H, dqn, 14.4, 7.2 Hz, $CH_3CH_AH_B$), 1.05 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTES), 1.05 (3H, d, 6.9 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.96-0.85 (45H, m, C*H*$_3$CH$_2$, CH(C*H*$_3$)CH$_3$, CH(CH$_3$)C*H*$_3$, CH(OTES)CH(C*H*$_3$)CHOTBS, CH(OTBS)CH(C*H*$_3$)CHOH, CH(OPMB)CH(C*H*$_3$)CHOTBS, Si(CH$_2$C*H*$_3$)$_3$, SiC(C*H*$_3$)$_3$ x 2), 0.55 (6H, q, 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.19 (3H, s, SiC*H*$_3$), 0.13 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.06 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.2, 158.9, 131.3, 128.8, 113.6, 80.4, 77.0, 76.7, 75.6, 72.7, 69.9, 55.2, 49.2, 47.3, 43.9, 40.6, 38.2, 31.1, 26.3, 25.9, 21.7, 20.8, 18.6, 18.0, 16.3, 14.7, 13.6, 11.0, 10.5, 8.8, 6.9, 5.2, −3.0, −4.2, −4.5, −4.7; **HRESIMS** calculated for $C_{47}H_{92}O_7Si_3Na^+$ $[M+Na]^+$: 875.6043; found 875.6036; **EIMS** *m/z* (%): 407 (7), 271 (5), 227 (5), 215 (12), 187 (40), 121 (100), 97 (7), 73 (20), 57 (17), 55 (13).



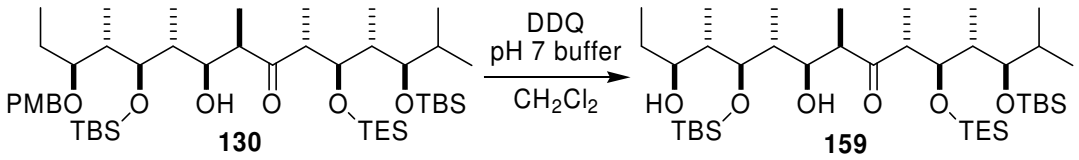
(3*R*,4*R*,5*R*,6*R*,8*R*,10*S*,11*S*,12*S*,13*S*)-3,11-bis-[tert-butyldimethylsilyloxy]-5-triethylsilyloxy-2,4,6,8,10,12,-hexamethyl-13-[4-methoxy-benzyloxy]-pentadec-7,9-dione (130). The oxidation was carried out according to the procedure of Swern and Mancuso.[5] To a solution of DMSO (27 μL, 0.39 mmol) in CH_2Cl_2 (500 μL) at −78 °C was added oxalyl chloride (97 μL of a 2 M solution in CH_2Cl_2, 0.19 mmol) dropwise. After 30 minutes, the alcohol **157** (11 mg, 12.9 μmol) in CH_2Cl_2 (3 x 100 μL) was added *via* cannula and the resulting mixture stirred at −78 °C for 1 hour. Triethylamine (108 μL, 0.77 mmol) was added and the resulting white solution was stirred at −78 °C for 30 minutes then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was partitioned between saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (30%

hexanes/CH_2Cl_2) to give the dione **130** (9.7 mg, 88%) as a clear oil and as a stable diketone, with no enol or epimeric forms. $\mathbf{R}_f$ = 0.53 (30% hexanes/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.45 (1H. d. 11.1 Hz, OCH_AH$_B$PMP), 4.38 (1H, d, 11.1 Hz, OCH$_A$$H_B$PMP), 4.22 (1H, dd, 7.5, 3.9 Hz, C*H*(OTBS)CH(CH_3)C=O), 4.18 (1H, dd, 8.4, 3.6 Hz, C*H*OTES), 3.92 (1H, q, 7.2 Hz, C(=O)C*H*(CH_3)C=O), 3.80 (3H, s, OCH_3), 3.61 (1H, dd, 8.4, 2.1 Hz, C*H*(OTBS)CH(CH_3)$_2$), 3.48 (1H, td, 6.6, 3.0 Hz, C*H*OPMB), 2.97 (1H, app qn, 7.2 Hz, C*H*(CH_3)CHOTES), 2.79 (1H, app qn, 7.2 Hz, CH(OTBS)C*H*(CH_3)C=O), 2.05-1.34 (5H, m, CH(OPMB)C*H*(CH_3)CHOTBS, CH(OTES)C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$, CH_3CH_AH$_B$, CH_3CH$_A$$H_B$), 1.20 (3H, d, 6.9 Hz, C(=O)CH(CH_3)C=O), 1.10 (6H, d, 6.9 Hz, CH(OTBS)CH(CH_3)C=O, CH(CH_3)CHOTES), 0.94-0.84 (42H, m, C$H_3$$CH_2$, CH(C$H_3$)$CH_3$, CH($CH_3$)C$H_3$, CH(OTES)CH(C$H_3$)CHOTBS, CH(OPMB)CH(C$H_3$)CHOTBS, Si($CH_2CH_3$)$_3$, SiC(C$H_3$)$_3$ x 2), 0.55 (6H, q, 7.9 Hz, Si(C$H_2$$CH_3$)$_3$), 0.18 (3H, s, SiC$H_3$), 0.05 (6H, s, SiC$H_3$ x 2), –0.07 (3H, s, SiCH_3).



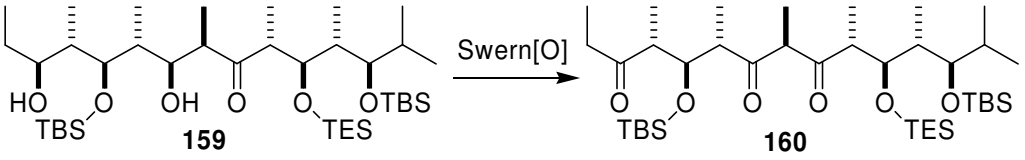
(3*R*,4*R*,5*R*,6*R*,8*R*,10*S*,11*S*,12*S*,13*S*)-3,11-bis-[tert-butyldimethylsilyloxy]-2,4,6,8,10,12,-hexamethyl-5-hydroxy-13-[4-methoxy-benzyloxy]-pentadec-7,9-dione (158). To a solution of the β-diketone **157** (9.7 mg, 11.4 μmol) in 1:1 MeOH/CH_2Cl_2 (2 mL) at 0 °C was added a few crystals of *p*-TSOH and the resulting solution was stirred at 0 °C for 1 hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (5 mL) and the product was extracted with CH_2Cl_2 (3 x 10mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by flash column chromatography (CH_2Cl_2) to give the deprotected β-hydroxy-β-diketone **158** (8.0 mg, 95%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.45 (1H. d. 11.1 Hz, OCH_AH$_B$PMP), 4.34 (1H, d, 11.1 Hz, OCH$_A$$H_B$PMP), 4.21 (1H, dd, 8.7, 3.6 Hz, C*H*OTBS), 3.99 (1H, q, 7.2 Hz, C(=O)C*H*(CH_3)C=O), 3.80 (3H, s, OCH_3), 3.66-3.39 (4H, m, C*H*(OTBS)CH(CH_3)$_2$, C*H*OPMB, C*H*OH, O*H*),

3.00 (2H, m, C*H*(CH_3)CHOH, CH(OTBS)C*H*(CH_3)C=O), 2.05-1.40 (5H, m, CH(OPMB)C*H*(CH_3)CHOTBS, CH(OH)C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$, $CH_3CH_AH_B$, $CH_3CH_AH_B$), 1.40-0.80 (42H, m, C(=O)CH(C*H*$_3$)C=O, CH(OTBS)CH(C*H*$_3$)C=O, CH(C*H*$_3$)CHOTES, C*H*$_3$CH$_2$, CH(C*H*$_3$)CH$_3$, CH(CH_3)C*H*$_3$, CH(OH)CH(C*H*$_3$)CHOTBS, CH(OPMB)CH(C*H*$_3$)CHOTBS, SiC(C*H*$_3$)$_3$ x 2), 0.06 (3H, s, SiC*H*$_3$), 0.04 (6H, s, SiC*H*$_3$ x 2), −0.07 (3H, s, SiC*H*$_3$). The purified product was taken up in $CDCl_3$ in an NMR tube and treated successively with PPTS, *p*-TSOH and TFA. The addition of PPTS and *p*-TSOH seemed to have no effect, but after several minutes with TFA the ^{1}H NMR spectrum showed peaks at ~ δ 1.7-1.5 indicative of vinyl methyl resonances. This suggested the formation of dihydropyrone compounds.



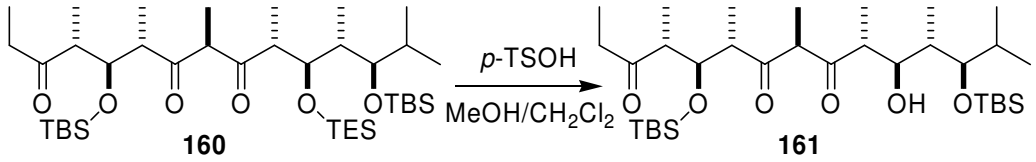
(3*R*,4*R*,5*R*,6*R*,8*R*,9*S*,10*S*,11*S*,12*S*,13*S*)-3,11-bis-[tert-butyldimethylsilyloxy]-5-triethylsilyloxy-9,13-hydroxy-2,4,6,8,10,12,-hexamethyl-pentadec-7-one (159). Deprotection was carried according to the procedure of Paterson *et al.*[23] To a solution of the *p*-methoxybenzyl ether **130** (37 mg, 43.4 μmol) in CH_2Cl_2 (2 mL) at 0 °C was added pH 7 buffer (400 μL) followed by DDQ (15 mg, 65.0 μmol). The resulting suspension was stirred at 0 °C for 30 minutes before being diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), then the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (CH_2Cl_2) gave the diol **159** (27mg, 90%) as a thick, colourless oil. **R**$_f$ = 0.21 (CH_2Cl_2); **[α]$^{20}_D$** = −16.6 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3504, 1716, 1472, 1464, 1388, 1362, 1253, 1048, 1024, 1004, 976, 871, 835, 775, 741, 726, 668 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.23 (1H, dd, 7.8, 3.9 Hz, C*H*OTES), 4.14 (1H, t, 4.2 Hz, C*H*(OTBS)CH(CH_3)CHOH), 3.83 (1H, dd, 10.2, 1.5 Hz, C*H*(OH)CH(CH_3)C=O), 3.63 (1H, dd, 7.8, 2.1 Hz, C*H*(OTBS)CH(CH_3)$_2$), 3.43 (1H,

td, 8.4, 2.7 Hz, CH_3CH_2CHOH), 3.00 (1H, qn, 7.2 Hz, $CH(CH_3)CHOTES$), 2.99 (2H, br s, O*H* x 2), 2.77 (1H, qd, 6.9, 1.5 Hz, $CH(OH)CH(CH_3)C{=}O$), 1.94-1.80 (3H, m, $CH(OTBS)CH(CH_3)CHOH$, $CH(OTES)CH(CH_3)CHOTBS$, $CH(CH_3)_2$), 1.76-1.59 (2H, m, $CH(OH)CH(CH_3)CHOTBS$, $CH_3CH_AH_B$), 1.40-1.22 (1H, m, $CH_3CH_AH_B$), 1.07 (3H, d, 7.2 Hz, $CH(CH_3)CHOTES$), 1.06 (3H, d, 6.9 Hz, $CH(OH)CH(CH_3)C{=}O$), 0.98-0.85 (45H, m, CH_3CH_2, $CH(CH_3)CH_3$, $CH(CH_3)CH_3$, $CH(OTES)CH(CH_3)CHOTBS$, $CH(OTBS)CH(CH_3)CHOH$, $CH(OH)CH(CH_3)CHOTBS$, $Si(CH_2CH_3)_3$, $SiC(CH_3)_3$ x 2), 0.57 (6H, q, 8.2 Hz, $Si(CH_2CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.13 (6H, s, $SiCH_3$ x 2), 0.06 (3H, s, $SiCH_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.7, 78.0, 77.1, 74.8, 74.5, 71.9, 48.6, 47.2, 43.8, 40.9, 40.9, 31.1, 26.8, 26.3, 25.9, 20.6, 18.6, 18.0, 16.5, 15.1, 13.5, 12.1, 11.0, 9.3, 7.2, 6.9, 5.2, −3.0, −4.4, −4.6, −4.7; **HRESIMS** calculated for $C_{39}H_{84}O_6Si_3Na^+$ $[M+Na]^+$: 755.5468; found 755.5468; **EIMS** *m/z* (%): 756 (28), 642 (100), 209 (4), 143 (8), 115 (11).



(3*S*,4*S*,5*S*,6*S*,7,8,10*R*,11*R*,12*R*,13*R*)-5,13-di-[tert-butyldimethylsilyloxy]-11-triethylsilyloxy-4,6,8,10,12,14-hexamethyl-pentadec-3,7,9-trione (160). The oxidation was carried out according to the procedure of Swern and Mancuso.[5] To a solution of DMSO (28 μL, 0.39 mmol) in CH_2Cl_2 (500 μL) at −78 °C was added oxalyl chloride (98 μL of a 2 M solution in CH_2Cl_2, 0.20 mmol) dropwise. After 30 minutes, the alcohol **159** (24 mg, 32.7 μmol) in CH_2Cl_2 (3 x 100 μL) was added *via* cannula and the resulting mixture stirred at −78 °C for 1 hour. Triethylamine (110 μL, 0.79 mmol) was added and the resulting white solution was stirred at −78 °C for 30 minutes then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was partitioned between saturated aqueous NH_4Cl (1 mL) and CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2) to give the trione **160** (21 mg, 88%) as a clear oil and as a stable tri-ketone, with no

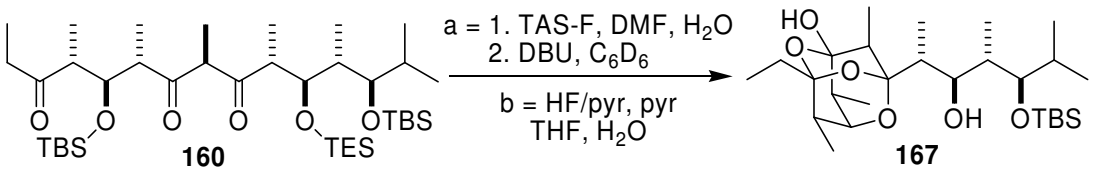
enol or epimeric forms. $\mathbf{R}_f$ = 0.70 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = −35.0 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1716, 1473, 1463, 1413, 1379, 1361, 1255, 1050, 1006, 972, 939, 850, 836, 776, 742, 668 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.48 (1H, dd, 7.2, 4.5 Hz, C*H*(OTBS)CH(CH_3)C=O), 4.19 (1H, dd, 8.7, 3.3 Hz, C*H*OTES), 3.93 (1H, q, 7.2 Hz, C(=O)C*H*(CH_3)C=O), 3.59 (1H, dd, 8.4, 2.1 Hz, C*H*(OTBS)CH(CH_3)$_2$), 2.88 (1H, qn, 7.2 Hz, CH(OTBS)C*H*(CH_3)C=O), 2.78 (1H, dq, 8.7, 7.2 Hz, C*H*(CH_3)CHOTES), 2.72 (1H, qd, 6.9, 4.5 Hz, C*H*(CH_3)CH(OTBS)CH(CH_3)C=O), 2.59 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_B$), 2.49 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_B$), 1.94-1.80 (2H, m, CH(OTES)C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$), 1.23 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$)C=O), 1.10 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOTES), 1.04 (3H, t, 7.2 Hz, C*H*$_3$CH$_2$), 0.96 (3H, d, 7.2 Hz, CH(OTBS)CH(C*H*$_3$)C=O), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.90 (9H, t, 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.93-0.85 (9H, m, CH(C*H*$_3$)CH$_3$, CH(CH_3)C*H*$_3$, CH(OTES)CH(C*H*$_3$)CHOTBS, 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 0.55 (6H, q, 8.1 Hz Si(C*H*$_2$CH$_3$)$_3$), 0.17 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.8, 209.8, 209.7, 77.3, 74.7, 73.7, 60.5, 51.8, 50.4, 50.1, 44.2, 35.3, 31.4, 26.3, 25.8, 20.2, 18.7, 17.9, 16.2, 13.4, 12.1, 11.7, 10.9, 10.0, 7.6, 6.9, 5.1, −2.9, −4.4, −4.6, −5.0; **HRESIMS** calculated for $C_{39}H_{80}O_6Si_3Na^+$ $[M+Na]^+$: 751.5155; found 751.5154; **EIMS** *m/z* (%): 752 (100), 637 (46), 597 (4), 466 (4), 243 (4), 85 (9).



(3*S*,4*S*,5*S*,6*S*,7,8,10*R*,11*R*,12*R*,13*R*)-5,13-di-[tert-butyldimethylsilyloxy]-4,6,8,10,12,14-hexamethyl-11-hydroxy-pentadec-3,7,9-trione (161). To a solution of the β-diketone **160** (20 mg, 27.4 μmol) in 1:1 MeOH/CH_2Cl_2 (2 mL) at 0 °C was added a few crystals of *p*-TSOH and the resulting solution was stirred at 0 °C for 1 hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (5 mL) and the product was extracted with CH_2Cl_2 (3 x 10mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by flash column chromatography (CH_2Cl_2) to give the deprotected β-hydroxy-β-

diketone **161** (15.0 mg, 89%) as a clear oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.39 (1H, dd, 7.6, 3.0 Hz, C*H*OTBS), 4.03 (1H, q, 7.2 Hz, C(=O)C*H*(CH_3)C=O), 3.60-3.45 (2H, m, C*H*(OTBS)CH(CH_3)$_2$, C*H*OH), 3.06-2.39 (5H, m, C*H*(CH_3)CHOH, CH(OTBS)C*H*(CH_3)C=O, C*H*(CH_3)CHOTBS, $CH_3CH_AH_B$, $CH_3CH_AH_B$), 1.97-1.71 (2H, m, CH(OH)C*H*(CH_3)CHOTBS, C*H*(CH_3)$_2$) 1.40-0.80 (42H, m, C(=O)CH(C*H$_3$*)C=O, CH(OTBS)CH(C*H$_3$*)C=O, CH(C*H*$_3$)CHOH, C*H*$_3$CH$_2$, CH(C*H$_3$*)CH$_3$, CH(CH_3)C*H$_3$*, CH(OH)CH(C*H$_3$*)CHOTBS, CH(C*H$_3$*)CHOTBS, SiC(C*H$_3$*)$_3$ x 2), 0.08 (3H, s, SiC*H*$_3$), 0.06 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H$_3$*), 0.07 (3H, s, SiC*H$_3$*).

The purified product was taken up in $CDCl_3$ in an NMR tube and treated successively with PPTS, *p*-TSOH and TFA. Unfortunately, cyclisation to the desired hemiacetal was not observed. The addition of PPTS and *p*-TSOH seemed to have no effect, but after several minutes with TFA the ^{1}H NMR spectrum showed peaks at ~ δ 1.7-1.5 indicative of vinyl methyl resonances. This suggested the formation of dihydropyrone compounds.

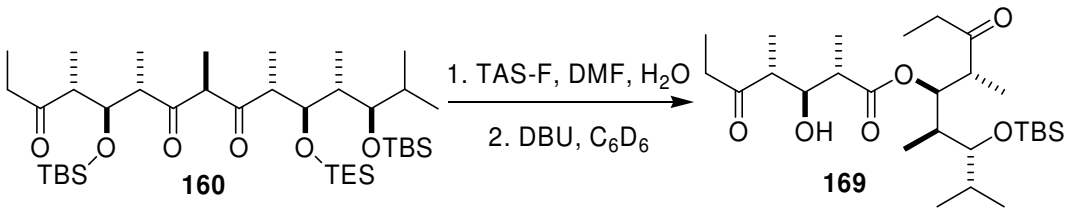


5-[(1*R*,3*R*,4*R*,5*R*)-4-*tert*-butyldimethylsilyloxy-2-hydroxy-1,3,5-trimethyl-hexyl]-3-ethyl-8,9,10-trimethyl-2,4,6-trioxa-tricyclo[3.3.1.13,7]decanol (167). TAS-F deprotection was performed according to a modification of the procedure of Roush *et al.*[24] a) To a solution of the trione **160** (30 mg, 41.1 μmol) in DMF (179 μL) and H_2O (7 μL, 411 μmol) was added a solution of TAS-F (57 mg, 206 μmol) in DMF (206 μL) and the resultant yellow mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc (5 mL) and washed with pH 7 buffer (5 x 2 mL). The combined aqueous washing's were extracted with EtOAc (3 x 10 mL), and then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave a mixture of products which was treated with DBU (a minimal amount of DBU was added to the mixture in C_6D_6 in an NMR

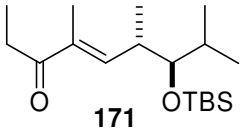
tube) for 5 minutes before being partitioned between into Et_2O (3 x 5 mL) and saturated aqueous NH_4Cl (2 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. Purification of the residue by column chromatography (10% Et_2O/CH_2Cl_2) gave the trioxaadamantane **167** (16 mg, 78%) as a clear oil.

b) HF deprotection was carried out according to the procedure of Hoffmann *et al.*[11] To a Teflon cylinder containing a solution of the tri-ketone **160** (23.0 mg, 43.5 μmol) in THF (0.5 mL) was added buffered pyridinium hydrofluoride (0.6 mL) and H_2O (30 μL). The resulting solution was stirred at room temperature for 7 days then diluted with Et_2O (10 mL) and washed with saturated aqueous $CuSO_4$ (3 x 5 mL), saturated aqueous $NaHCO_3$ (2 x 5 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2, using buffered silica) to give the trioxaadamantane **167** (14.0 mg, 88%) as a clear oil.

R_f = 0.42 (10% Et_2O/CH_2Cl_2); **IR** (C_6D_6, FT, film) 3506, 1463, 1380, 1308, 1251, 1186, 1146, 1118, 1056, 1043, 1007, 977, 899, 886, 836, 772 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 4.27 (1H, dd, 5.1, 2.1 Hz, C*H*OTBS), 4.23 (1H, d, 5.1 Hz, CHO*H*), 3.84 (1H, dt, 5.1, 3.9 Hz, C*H*OH), 3.26 (1H, br s, C*H*-O-C), 2.54 (1H, m, CH(OH)C*H*(CH_3)CHOTBS), 2.31 (1H, hep d, 6.9, 2.1 Hz, C*H*(CH_3)$_2$), 2.19 (1H, br s, O*H*), 2.10 (1H, qd, 7.2, 3.9 Hz, C*H*(CH_3)CHOH), 1.96 (1H, q, 6.6 Hz, C(OH)C*H*(CH_3)C), 1.70-1.64 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_B$), 1.46 (1H, qd, 7.2, 4.2 Hz, C(-O-)$_2$C*H*(CH_3)CH-O-), 1.45-1.39 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_B$), 1.17 (1H, br q, 7.2 Hz, C(-O-)OHC*H*(CH_3)CH(-O-), 1.16 (3H, d, 6.9 Hz, CH(OH)CH(C*H*$_3$)CHOTBS), 1.15 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 1.10 (3H, d, 6.9 Hz, CH(CH_3)C*H*$_3$), 1.08 (9H, s, SiC(C*H*$_3$)$_3$), 1.05 (3H, d, 6.9 Hz, C(O)$_2$C*H*(CH_3)CHOH), 0.99-0.93 (9H, m, C*H*$_3$$CH_2$, C(-O-)$_2$CH(C*H*$_3$)CH-O-, C(-O-)OHCH(C*H*$_3$)), 0.89 (3H, d, 6.6 Hz, CH(OH)CH(C*H*$_3$)C(O)$_2$), 0.22 (3H, s, SiC*H*$_3$), 0.19 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 106.5, 102.4, 97.1, 79.1, 78.8, 77.1, 44.6, 43.2, 38.3, 35.4, 30.1, 29.7, 26.4, 23.2, 18.7, 18.0, 14.0, 13.2, 13.1, 12.9, 6.8, 5.9, −3.7, −4.2; **HRESIMS** calculated for $C_{27}H_{52}O_6SiH^+$ $[M+H]^+$: 501.3606; found 501.3607.

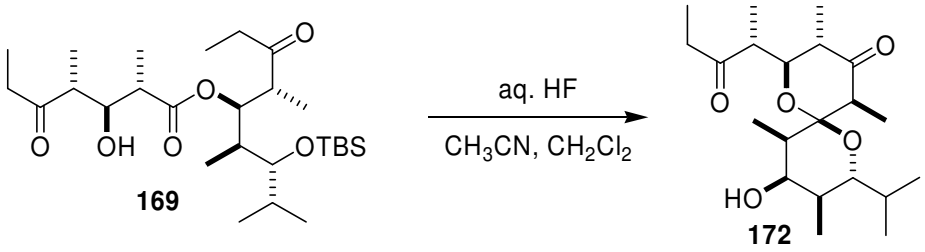


(4*R*,5*R*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-4,6,8-trimethyl-5-[2*S*,3*S*,4*R*-(1,5-dioxo-2,4-dimethyl-3-hydroxy-heptoxy)]-non-3-one (169). Following the procedure[24] described above for the preparation of trioxaadamantane **167** using the following quantities: trione **160** (20 mg, 27.4 μmol) in DMF (114 μL) and H_2O (5 μL, 274 μmol) was treated with TAS-F (38 mg, 137 μmol) in DMF (137 μL), followed by an identical work-up to that described above. The chromatographed mixture was taken up in C_6D_6 (~ 1 mL) and transferred to an NMR tube and a minimal amount of DBU was added.[12] The reaction was allowed to continue for 6 hours with ester formation being monitored by ^{1}H NMR. After optimum conversion was reached the solvent was removed and the residue purified by column chromatography (10% Et_2O/CH_2Cl_2) to obtain the ester **169** (12.4 mg, 90%) as a clear oil. $\mathbf{R}_f$ = 0.50 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.28 (1H, dd, 9.0, 4.2 Hz, C*H*OC=O), 3.72 (1H, t, 6.6 Hz, C*H*OH), 3.53 (1H, t, 3.6 Hz, C*H*OTBS), 2.92 (1H, qd, 7.2, 4.2 Hz, CH(OC=O)C*H*(CH_3)C=O), 2.82 (1H, qn, 6.9 Hz, C(=O)C*H*(CH_3)CHOH), 2.65 (1H, qd, 7.2, 6.6 Hz, CH(OH)C*H*(CH_3)CO_2), 2.61-2.47 (4H, m, CH_3CH_2 x 2), 2.06 (1H, dqd, 9.0, 7.2, 3.6 Hz, CH(OC=O)C*H*(CH_3)CHOTBS), 1.81 (1H, hep d, 7.2, 3.6 Hz, C*H*(CH_3)$_2$), 1.26 (1H, br s, O*H*), 1.25 (3H, d, 7.2 Hz, CH(OH)CH(C*H*$_3$)CO_2), 1.17 (3H, d, 7.2 Hz, C(=O)CH(C*H*$_3$)CHOH), 1.14 (3H, d, 7.2 Hz, CH(OC=O)CH(C*H*$_3$)C=O), 1.05 (3H, t, 7.2 Hz, C*H*$_3$$CH_2$), 1.05 (3H, t, 7.2 Hz, C*H*$_3$$CH_2$), 0.91 (3H, d, 7.2 Hz, CH(OC=O)CH(C*H*$_3$)CHOTBS), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.90 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_3), 0.87 (3H, d, 7.2 Hz, CH(CH_3)C*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 76.3, 76.2 x 2, 48.6, 48.4, 43.4, 41.0, 36.1, 34.9, 30.2, 26.0, 22.0, 18.4, 18.0, 15.1, 14.6, 12.6, 11.8, 7.8, 7.4, –4.0, –4.5 (4 x carbons not seen-HMBC shows peaks at ~ 215, 212, 174, 18); **HRESIMS** calculated for $C_{27}H_{52}O_6SiNa^+$ $[M+Na]^+$: 523.3425; found 523.3422.



171

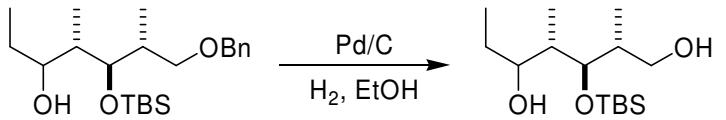
(6*S*,7*R*)-7-*tert*-butyldimethylsilyloxy-4,6,8-trimethylnon-4-ene-3-one (171). Elimination product from esterification and retro-Claisen reactions. $\mathbf{R}_f$ = 0.70 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CHCl_3$) δ 6.86 (1H, d, 9.3 Hz, C(CH_3)=C*H*), 3.43 (1H, dd, 5.4, 2.7 Hz, C*H*OTBS), 2.75 (1H, dqd, 9.3, 7.2, 2.7 Hz, C*H*(CH_3)CHOTBS), 2.67 (2H, qd, 7.2 Hz, CH_3CH_2), 1.78 (3H, d, 1.2 Hz, C(CH_3)=CH), 1.73-1.64 (1H, m, C*H*(CH_3)CH_3), 1.10 (3H, t, 7.2 Hz, CH_3CH_2), 1.02 (3H, d,.7.2 Hz, CH(CH_3)CHOTBS), 0.94 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, d, 6.9 Hz, CH(CH_3)CH_3), 0.83 (3H, d, 6.9 Hz, CH(CH_3)C*H*$_3$), 0.07 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 145.2, 80.7, 36.3, 33.7, 30.3, 26.0, 18.9, 18.7, 18.6, 11.4, 9.0, –3.7, –4.0, 3 x quaternary carbons unsighted.



169 **172**

(2*S*,3*S*,5*S*,8*R*,9*S*,10*R*,11*R*)-8-(1-methyl)-ethyl-10-hydroxy-3,5,9,11-tetramethyl-2-[1*R*-(1-methyl-2-oxo-butyl)]-1,7-dioxaspiro[5.5]undecan-4-one (172). Deprotection was performed according to the procedure of Evans *et al.*[25] To a solution of the ester **169** (3.0 mg, 6.0 μmol) in CH_3CN (600 μL) and CH_2Cl_2 (600 μL) was added aqueous hydrofluoric acid (100 μL) and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with H_2O (10 mL) and quenched with the slow addition of saturated aqueous $NaHCO_3$ (10 mL), then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave the spiroacetal **172** (2.6 mg, 90%) as a white film. $\mathbf{R}_f$ = 0.35 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (600 MHz, C_6D_6) δ 3.72 (1H, dd, 10.8, 2.4 Hz, C*H*(-O)CH(CH_3)$_2$), 3.60 (1H, dd, 10.8, 3.0 Hz, C*H*(-

O)CH(CH_3)C=O), 3.37 (1H, dt, 10.8, 2.7 Hz, C*H*OH), 3.05 (1H, d, 10.8 Hz, O*H*), 2.65 (1H, dq, 10.8, 7.2 Hz, CH(-O)C*H*(CH_3)C=O), 2.33 (1H, q, 6.6, Hz, C(=O)C*H*(CH_3)C($O)_2$), 2.25 (1H, qd, 7.2, 2.4 Hz, CH_3CH_2C(=O)C*H*(CH_3), 2.06 (1H, dq, 18.6, 7.2 Hz, $CH_3CH_AH_B$), 1.99 (1H, dq, 18.6, 7.2 Hz, $CH_3CH_AH_B$), 1.73 (1H, qn d, 6.6, 2.4 Hz, C*H*(CH_3)CH_3), 1.39 (1H, qd, 7.2, 3.0 Hz, C(-$O)_2$C*H*(CH_3)CHOH), 1.29-1.23 (1H, m, CH(-O)C*H*(CH_3)CHOH), 1.05 (3H, d, 6.6 Hz, C(=O)CH(C*H*$_3$)C(-O), 0.97 (3H, d, 7.2 Hz, CH_3CH_2C(=O)CH(C*H*$_3$)), 0.96 (3H, d, 7.2 Hz, C(-$O)_2$CH(C*H*$_3$)CHOH), 0.95 (3H, d, 6.6 Hz, CH(C*H*$_3$)CH_3), 0.95 (3H, d, 7.2 Hz, CH(-O)CH(C*H*$_3$)CHOH), 0.94 (3H, t, 7.2 Hz, C*H*$_3CH_2$), 0.93 (3H, d, 7.2 Hz, CH(-O)CH(C*H*$_3$)C=O), 0.74 (3H, d, 6.6 Hz, CH(CH_3)C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 79.2, 74.5, 72.8, 47.4, 45.9, 44.9, 39.2, 37.9, 36.1, 28.4, 20.6, 14.1, 14.0, 13.9 x 2, 12.7, 11.8, 8.3 (3 x carbons unsighted-HMBC correlations at ~ 210, 208, 105); HRESIMS calculated for $C_{21}H_{36}O_5Na^+$ $[M+Na]^+$: 391.2455; found 391.2474.



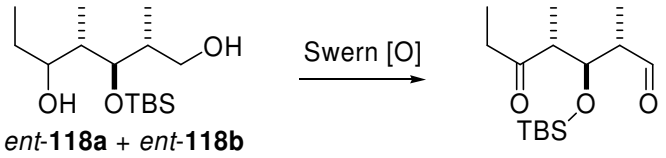
142a + **142b** — *ent*-**118a** + *ent*-**118b**

(2*S*,3*R*,4*R*,5*R*/*S*)-3-tert-butyldimethylsilyloxy-2,4-dimethylheptan-1,3-diol (*ent*-118a and *ent*-118b).[26] A solution of the combined benzyl ethers **142a** and **142b** (360 mg, 0.95 mmol) and 10% Pd/C (36 mg, 10% w/w) in EtOH (10 mL) under an atmosphere of H_2 was stirred at room temperature for 1 hour. The reaction mixture was then filtered through celite (Et_2O), concentrated *in vacuo* and the residue purified by column chromatography (25% Et_2O/CH_2Cl_2) to give first the minor diol *ent*-**118b** (66.4 mg, 24%) followed by the major diol *ent*-**118a** (199.1 mg, 73%) both as clear oils.

Minor isomer *ent*-118b: $\mathbf{R}_f$ = 0.37 (25% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = 0.0 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3417, 1469, 1410, 1385, 1256, 1037, 974, 837, 777 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.91 (1H, ddd, 7.8, 6.2, 1.6 Hz, C*H*OH), 3.72 (1H, dd, 6.8, 3.2 Hz, C*H*OTBS), 3.64 (1H, dd, 10.8, 5.1 Hz, CHCH_AH_BOH), 3.57 (1H, dd, 10.8, 5.7 Hz, CHCH_AH_BOH), 2.66 (2H, s, OH x 2), 2.04-1.90 (1H, m, C*H*(CH_3)CH_2OH), 1.72-1.63 (1H, m, C*H*(CH_3)CHOTBS), 1.60-1.43 (1H, m,

$CH_3CH_AH_B$), 1.40-1.26 (1H, m, $CH_3CH_AH_B$), 0.96 (3H, d, 6.9 Hz, $CH(CH_3)CH_2OH$), 0.96 (3H, d, 7.2 Hz, $CH(CH_3)CHOTBS$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, t, 7.5 Hz, CH_3CH_2), 0.11 (6H, $Si(CH_3)_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 80.6, 72.4, 64.9, 39.2, 37.9, 27.7, 26.1, 18.2, 14.6, 11.4, 10.4, −3.9, −4.3.

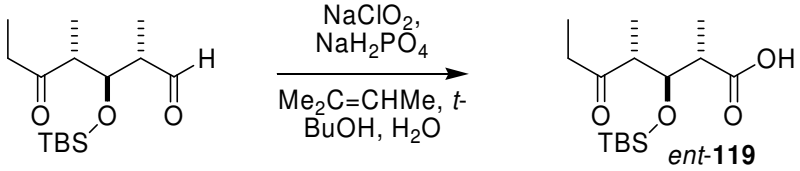
Major isomer *ent*-118a: R_f = 0.28 (25% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = −1.94 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3386, 1464, 1386, 1255, 1031, 975, 837, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.85 (1H, t, 4.5 Hz, C*H*OTBS), 3.64 (1H, dd, 11.1, 6.6 Hz, $CHCH_AH_BOH$), 3.56 (1H, dd, 11.1, 5.0 Hz, $CHCH_AH_BOH$), 3.45 (1H, td, 8.6, 2.7 Hz, C*H*OH), 2.63 (2H, s, O*H* x 2), 2.02-1.89 (1H, m, $CH(CH_3)CH_2OH$), 1.87-1.77 (1H, m, $CH(CH_3)CHOTBS$), 1.71-1.58 (1H, m, $CH_3CH_AH_B$), 1.41-1.24 (1H, m, $CH_3CH_AH_B$), 0.97 (3H, d, 7.2 Hz, $CH(CH_3)CH_2OH$), 0.96 (3H, t, 7.5 Hz, CH_3CH_2), 0.92 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, d, 6.9 Hz, $CH(CH_3)CHOTBS$), 0.12 (3H, $SiCH_3$), 0.11 (3H, s, $SiCH_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 79.8, 74.6, 65.6, 43.1, 39.0, 27.2, 26.0, 18.1, 15.6, 14.0, 9.3, −4.2, −4.5; **HRESIMS** calculated for $C_{15}H_{34}O_3SiNa^+$ $[M+Na]^+$: 313.2175; found 313.2169.



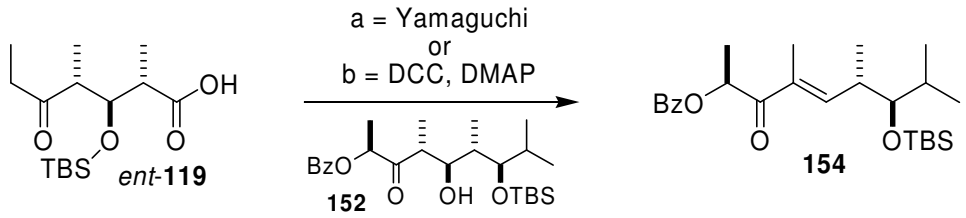
ent-**118a** + *ent*-**118b**

(2*S*,3*R*,4*R*)-3-tert-butyldimethylsilyloxy-2,4-dimethyl-5-oxoheptanal.[27] Oxidation was performed according to the procedure of Swern and Mancuso.[5] To a solution of DMSO (73 μL, 1.03 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added oxalyl chloride (258 μL of a 2 M solution in CH_2Cl_2, 0.52 mmol) over 5 mins. After 30 minutes, the alcohol *ent*-**118a** and *ent*-**118b** (30 mg, 0.10 mmol) in CH_2Cl_2 (3 x 0.5 mL) was added *via* cannula and the resulting mixture stirred at −78 °C for 1.5 hours. Triethylamine (216 μL, 1.55 mmol) was added over 5 minutes and the resulting white solution was stirred at −78 °C for 30 minutes then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was partitioned between saturated aqueous NH_4Cl (3 mL) and CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with

pentane and the triturant was concentrated *in vacuo* to give the crude ketoaldehyde, which was submitted for further oxidation without purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.79 (1H, d, 1.5 Hz, C*H*O), 4.36 (1H, dd, 8.1, 2.9 Hz, C*H*OTBS), 2.85 (1H, dq, 8.1, 7.2 Hz, C*H*(CH_3)CHOTBS), 2.62-2.41 (3H, m, CH_3CH_2, C*H*(CH_3)CHO), 1.14 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHO), 1.03 (3H, t, 7.2 Hz, C*H*$_3$$CH_2$), 0.92 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 0.09 (3H, SiC*H*$_3$), –0.02 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 213.1, 203.4, 74.9, 50.9, 50.1, 36.9, 25.8, 18.1, 13.1, 9.9, 7.3, –4.7, –4.8.



(2*S*,3*R*,4*R*)-3-tert-butyldimethylsilyloxy-2,4-dimethyl-5-oxoheptanoic acid (*ent*-119).[27] Oxidation was performed according to the procedure of Paterson *et al*.[28] To a solution of the crude ketoaldehyde (ex. 30 mg, ~ 0.10 mmol) in *tert*-butanol (2.1 mL) and 2-methyl-2-butene (few drops) at room temperature was added dropwise a solution of $NaClO_2$ (117 mg, 1.29 mmol) and NaH_2PO_4 (161 mg, 1.03 mmol) in H_2O (2.1 mL). The reaction mixture was stirred for 1 hour then poured into brine (10 mL) and extracted with Et_2O (6 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by column chromatography (15% Et_2O/CH_2Cl_2 + 1% AcOH) to give the acid *ent*-**119** (28 mg, 96%, two steps) as a colourless oil. $\mathbf{R}_f$ = 0.26 (15% Et_2O/CH_2Cl_2 + 1% AcOH); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.34 (1H, dd, 8.1, 3.6 Hz, C*H*OTBS), 2.87 (1H, dq, 8.1, 7.2 Hz, C*H*(CH_3)CHOTBS), 2.70 (1H, qd, 7.2, 3.6 Hz, C*H*(CH_3)CO_2H), 2.57 (1H, dq, 18.6, 7.2 Hz, $CH_3CH_AH_B$), 2.46 (2H, dq, 18.6, 7.2 Hz, $CH_3CH_AH_B$), 1.19 (3H, d, 7.2 Hz, CH(C*H*$_3$)CO_2H), 1.03 (3H, t, 7.2 Hz, C*H*$_3$$CH_2$), 0.99 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.11 (3H, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 213.3, 177.3, 75.3, 49.9, 43.8, 36.7, 27.7, 18.0, 12.6, 11.6, 7.3, –4.7, –5.0.

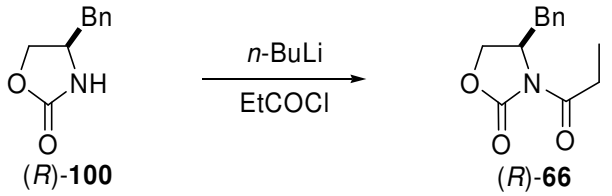


(2*S*,6*S*,7*R*)-2-benzoyloxy-7-*tert*-butyldimethylsilyloxy-4,6,8-trimethylnon-4-ene-3-one (154). Yamaguchi esterification was attempted according to the procedure of Paterson *et al*.[28] a) 2,4,6-Trichlorobenzoyl chloride (9 μL, 59.5 μmol) was added to a solution of the acid *ent*-**119** (15 μL, 49.6 μmol), alcohol **152** (22 mg, 49.6 μmol), DMAP (24 mg, 198 μmol) and Et_3N (9 μL, 64.5 μmol) in toluene (0.5 mL) at −78 °C. After 15 mins the reaction was warmed to 0 °C and allowed to stir for a further 15 minutes before being warmed to room temperature and stirred for an additional 1 hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (15 mL), the layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow slurry. Purification by column chromatography (CH_2Cl_2) gave the enone **154** exclusively, as a clear oil.

b) Esterification was attempted according to the procedure of Keck *et al*.[29] To a solution of DCC (14 mg, 66.1 μmol), DMAP (12 mg, 99.2 μmol) and DMAP•HCl (11 mg, 66.1 μmol) in $CHCl_3$ at reflux was added a solution of the acid *ent*-**119** (10 mg, 33.1 μmol) in $CHCl_3$. The mixture was heated at reflux for 30 minutes then cooled to room temperature at which point a solution of the alcohol **152** (15 mg, 33.1 μmol) in $CHCl_3$ was added. The reaction mixture was stirred at ambient temperature for 1 hour, then the volatiles were removed *in vacuo* and the residue was immediately purified by column chromatography (CH_2Cl_2) to afford the enone **154**.
$\mathbf{R}_f$ = 0.4 (CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (2H, d, 7.2 Hz, Ar*H*), 7.55 (1H, t, 7.2 Hz, Ar*H*), 7.42 (2H, d, 7.2 Hz, Ar*H*), 6.96 (1H, dd, 9.3, 0.6 Hz, C(CH_3)=C*H*CH), 5.91 (1H, q, 6.9 Hz, BzOC*H*(CH_3)), 3.42 (1H, dd, 5.4, 2.1 Hz, C*H*OTBS), 2.79 (1H, dqn, 9.3, 7.2 Hz, C=CHC*H*(CH_3)CHOTBS), 1.83 (3H, s, C(C*H*$_3$)=CH), 1.72-1.59 (1H, m, C*H*(CH_3)$_2$), 1.58 (3H, d, 6.9 Hz, BzOCH(C*H*$_3$)), 1.02 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.95 (9H, s, SiC(C*H*$_3$)$_3$), 0.84 (3H, d, 6.6

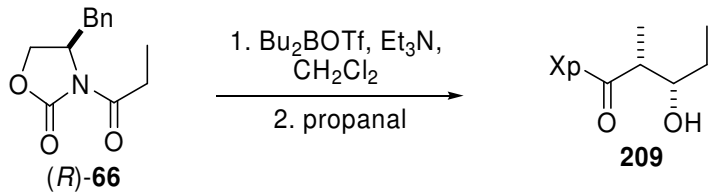
Hz, $CH(C\mathit{H}_3)CH_3$), 0.81 (3H, d, 6.9 Hz, $CH(CH_3)C\mathit{H}_3$), 0.07 (3H, s, $SiC\mathit{H}_3$), 0.07 (3H, s, $SiC\mathit{H}_3$).

5.4 Experimental Procedures for Chapter Four



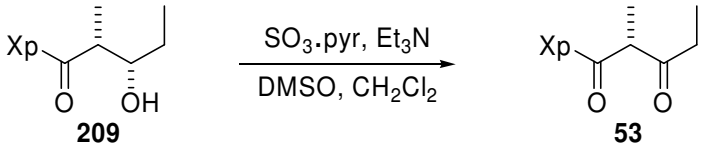
(*R*)-**100** (*R*)-**66**

(4*R*)-3-(1-oxo-propyl)-4-(phenylmethyl)-2-oxazolidinone [(*R*)-66].[2] *N*-acylation was performed according to the procedure of Evans and Gage.[2] To a solution of (*R*)-4-(phenylmethyl)-2-oxazolidinone [(*R*)-**100**] (6.8 g, 38.4 mmol) in THF (110 mL) at −78 °C was added *n*-BuLi (28.2 mL of a 1.6 M solution in hexanes, 38.8 mmol) dropwise over several minutes. The resulting yellow solution was treated with propionyl chloride (3.67 mL, 42.2 mmol) in one portion and the reaction mixture was stirred at −78 °C for 30 minutes and then allowed to warm room temperature over 30 minutes. The reaction was quenched with the addition of saturated aqueous NH_4Cl (20 mL) then the volatiles were removed *in vacuo*. The resulting slurry was extracted with CH_2Cl_2 (3 x 30 mL) and the extracts were washed with a 1 M solution of NaOH (30 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil that crystallised in the refrigerator. The solid material was broken-up, then triturated with ice cold hexanes, filtered and dried to give the *N*-acylated material (*R*)-**66** (8.70 g, 97%) as white plates. **m.p.** 42-44 °C (lit. 44-46 °C)[2]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.20 (5H, m, Ar*H*), 4.71-4.63 (1H, m, CH_2CHN), 4.24-4.17 (2H, m, $CHCH_2O$), 3.31 (1H, dd, 13.2, 3.3 Hz, $CHCH_AH_BPh$), 3.00 (1H, dq, 18.0, 7.4 Hz, $CH_AH_BCH_3$), 2.92 (1H, dq, 18.0, 7.4 Hz, $CH_AH_BCH_3$), 2.77 (1H, dd, 13.2, 9.6 Hz, $CHCH_AH_BPh$), 1.21 (3H, t, 7.4 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 174.1, 153.0, 135.3, 129.4, 128.9, 127.3, 66.2, 55.2, 37.9, 29.2, 8.3.



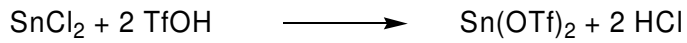
(*R*)-**66** **209**

[[3-(2*R*,3*S*)-4*R*]-3-(3-hydroxy-2-methyl-1-oxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (209).[30] The aldol addition was performed according to the procedure of Evans *et al.*[30] To a solution of (4*R*)-3-(1-oxo-propyl)-4-(phenylmethyl)-2-oxazolidinone [(*R*)-**66**] (7.60 g, 32.6 mmol) in CH_2Cl_2 (73 mL) at 0 °C was added $(Bu)_2BOTf$ (40 mL, 39.2 mmol) dropwise. After 30 minutes the red solution was treated with Et_3N (5.91 mL, 42.4 mmol) and the resulting yellow solution was stirred for a further 30 minutes before being cooled to −78 °C. Propanal (4.70 mL, 65.3 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 30 minutes and then at 0 °C for 1 hour after which the reaction was quenched with the addition of pH 7 phosphate buffer (76 mL) and MeOH (114 mL). To this solution was added 2:1 $MeOH/H_2O_2$ (114 mL) dropwise. After 1 hour of stirring at room temperature the volatiles were removed *in vacuo* and the slurry was extracted with Et_2O (3 x 150 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil that crystallised on standing. Recrystallisation of the crude material from 1:1 Et_2O/hexanes gave white needles (7.7 g). The mother liquor was concentrated *in vacuo* and the residue was purified by flash chromatography (10% Et_2O/CH_2Cl_2) affording an additional 1.2 g of the aldol adduct **209** (total yield, 94%). **m.p.** 79-81 °C (lit. 82-83 °C)[30]; $\mathbf{R}_f$ = 0.38 (10% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −44.2 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3530, 1791, 1684, 1457, 1355, 1212, 1116, 972, 703 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, Ar*H*), 4.74-4.66 (1H, m, CH_2CHN), 4.26-4.16 (2H, m, $CHCH_2O$), 3.89-3.84 (1H, m, C*H*OH), 3.79 (1H, qd, 7.0, 2.7 Hz, $CH(CH_3)CHOH$), 3.25 (1H, dd, 13.5, 3.3 Hz, $CHCH_AH_BPh$), 2.79 (1H, dd, 13.5, 9.3 Hz, $CHCH_AH_BPh$), 2.75 (1H, br s, O*H*), 1.65-1.39 (2H, m, CH_2CH_3), 1.25 (3H, d, 7.0 Hz, $CH(CH_3)CHOH$), 0.98 (3H, t, 7.4 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 177.5, 153.0, 135.0, 129.4, 128.9, 127.4, 72.9, 66.1, 55.1, 41.7, 37.8, 26.7, 10.4, 10.2.



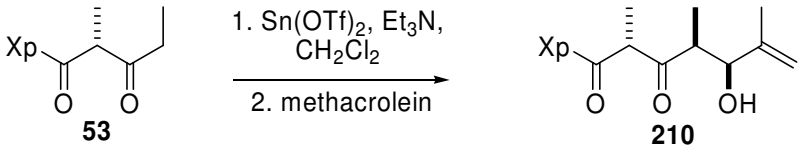
209 **53**

[[3-(2*R*)-4*R*]-3-(2-methyl-1,3-dioxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (53).[30] The oxidation was performed according to the procedure of Evans *et al.*[30] To a solution of [[3-(2*R*,3*S*)-4*R*]-3-(3-hydroxy-2-methyl-1-oxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (**209**) (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 minutes. The reaction mixture was warmed to room temperature and stirred for 3 hours, before being diluted with Et_2O (300 mL) and extracted with successive portions of 1 M solution of $NaHSO_4$, saturated aqueous $NaHCO_3$ and brine (300 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. Recrystallisation of the crude material from 1:1 Et_2O/pentane afforded white diamonds (3.5 g). Concentration of the mother liquor followed by flash chromatography (40% EtOAc/hexanes) of the residue yielded a further 311 mg of the β-ketoimide **53** (total yield, 95%); **m.p.** 76-78 °C (lit. 76-77 °C)[30]; $\mathbf{R}_f$ = 0.47 (40% EtOAc/hexanes); $[\alpha]^{20}_{D}$ = −162.6 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1775, 1718, 1701, 1456, 1394, 1361, 1250, 763, 705 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.18 (5H, m, Ar*H*), 4.78-4.70 (1H, m, CH_2CHN), 4.60 (1H, q, 7.2 Hz, $CH(CH_3)C{=}O$), 4.27-4.14 (2H, m, $CHCH_2O$), 3.31 (1H, dd, 13.2, 3.3 Hz, $CHCH_AH_BPh$), 2.76 (1H, dd, 13.2, 9.6 Hz, $CHCH_AH_BPh$), 2.68 (1H, dq, 18.0, 7.4 Hz, $CH_AH_BCH_3$), 2.64 (1H, dq, 18.0, 7.4 Hz, $CH_AH_BCH_3$), 1.43 (3H, d, 7.2 Hz, $CH(CH_3)C{=}O$), 1.07 (3H, t, 7.4 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.2, 170.2, 152.4, 135.1, 129.4, 129.0, 127.4, 66.5, 55.3, 52.7, 38.0, 34.0, 12.9, 7.5.



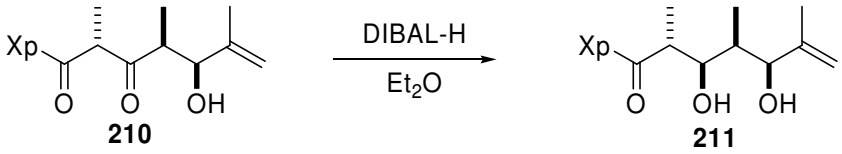
Tin triflate. Tin triflate was prepared according to the procedure of Evans *et al.*[31] $SnCl_2$ (8.0 g, 47.2 mmol) was dried by heating at 120 °C on a high vacuum pump for

2 hours. Trifluoromethanesulphonic acid (20 mL) was added and the resulting mixture was heated at 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 fine white powder was then dried on a high vacuum pump for 24 hours before use, with transferral to reaction flask carried out in an argon glove bag.



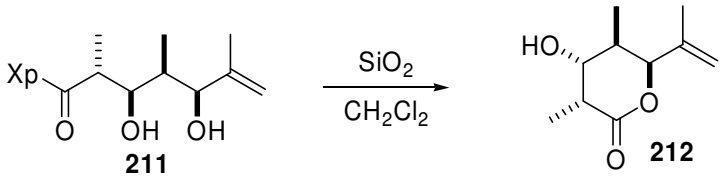
[[3-(2*R*,4*S*,5*S*)-4*R*]-3-(5-hydroxy-2,4,6-trimethyl-1,3-dioxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (210).[30] The aldol addition was performed according to the procedure of Evans *et al.*[30] To a suspension of $Sn(OTf)_2$ (3.48 g, 8.35 mmol) in CH_2Cl_2 (32 mL) at 0 °C was added Et_3N (1.16 mL, 8.35 mmol) dropwise and the resulting yellow suspension was cooled to −20 °C and stirred for 10 mins. The β-ketoimide **53** (1.86 g, 6.42 mmol) in CH_2Cl_2 (9 mL) was added *via* cannula over several minutes and the resulting solution was stirred for 1 h, then cooled to −78 °C. To the yellow enolate was added methacrolein (977 μL, 9.63 mmol) and the reaction mixture was stirred at −78 °C for 30 minutes and then transferred *via* cannula to a cooled (0 °C), vigorously stirring 1:1 mixture of CH_2Cl_2/1 M $NaHSO_4$ (70 mL). After 10 minutes the mixture was diluted with additional 1:1 CH_2Cl_2/1 M $NaHSO_4$ (70 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2) to give the adduct **210** (1.4 g, 84%) as a clear oil. $\mathbf{R}_f$ = 0.31 (10% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −97.1 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3532, 1780, 1714, 1692, 1454, 1392, 1360, 1215, 1120, 909, 703 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.18 (5H, m, Ar*H*), 5.09 (1H, m, $C(CH_3)=CH_AH_B$), 4.96 (1H, m, $C(CH_3)=CH_AH_B$), 4.88 (1H, q, 7.5 Hz, C(=O)C*H*(CH_3)C=O), 4.79-4.71 (1H, m, CH_2CHN), 4.44 (1H, br s, C*H*OH), 4.26 (1H, t, 8.7 Hz, $CHCH_AH_BO$), 4.18 (1H, dd, 9.3, 3.3 Hz, $CHCH_AH_BO$), 3.30 (1H, dd, 13.5, 3.3 Hz, $CHCH_AH_BPh$), 2.93 (1H, qd,

7.2, 3.0 Hz, C*H*(CH_3)CHOH), 2.77 (1H, dd, 13.5, 9.6 Hz, $CHCH_AH_BPh$), 2.41 (1H, br s, O*H*), 1.70 (3H, br s, C(CH_3)=CH_2), 1.49 (3H, d, 7.5 Hz, C(=O)CH(CH_3)C=O), 1.17 (3H, d, 7.2 Hz, C(=O)CH(CH_3)CHOH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.2, 170.2, 153.6, 143.5, 135.0, 129.3, 129.0, 127.4, 112.0, 73.6, 66.5, 55.3, 51.8, 46.6, 37.9, 19.4, 12.9, 9.6.

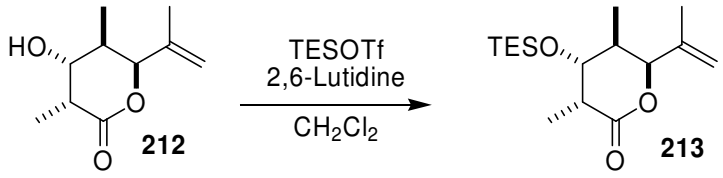


210 **211**

[[3-(2*R*,3*R*,4*R*,5*S*)-4*R*]-3-(3,5-dihydroxy-2,4,6-trimethyl-1-oxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (211). To a solution β-hydroxy ketone **210** (100 mg, 0.28 mmol) in Et_2O (11 mL) at −78 °C was added DIBAL-H (1.11 mL of a 1 M solution in THF, 1.11 mmol) and the resulting mixture was stirred for 1 hour. The reaction mixture was then added to vigorously stirring solution of 10% aqueous HCl/CH_2Cl_2 (20 mL, 1:1) *via* cannula. The biphasic mixture was stirred at 0 °C for 5 minutes then separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on buffered silica (20% Et_2O/CH_2Cl_2) gave the diol **211** (89 mg, 92%, based on recovered starting material) as a clear oil. $\mathbf{R}_f$ = 0.19 (20% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −60.7 (*c* 0.6, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.15 (5H, m, Ar*H*), 5.04 (1H, br s, C(CH_3)=CH_AH_B), 4.96 (1H, br s, C(CH_3)=CH_AH_B), 4.76-4.68 (1H, m, CH_2CHN), 4.27-4.08 (4H, m, $CHCH_AH_BO$, C*H*OH x 2), 3.99 (1H, dq, 9.0, 6.9 Hz, C(=O)C*H*(CH_3)CHOH), 3.25 (1H, dd, 13.2, 3.0 Hz, $CHCH_AH_BPh$), 3.01 (2H, br s, OH x 2), 2.79 (1H, dd, 13.2, 9.6 Hz, $CHCH_AH_BPh$), 1.90-1.83 (1H, m, CH(OH)C*H*(CH_3)CHOH), 1.70 (3H, br s, C(CH_3)=CH_2), 1.17 (3H, d, 6.9 Hz, C(=O)CH(CH_3)CHOH), 0.87 (3H, d, 6.9 Hz, CH(OH)CH(CH_3)CHOH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 176.5, 153.4, 145.3, 135.2, 129.4, 128.9, 127.3, 111.0, 79.3, 77.9, 66.2, 55.2, 41.2, 37.9, 35.4, 19.3, 14.5, 4.7; **LSIMS** calculated for $C_{20}H_{27}NO_5H^+$ $[M+H]^+$: 362.1958; found 362.1962.

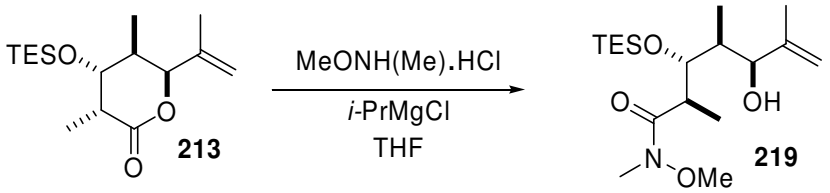


(3*R*,4*R*,5*R*,6*S*)-4-Hydroxy-6-isopropenyl-3,5-dimethyl-tetrahydro-pyran-2-one (212). To a solution of the diol **211** (100 mg, 0.54 mmol) in CH_2Cl_2 (23 mL) was added silica gel (7 g) and the resulting slurry was stirred overnight, then filtered with rinsing (Et_2O). The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (20% Et_2O/CH_2Cl_2) to give the γ-lactone **212** (50 mg, 99%) as a clear oil. $\mathbf{R}_f$ = 0.48 (20% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −22.9 (*c* 1.7, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3448, 1715, 1453, 1386, 1207, 1122, 1092, 1068, 995 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.17 (1H, br s, CH(CH_3)C*H*(-O-)C), 5.11 (1H, m, C(CH_3)=CH_AH_B), 4.97 (1H, q, 1.5 Hz, C(CH_3)=CH_AH_B), 3.98 (1H, t, 3.6 Hz, C*H*OH), 2.79 (1H, br s, O*H*), 2.64 (1H, qd, 7.2, 3.6 Hz, C(=O)C*H*(CH_3)CHOH), 2.34 (1H, qdd, 7.2, 3.6, 3.6 Hz, C*H*(CH_3)CH(-O-)C), 1.68 (3H, br s, C(CH_3)=CH_2), 1.31 (3H, d, 7.2 Hz, C(=O)CH(CH_3)CHOH), 0.83 (3H, d, 7.2 Hz, CH(CH_3)CH(-O-)C); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 174.1, 140.1, 111.4, 79.6, 72.4, 36.5, 35.7, 19.2, 12.1, 10.2; **HRLSIMS** calculated for $C_{10}H_{16}O_3Na^+$ $[M+Na]^+$: 207.0992; found 207.0998.



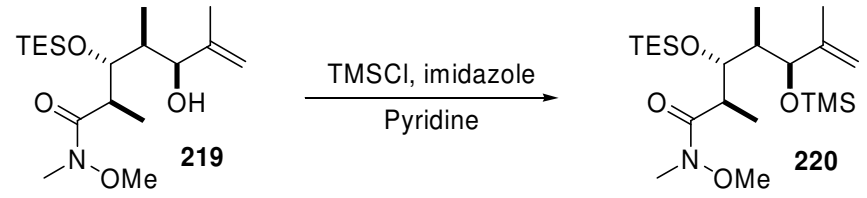
(3*R*,4*R*,5*R*,6*S*)-4-triethylsilyloxy-6-isopropenyl-3,5-dimethyl-tetrahydro-pyran-2-one (213). To a solution of the γ-lactone **212** (46 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added 2,6-lutidine (116 μL, 0.99 mmol) followed by TESOTf (169 μL, 0.75 mmol) and the resulting mixture was stirred at −78 °C for 30 mins. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL), then partitioned between H_2O (10 mL) and CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was

purified by column chromatography (CH_2Cl_2) to give the protected γ-lactone **213** (70 mg, 95%) as a clear oil. $\mathbf{R}_f$ = 0.38 (CH_2Cl_2); $[\alpha]^{20}_D$ = −14.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1740, 1457, 1385, 1190, 1124, 1051, 1019, 1004, 900, 849, 747 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.14 (2H, br s, CH(CH_3)C*H*(-O-)C, C(CH_3)=CH_AH_B), 4.98 (1H, m, C(CH_3)=CH_AH_B), 3.93 (1H, t, 3.6 Hz, C*H*OTES), 2.60 (1H, qd, 7.0, 3.6 Hz, C(=O)C*H*(CH_3)CHOTES), 2.07 (1H, qdd, 7.2, 3.6, 3.6 Hz, C*H*(CH_3)CH(-O-)C), 1.68 (3H, br s, C(CH_3)=CH_2), 1.26 (3H, d, 7.0 Hz, C(=O)CH(CH_3)CHOTES), 0.96 (9H, t, 7.8 Hz, Si(CH_2CH_3)$_3$), 0.83 (3H, d, 7.2 Hz, CH(CH_3)CH(-O-)C), 0.63 (6H, q, 7.8 Hz, Si(C$H_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 173.7, 140.1, 111.5, 79.4, 73.7, 37.0, 36.6, 19.3, 12.7, 10.4, 6.8, 4.8.

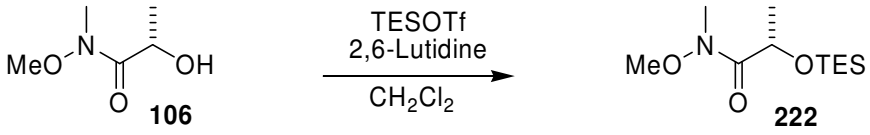


(2*R*,3*R*,4*R*,5*S*)-3-triethylsilyloxy-5-hydroxy-*N*-methoxy-*N*-methyl-2,4,6-trimethyl-hept-7-eneionamide (219). The amide was synthesised according to the procedure of Paterson *et al*.[7] To a mixture of γ-lactone **213** (60 mg, 0.20 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (49 mg, 0.50 mmol) in THF (600 μL) at −20 °C was added ^{i}PrMgCl (503 μL of a 2 M solution in THF, 1.0 mmol) dropwise. The reaction mixture was stirred at −20 °C for a 30 minutes and then at 0 °C for a further 30 minutes before saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (4 x 2mL) and CH_2Cl_2 (4 x 2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (10% Et_2O/CH_2Cl_2) to give the Weinreb amide **219** (60 mg, 83%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.04 (1H, br s, C(CH_3)=CH_AH_B), 4.91 (1H, br s, C(CH_3)=CH_AH_B), 4.12 (1H, dd, 8.7, 2.4 Hz, C*H*OTES), 4.10 (1H, br s C*H*OH), 3.70 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 3.20-3.08 (1H, m, C(=O)C*H*(CH_3)CHOTES), 2.36 (1H, br s, O*H*), 1.83 (1H, qdd, 6.8, 4.5, 2.1 Hz, C*H*(CH_3)CHOH), 1.67 (3H, br s, C(CH_3)=CH_2), 1.04 (3H, d, 7.2 Hz, C(=O)CH(CH_3)CHOTES), 0.93 (9H, t, 7.8 Hz, Si(CH_2CH_3)$_3$), 0.90 (3H, d, 6.8 Hz, CH(CH_3)CHOH), 0.62 (6H, q, 7.8 Hz,

Si(CH_2CH_3)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.9, 145.6, 111.9, 77.7, 76.2, 61.2, 40.7, 37.1, 32.0, 18.8, 14.0, 7.0, 6.8, 5.2.

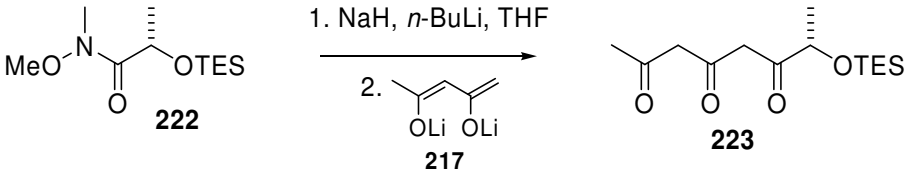


(2*R*,3*R*,4*R*,5*S*)-3-triethylsilyloxy-*N*-methoxy-*N*-methyl-5-trimethylsilyloxy-2,4,6-trimethyl-hept-7-eneionamide (220). To a solution of the alcohol **219** (32 mg, 89.0 μmol) in pyridine (1.3 mL) was added hexamethyldisilazane (56 μL, 267 μmol) and TMSCl (34 μL, 267 μmol). A white precipitate formed during the course of the reaction. After 1 hour the reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (10% Et_2O/CH_2Cl_2) to give the bis-protected amide **220** (32 mg, 83%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.06 (1H, br s, C(CH_3)=CH_AH$_B$), 4.89 (1H, br s, C(CH_3)=CH$_A$$H_B$), 4.12 (2H, m, C*H*OTES, C*H*OTMS), 3.22-3.15 (1H, m, C(=O)C*H*(CH_3)CHOTES), 3.20 (3H, s, OCH_3), 2.91 (3H, s, NCH_3), 1.96 (1H, qn, 6.9 Hz, C*H*(CH_3)CHOTMS), 1.69 (3H, br s, C(CH_3)=CH_2), 1.23 (3H, d, 6.6 Hz, C(=O)CH(CH_3)CHOTES), 1.10 (9H, t, 8.0 Hz, Si(CH_2CH_3), 1.04 (3H, d, 6.9 Hz, CH(OTES)CH(CH_3)CHOTMS), 0.87 (3H, dq, 15.0, 8.0 Hz, Si(CH_AH$_B$$CH_3$)$_3$), 0.78 (3H, dq, 15.0, 8.0 Hz, Si(CH$_A$$H_B$$CH_3$)$_3$), 0.19 (9H, s, Si(C$H_3$)$_3$; **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 176.0, 146.8, 114.9, 79.6, 73.6, 60.8, 40.8, 39.0, 31.8, 16.5, 14.7, 10.2, 7.5, 6.1, 0.4.



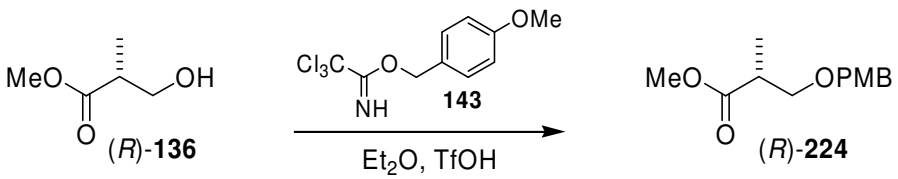
(2*S*)-2-trietylsilyloxy-*N*-methoxy-*N*-methylpropionamide (222). To a solution of the Weinreb amide **106** (200 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) at –78 °C was added 2,6-lutidine (350 μL, 3.00 mmol) followed by TESOTf (510 μL, 2.25 mmol).

The reaction mixture was stirred at –78 °C for 30 minutes before being quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and partioned with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (20% Et_2O/CH_2Cl_2) to give the protected product **222** (353 mg, 95%) as a clear oil. $\mathbf{R}_f$ = 0.65 (20% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.67 (1H, br q, 6.6 Hz, C*H*(CH_3)OTES), 3.68 (3H, s, OC*H*$_3$), 3.19 (3H, s, NC*H*$_3$), 1.34 (3H, d, 6.6 Hz, CH(C*H*$_3$)OTES), 0.94 (9H, t, 7.5 Hz, Si($CH_2C\mathit{H}_3$)$_3$), 0.61 (6H, q, 7.5 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.4, 66.1, 61.2, 32.4, 21.0, 6.7, 4.7.

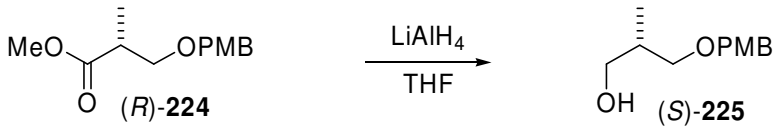


(7S)-7-triethylsilyloxyoctan-2,4,6-trione 223. To a slurry of NaH (32 mg, 0.81 mmol) in THF (2 mL) at 0 °C was added pentan-2,4-dione **217** (83 μL, 0.81 mmol) and the resulting mixture was stirred for 10 minutes, before being cooled to –10 °C. *n*-BuLi (558 mL of a 1.6 M solution in hexanes, 0.81 mmol) was added and the resulting solution was stirred at –10 °C for 10 minutes before being cooled to –78 °C. To the reaction mixture was added the Weinreb amide **222** (100 mg, 0.40 mmol) and stirring maintained at –78 °C for 30 minutes before the addition of saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (20% Et_2O/CH_2Cl_2) to give the β-triketone **223** (93 mg, 80%) as a mixture of keto and enol forms and as a bright red oil. $\mathbf{R}_f$ = 0.80 (20% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.97 (0.25H, s, C*H*=COH), 5.55 (0.25H, s, C*H*=COH), 5.51 (0.25H, s, C*H*=COH), 5.23 (0.25H, s, C*H*=COH), 4.29-4.20 (1H, m, C*H*(CH_3)OTES), 3.60 (0.5H, s, C(=O)C*H*$_2$C=O), 3.44 (0.5H, s, C(=O)C*H*$_2$C=O), 2.26 (1H s, C*H*$_3$C(=O)CH_2), 2.06 (1H s, C*H*$_3$C(=O)CH_2), 1.99 (1H s, C*H*$_3$C(OH)=CH), 1.37 (1H, d, 6.6 Hz, CH(C*H*$_3$)OTES), 1.36 (1H, d, 6.6 Hz, CH(C*H*$_3$)OTES), 1.32 (1H, d,

6.6 Hz, CH(CH_3)OTES), 0.99-0.93 (9H, m, Si(CH$_2$CH_3)$_3$), 0.66-0.58 (6H, m, Si(CH_2CH$_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 207.6, 201.7, 197.3, 194.5, 189.6, 188.5, 187.1, 183.4, 178.8, 101.1, 100.0, 99.3, 96.6, 94.7, 74.6, 70.1, 68.1, 54.0, 47.4, 30.2, 22.6, 22.1, 21.8, 20.6, 17.9, 6.7, 6.6 x 2, 4.7, 4.6 x 2.

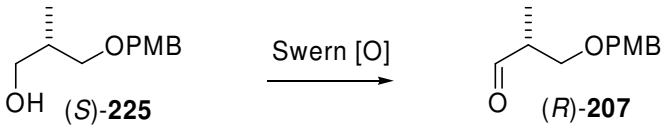


(2*R*)-Methyl-3-(4-methoxybenzyl)oxy-2-methylpropionate [(*R*)-224].[32] Protection of the hydroxy ester was performed according to the procedure oe Wessel *et al.*[14] To a solution of the crude acetimidate **143** (10.8 g, 38.1 mmol) in Et_2O (46 mL) at room temperature was added methyl-(2*R*)-3-hydroxy-2-methylpropionate (3.00 g, 25.4 mmol) followed by trifluoromethanesulfonic acid (7 μL, 76.2 μmoL). The reaction mixture was stirred at room temperature for 2 hours before careful addition of saturated aqueous $NaHCO_3$ (50 mL). The organic phase was separated, washed with brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a slurry. The product was triturated several times with 1:1 hexanes/CH_2Cl_2 to give the ester (*R*)-**224** (5.4 g, 89%) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.45 (2H, s, OCH_2PMP), 3.80 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.63 (1H, dd, 9.3, 7.5 Hz, CH(CH$_3$)CH_AH$_B$OPMB), 3.46 (1H, dd, 9.3, 6.0 Hz, CH(CH$_3$)CH$_A$$H_B$OPMB), 2.77 (1H, dqd, 7.5, 7.2, 6.0 Hz, CH(CH$_3$)CH$_A$$H_B$OPMB), 1.17 (3H, d, 7.2 Hz, CH(CH_3)CH$_2$OPMB); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.5, 159.3, 130.4, 129.3, 113.9, 72.9, 71.8, 55.4, 51.8, 40.3, 14.1.



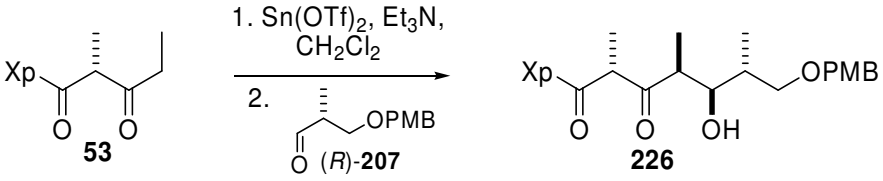
(2*S*)-3-(4-methoxybenzyl)oxy-2-methylpropan-1-ol [(*S*)-225].[32] To a slurry of $LiAlH_4$ (1.00 g, 27.2 mmol) in THF (41 mL) at 0 °C was added a solution of (2*R*)-Methyl-3-(4'-methoxybenzyl)oxy-2-methylpropionate [(*R*)-**224**] (5.40 g, 22.7 mmol)

in THF (45 mL) *via* cannula. The reaction mixture was warmed to room temperature and stirred for 30 minutes, before being cooled to 0 °C and quenched with the dropwise addition of H_2O (3 mL), 15% NaOH (3 mL) and H_2O (5 mL). The resulting mixture was diluted with Et_2O (100 mL), dried ($MgSO_4$) and filtered. The filter cake was rinsed with Et_2O and the organics were concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (30% Et_2O/CH_2Cl_2) to afford (2*R*)-3-(4'-methoxybenzyl)oxy-2-methylpropan-1-ol [(*S*)-**225**] (4.2 g, 89%) as a clear oil. $\mathbf{R}_f$ = 0.43 (30% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.88 (2H, d, 8.7 Hz, Ar*H*), 4.44 (2H, s, OC*H*$_2$PMP), 3.80 (3H, s, OC*H*$_3$), 3.63-3.55 (2H, m, C*H*$_2$OH), 3.51 (1H, dd, 9.0, 4.8 Hz, CH(CH_3)C*H*$_A$H$_B$OPMB), 3.39 (1H, dd, 9.0, 8.1 Hz, CH(CH_3)CH$_A$*H*$_B$OPMB), 2.70 (1H, br s, O*H*), 2.12-1.97 (1H, m, C*H*(CH_3)CH_2OPMB), 0.87 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_2OPMB); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.2, 130.1, 129.2, 113.8, 74.9, 72.9, 67.6, 55.2, 35.5, 13.4.



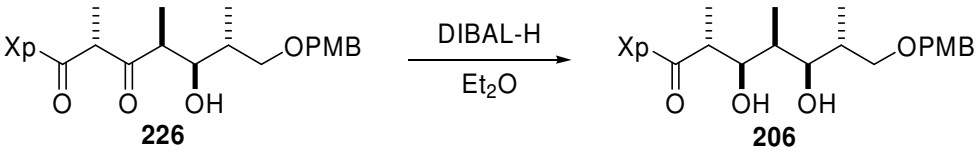
(2*R*)-3-(4-methoxybenzyl)oxy-2-methylpropan-1-al [(*R*)-207].[32] Oxidation was performed according to Smith's modification of the Swern procedure.[10] To a solution of DMSO (4.27 mL, 60.2 mmol) in CH_2Cl_2 (86 mL) at −78 °C was added oxalyl chloride (15.1 mL of a 2 M solution in CH_2Cl_2, 30.1 mmol) over 5 mins. After 30 minutes, a solution of (2*R*)-3-(4'-methoxybenzyl)oxy-2-methylpropan-1-ol [(*S*)-**225**] (4.22 g, 20.1 mmol) in CH_2Cl_2 (15 mL) was added *via* cannula and the resulting mixture stirred at −78 °C for 45 minutes. Triethylamine (16.8 mL, 120.0 mmol) was added over 5 minutes and the resulting white solution was stirred at −78 °C for 30 minutes then at 0 °C for 30 minutes. The reaction was quenched by pouring into a rapidly stirring 1 M solution of $NaHSO_4$ (120 mL), then the layers were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic extracts were concentrated *in vacuo*, the residue diluted with Et_2O (100 mL) then washed successively with 1 M solution of $NaHSO_4$ (3 x 30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column

chromatography (10% Et_2O/CH_2Cl_2, buffered silica) to give (2*R*)-3-(4'-methoxybenzyl)oxy-2-methylpropan-1-al [(*R*)-**207**] (4.15 g, 99%) as a clear oil. $\mathbf{R_f}$ = 0.62 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.70 (1H, d, 1.5 Hz, C*H*O), 7.23 (2H, d, 8.7 Hz, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.45 (2H, s, OCH_2PMP), 3.79 (3H, s, OCH_3), 3.65 (1H, dd, 9.3, 6.3 Hz, CH(CH_3)C$H_A$$H_B$OPMB), 3.60 (1H, dd, 9.3, 5.4 Hz, CH(CH_3)C$H_A$$H_B$OPMB), 2.65 (1H, m, C*H*(CH_3)CH_2OPMB), 1.11 (3H, d, 7.2 Hz, CH(CH_3)CH_2OPMB); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 203.8, 159.2, 129.9, 129.2, 113.7, 72.9, 69.7, 55.2, 46.7, 10.6.



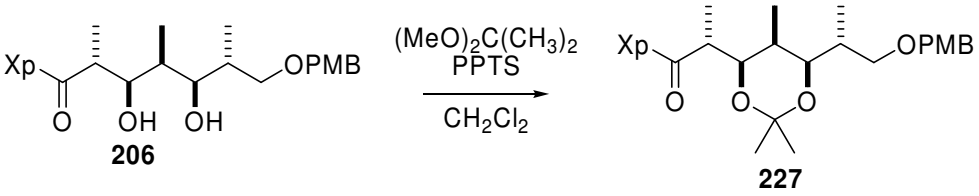
[[3-(2*R*,4*S*,5*S*,6*R*)-4*R*]-3-(5-hydroxy-7-[4-methoxybenzyl]oxy-2,4,6-trimethyl-1,3-dioxo-heptane)-4-(phenylmethyl)]-2-oxazolidinone (226). The aldol addition was performed according to the procedure of Evans *et al.*[30] To a suspension of $Sn(OTf)_2$ (6.75 g, 16.2 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added Et_3N (2.26 mL, 16.2 mmol) dropwise and the resulting yellow suspension was cooled to −20 °C and stirred for 10 mins. The β-ketoimide **53** (3.78 g, 12.5 mmol) in CH_2Cl_2 (22 mL) was added *via* cannula over several minutes and the resulting solution was stirred for 1 h, then cooled to −78 °C. To the yellow enolate was added a solution of (2*R*)-3-(4'-methoxybenzyl)oxy-2-methylpropan-1-al [(*R*)-**207**] (3.89 g, 18.7 mmol) in CH_2Cl_2 (10 mL) *via* cannula. The reaction mixture was stirred at −78 °C for 30 minutes and then transferred *via* cannula to a cooled (0 °C), vigorously stirring 1:1 mixture of CH_2Cl_2/1 M $NaHSO_4$ (1 L). After 10 minutes the mixture was diluted with additional 1:1 CH_2Cl_2/1 M $NaHSO_4$ (500 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2) to give a single isomer of the aldol adduct **226** (5.6 g, 91%, >95% ds) as a clear oil. $\mathbf{R_f}$ = 0.26 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = −54.8 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3479, 1778, 1731, 1692, 1612, 1513, 1454, 1359, 1301, 1247,

1213, 1178, 1081, 1032, 1006, 820, 703 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.18 (7H, m, Ar*H*), 6.86 (2H, d, 8.7 Hz, Ar*H*), 4.94 (1H, q, 7.2 Hz, C(=O)C*H*(CH_3)C=O), 4.71 (1H, m, OCH_2CHN), 4.44 (2H, s, CH_2OCH_2PMP), 4.18 (2H, m, OCH_2CHN), 3.90 (1H, dd, 8.7, 3.0 Hz, C*H*OH), 3.79 (3H, s, OCH_3), 3.54 (2H, d, 5.4 Hz, $CHCH_2OPMB$), 3.29 (1H, dd, 13.5, 3.3 Hz, $CHCH_AH_BPh$), 2.91 (1H, qd, 7.2, 3.0 Hz, C(=O)C*H*(CH_3)CHOH), 2.76 (1H, dd, 13.5, 9.6 Hz, $CHCH_AH_BPh$), 1.95-1.83 (1H, m, C*H*(CH_3)CH_2OPMB), 1.47 (3H, d, 7.2 Hz, C(=O)CH(CH_3)C=O), 1.18 (3H, d, 7.2 Hz, C(=O)CH(CH_3)CHOH), 0.90 (3H, d, 6.9 Hz, CH(CH_3)CH_2OPMB); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.3, 170.4, 159.2, 153.5, 135.0, 130.0, 129.4, 129.3, 128.9, 127.4, 113.8, 74.4, 74.0, 73.0, 66.4, 55.4, 55.2, 50.8, 47.4, 37.8, 35.9, 13.9, 13.4, 9.0; **HRESIMS** calculated for $C_{28}H_{35}NO_7Na^+$ $[M+Na]^+$: 520.2306; found 520.2311; **EIMS** *m/z* (%): 217 (1), 140 (27), 125 (7), 121 (100), 111 (8), 99 (2), 91 (3), 77 (4), 69 (2), 57 (3).



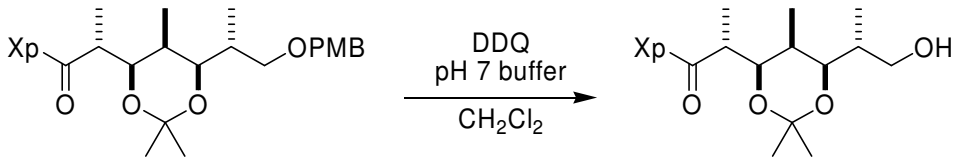
[[3-(2*R*,4*S*,5*S*,6*R*)-4*R*]-3-(7-[4-methoxybenzyl]oxy-2,4,6-trimethyl-1-oxo-heptan-3,5-diol)-4-(phenylmethyl)]-2-oxazolidinone (206). To a solution β-hydroxy ketone **226** (500 mg, 0.98 mmol) in Et_2O (40 mL) at −78 °C was added DIBAL-H (3.91 mL of a 1 M solution in THF, 3.91 mmol) and the resulting mixture was stirred at −78 °C for 1 hour. The reaction mixture was then added to a vigorously stirring solution of 10% aqueous HCl/CH_2Cl_2 (100 mL, 1:1) *via* cannula. The biphasic mixture was stirred at 0 °C for 5 minutes then separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on buffered silica (30% Et_2O/CH_2Cl_2) gave the diol **206** (419 mg, 93%, based on 90% conversion) as a clear oil. $\mathbf{R}_f$ = 0.34 (30% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −53.8 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3443, 1782, 1699, 1514, 1456, 1388, 1353, 1249, 1212, 1180, 1089, 1034, 971, 749, 703 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.20 (7H, m, Ar*H*), 6.87

(2H, d, 8.7 Hz, Ar*H*), 4.75-4.61 (1H, m, OCH_2CHN), 4.51 (2H, s, CH_2OCH_2PMP), 4.19-3.99 (4H, m, OCH_2CHN, $C(=O)CH(CH_3)CHOH$, $C(=O)CH(CH_3)CHOH$), 3.79 (3H, s, OCH_3), 3.79 (2H, br s, 2 x O*H*), 3.73 (1H, dd, 9.0, 2.1 Hz, $CH(OH)CH(CH_3)CH_2OPMB$), 3.58 (1H, dd, 9.0, 4.2 Hz, $CHCH_AH_BOPMB$), 3.44 (1H, t, 9.0 Hz, $CHCH_AH_BOPMB$), 3.27 (1H, dd, 13.5, 3.3 Hz, $CHCH_AH_BPh$), 2.78 (1H, dd, 13.5, 9.6 Hz, $CHCH_AH_BPh$), 2.00 (1H, m, $CH(CH_3)CH_2OPMB$), 1.76 (1H, q, 6.9 Hz, $CH(OH)CH(CH_3)CHOH$), 1.13 (3H, d, 6.3 Hz, $C(=O)CH(CH_3)CHOH$), 0.94 (3H, d, 6.9 Hz, $C(OH)CH(CH_3)CHOH$), 0.78 (3H, d, 7.2 Hz, $CH(CH_3)CH_2OPMB$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 176.5, 159.3, 153.3, 135.4, 129.4 x 2, 129.3, 128.8, 127.2, 113.9, 82.3, 79.0, 76.1, 73.1, 66.0, 55.4, 55.2, 40.3, 37.9, 35.8, 34.7, 14.2, 13.0, 4.3; **HRESIMS** calculated for $C_{28}H_{37}NO_7Na^+$ $[M+Na]^+$: 522.2462; found 522.2467; **EIMS** *m/z* (%): 273 (5), 190 (15), 178 (14), 137 (39), 121 (100), 92 (33), 85 (25), 57 (13).



[[3-(2*R*,3*R*,4*S*,5*S*,6*R*)-4*R*]-3-(3,5-[[bis-dimethyl-methylene]dioxy]-7-[4-methoxybenzyl]oxy-2,4,6-trimethyl-1-oxo-heptane)-4-(phenylmethyl)]-2-oxazolidinone 227. The acetonide was synthesised according to the procedure of Kitamura *et al*.[33] To a solution of the diol **206** (60 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added dimethoxypropane (2 mL) and a few crystals of PPTS and the resulting solution was stirred at room temperature for 3 hours. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2) to afford the acetonide **227** (55 mg, 85%) as a clear oil. $\mathbf{R}_f$ = 0.37 (5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −33.7 (*c* 1.7, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 1783, 1698, 1613, 1514, 1454, 1386, 1353, 1246, 1201, 1152, 1102, 1012, 974, 866, 748, 701 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.21 (7H, m, Ar*H*), 6.87 (2H, d, 8.7 Hz, Ar*H*), 4.69-4.62 (1H, m, OCH_2CHN), 4.46 (1H, d, 11.7 Hz, $CH_2OCH_AH_BPMP$), 4.38 (1H, d, 11.7 Hz, $CH_2OCH_AH_BPMP$), 4.18-4.13

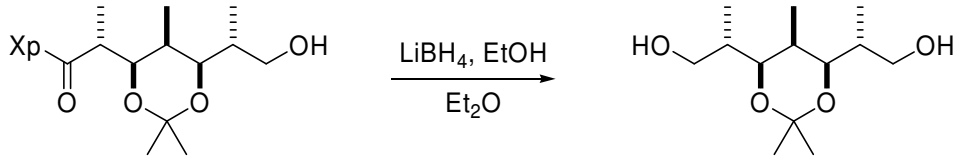
(3H, m, OC*H*$_2$CHN, C(=O)CH(CH$_3$)C*H*O-), 3.99 (1H, dq, 10.2, 6.9 Hz, C(=O)C*H*(CH$_3$)CHO-), 3.80 (3H, s, OC*H*$_3$), 3.73 (1H, dd, 10.2, 1.8 Hz, C*H*(-O-)CH(CH$_3$)CH$_2$OPMB), 3.52 (1H, dd, 8.7, 3.0 Hz, CHC*H*$_A$H$_B$OPMB), 3.43 (1H, dd, 8.7, 6.0 Hz, CHCH$_A$*H*$_B$OPMB), 3.25 (1H, dd, 13.2, 3.3 Hz, CHC*H*$_A$H$_B$Ph), 2.78 (1H, dd, 13.5, 6.6 Hz, CHCH$_A$*H*$_B$Ph), 1.84 (1H, m, C*H*(CH$_3$)CH$_2$OPMB), 1.57 (1H, q, 6.9 Hz, CH(-O-)C*H*(CH$_3$)CH-O-), 1.36 (3H, s, C(C*H*$_3$)CH$_3$), 1.28 (3H, s, C(CH$_3$)C*H*$_3$), 1.12 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$)CH-O-), 0.94 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH$_2$OPMB), 0.88 (3H, d, 6.9 Hz, C(-O-)CH(C*H*$_3$)CH-O-); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 175.6, 159.0, 153.1, 135.3, 131.0, 129.4, 129.0, 128.8, 127.2, 113.6, 98.8, 75.4, 73.8, 72.7, 71.9, 65.9, 55.4, 55.2, 39.2, 37.9, 35.3, 29.8, 29.6, 19.4, 12.6, 12.4, 4.4; **HRESIMS** calculated for $C_{31}H_{41}NO_7Na^+$ $[M+Na]^+$: 562.2775; found 562.2779; **EIMS** *m/z* (%): 524 (1), 304 (2), 248 (7), 233 (3), 178 (7), 137 (20), 121 (100), 91 (6), 69 (5), 59 (3).



227 **228**

[[3-(2*R*,3*R*,4*S*,5*S*,6*R*)-4*R*]-3-(3,5-[[bis-dimethyl-methylene]dioxy]-7-hydroxy-2,4,6-trimethyl-1-oxo-heptane)-4-(phenylmethyl)]-2-oxazolidinone (228). Deprotection was performed according to the procedure of Paterson *et al*.[23] To a solution of the benzyl ether **227** (45 mg, 83.4 μmol) in CH_2Cl_2 (5 mL) at 0 °C was added pH 7 phosphate buffer (1 mL) followed by DDQ (32 mg, 0.14 mmol) and the resultant slurry was stirred at 0 °C for 3 hours. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous $NaHCO_3$ (30 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/CH_2Cl_2) to give the alcohol **228** (32 mg, 92%) as a clear oil. $\mathbf{R}_f$ = 0.35 (30% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = −75.6 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, FT, film) 3519, 1783, 1699, 1386, 1353, 1262, 1201, 1147, 1102, 1012, 974, 748 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.20 (5H, m, Ar*H*), 4.70-4.62 (1H, m, OCH$_2$C*H*N), 4.22-4.13

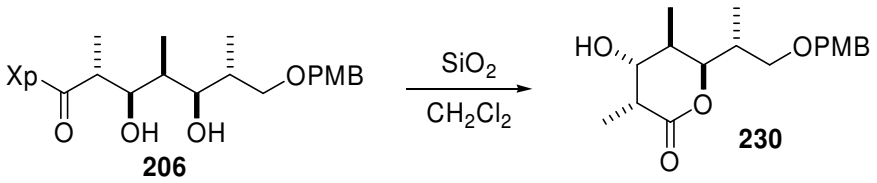
(3H, m, OC*H*$_2$CHN, C(=O)CH(CH$_3$)C*H*O-), 3.98 (1H, dq, 9.9, 6.9 Hz, C(=O)C*H*(CH$_3$)CHO-), 3.77 (1H, dd, 9.9, 2.1 Hz, C*H*(-O-)CH(CH$_3$)CH$_2$OH), 3.61 (1H, dd, 10.8, 7.5 Hz, CHC*H$_A$*H$_B$OH), 3.54 (1H, dd, 10.8, 3.6 Hz, CHCH$_A$*H$_B$*OH), 3.24 (1H, dd, 13.5, 3.3 Hz, CHC*H$_A$*H$_B$Ph), 2.80 (1H, br s, O*H*), 2.78 (1H, dd, 13.5, 9.6 Hz, CHCH$_A$*H$_B$*Ph), 2.00-1.86 (1H, m, C*H*(CH$_3$)CH$_2$OH), 1.58 (1H, q, 6.9 Hz, CH(-O-)C*H*(CH$_3$)CH-O-), 1.44 (3H, s, C(C*H$_3$*)CH$_3$), 1.30 (3H, s, C(CH$_3$)C*H$_3$*), 1.11 (3H, d, 6.9 Hz, C(=O)CH(C*H*$_3$)CH-O-), 0.91 (3H, d, 6.9 Hz, C(-O-)CH(C*H*$_3$)CH-O-) 0.79 (3H, d, 6.9 Hz, CH(C*H$_3$*)CH$_2$OH); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 175.4, 153.1, 135.3, 129.4, 128.9, 127.3, 99.0, 79.7, 75.1, 68.7, 66.0, 55.3, 39.2, 37.9, 36.3, 30.1, 29.8, 19.4, 12.4, 12.0, 4.6; **HRESIMS** calculated for $C_{23}H_{33}NO_6Na^+$ $[M+Na]^+$: 442.2200; found 442.2201; **EIMS** *m/z* (%): 406 (1), 304 (2), 248 (8), 233 (5), 178 (8), 137 (21), 121 (100), 96 (8), 69 (8), 55 (3).



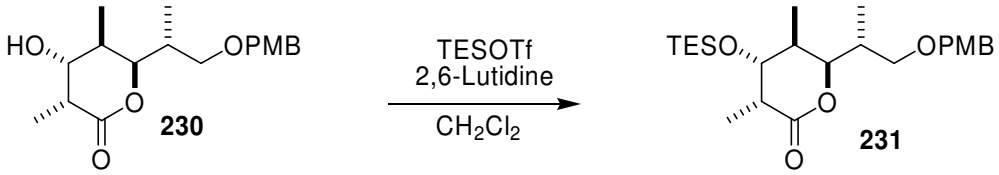
228 **229**

(2*R*,3*R*,4*S*,5*S*,6*R*)-3,5-[[bis-dimethyl-methylene]dioxy]-2,4,6-trimethyl-heptan-1,7-diol (229). Reductive cleavage was performed according to the procedure of Penning *et al.*[3] To a solution of the oxazolidinone **228** (32 mg, 76.3 μmol) in Et$_2$O (1.5 mL) at −10 °C was added EtOH (11 μL, 0.18 mmol) followed by LiBH$_4$ (92 mL of a 2.0 M solution in THF, 0.18 mmol). The reaction mixture was stirred at −10 °C for 1.5 hours then quenched by the addition of NaOH (381 μL of a 1M solution, 0.38 mmol). The mixture was extracted with Et$_2$O (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL) then dried (MgSO$_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et$_2$O/CH$_2$Cl$_2$) to give the *meso*-diol **229** (11 mg, 62%) as a clear oil. **R$_f$** = 0.17 (30% Et$_2$O/CH$_2$Cl$_2$); **[α]$^{20}_D$** = 0.0 (*c* 0.6, CHCl$_3$); **IR** (CHCl$_3$, FT, film) 3383, 1379, 1353, 1263, 1202, 1184, 1149, 1036, 1011, 975, 861 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 3.74 (2H, dd, 9.9, 2.1 Hz, C*H*O-), 3.61 (2H, dd, 10.8, 7.5 Hz, CHC*H$_A$*H$_B$OH x 2), 3.55 (2H, dd, 10.8, 3.6 Hz, CHCH$_A$*H$_B$*OH x 2), 2.88 (2H, br s, O*H* x 2), 2.00-1.86 (2H, m,

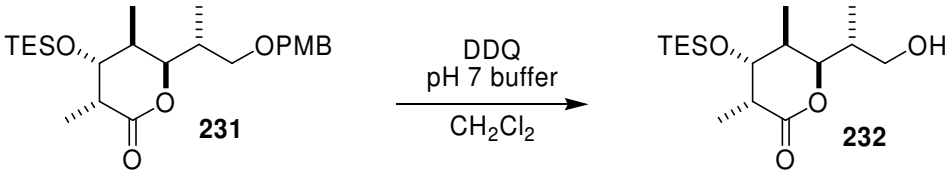
C*H*(CH_3)CH_2OH x 2), 1.59-1.51 (1H, m, CH(-O-)C*H*(CH_3)CH-O-), 1.49 (3H, s, C(C*H*$_3$)CH_3), 1.40 (3H, s, C(CH_3)C*H*$_3$), 0.91 (3H, d, 6.9 Hz, C(-O-)CH(C*H*$_3$)CH-O-), 0.78 (6H, d, 7.2 Hz, CH(C*H*$_3$)CH_2OH x 2); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 99.0, 79.8, 68.6, 36.3, 31.0, 29.9, 19.8, 12.0, 4.7; **HRESIMS** calculated for $C_{13}H_{26}NO_4Na^+$ $[M+Na]^+$: 269.1723; found 269.1724; **EIMS** *m/z* (%): 231 (8), 171 (6), 147 (14), 141 (4), 129 (4), 123 (9), 111 (8), 99 (6), 95 (7), 89 (43), 83 (16), 69 (24), 59 (100), 55 (13).



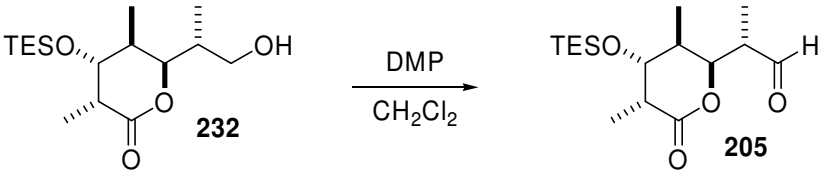
(3*R*,4*R*,5*R*,6*R*-[1*R*])-4-Hydroxy-6-[2-(4-methoxybenzyl)oxy-1-methylethyl]-3,5-dimethyl-tetrahydro-pyran-2-one (230). To a slurry of SiO_2 (10 g) in CH_2Cl_2 (15 mL) was added a solution of the diol **206** (200 mg, 0.40 mmol) in CH_2Cl_2 (5 mL). After stirring overnight at ambient temperature the silica was washed thoroughly with Et_2O and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the γ-lactone **230** (130 mg, 99%) as a clear oil. **R_f** = +0.39 (30% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = +35.5 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3455, 1713, 1698, 1613, 1514, 1455, 1383, 1302, 1247, 1208, 1173, 1111, 1064, 1031, 986, 821 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.86 (2H, d, 8.7 Hz, Ar*H*), 4.59 (1H, dd, 10.8, 2.7 Hz, C*H*(O-)CH(CH_3)CH_2OPMB), 4.44 (2H, s, OC*H*$_2$PMP), 3.86 (1H, t, 3.6 Hz, C*H*OH), 3.79 (3H, s, OC*H*$_3$), 3.70 (1H, dd, 9.0, 3.0 Hz, C*H*$_A$H$_B$OPMB), 3.48 (1H, dd, 9.0, 6.6 Hz, CH$_A$*H*$_B$OPMB), 2.59 (1H, qd, 7.2, 3.6 Hz, CH(OH)C*H*(CH_3)C=O), 2.50 (1H, br s, O*H*), 2.14-2.06 (1H, m, CH(OH)C*H*(CH_3)CHO-), 2.05-1.96 (1H, m, C*H*(CH_3)CH_2OPMB), 1.29 (3H, d, 7.2 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.96 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_2OPMB), 0.94 (3H, d, 7.2 Hz, CH(OH)CH(C*H*$_3$)CHO-); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 173.8, 159.0, 130.7, 129.1, 113.7, 78.7, 72.8, 72.4, 71.6, 55.2, 36.5, 35.2, 34.8, 13.0, 12.1, 9.7; **HRESIMS** calculated for $C_{18}H_{26}O_5Na^+$ $[M+Na]^+$: 345.1672; found 345.1663; **EIMS** *m/z* (%): 304 (3), 217 (4), 191 (15), 176 (5), 168 (5), 137 (29), 121 (100), 111 (6), 96 (9), 77 (8), 69 (10), 53 (6).



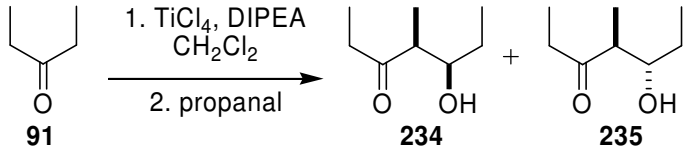
(3*R*,4*R*,5*R*,6*R*-[1*R*])-4-triethylsilyloxy-6-[2-(4-methoxybenzyl)oxy-1-methylethyl]-3,5-dimethyl-tetrahydro-pyran-2-one (231). To a solution of the γ-lactone **230** (120 mg, 0.37 mmol) in CH_2Cl_2 (5.6 mL) at −78 °C was added 2,6-lutidine (130 μL, 1.12 mmol) followed by TESOTf (189 μL, 0.84 mmol) and the resulting mixture was stirred at −78 °C for 30 mins. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (20 mL), then partitioned between H_2O (20 mL) and CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (10% Et_2O/CH_2Cl_2) to give the protected γ-lactone **231** (161 mg, 99%) as a clear oil. $\mathbf{R}_f$ = 0.60 (10% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = +26.4 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1733, 1515, 1464, 1456, 1247, 1196, 1173, 1122, 1075, 1041, 1009, 988, 748 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.86 (2H, d, 8.7 Hz, Ar*H*), 4.59 (1H, dd, 10.8, 2.7 Hz, C*H*(O-)CH(CH_3)CH_2OPMB), 4.45 (2H, s, OCH_2PMP), 3.87 (1H, t, 3.6 Hz, C*H*OTES), 3.79 (3H, s, OCH_3), 3.74 (1H, dd, 9.0, 3.0 Hz, C$H_A$$H_B$OPMB), 3.47 (1H, dd, 9.0, 7.2 Hz, C$H_A$$H_B$OPMB), 2.57 (1H, qd, 6.9, 3.6 Hz, CH(OTES)C*H*(CH_3)C=O), 2.07-1.97 (2H, m, CH(OTES)C*H*(CH_3)CHO-, C*H*(CH_2)CH_2OPMB), 1.25 (3H, d, 6.9 Hz, CH(OTES)CH(CH_3)C=O), 0.98-0.93 (15H, m, Si(CH_2CH_3)$_3$, CH(CH_3)CH_2OPMB), CH(OTES)CH(CH_3)CHO-), 0.60 (6H, q, 8.0 Hz, Si(C$H_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 173.8, 158.9, 130.9, 128.9, 113.6, 78.7, 73.6, 72.8, 71.7, 55.2, 37.0, 35.6, 35.2, 13.0, 12.7, 9.8, 6.8, 4.8.



(3*R*,4*R*,5*R*,6*S*-[1*R*])-4-triethylsilyloxy-6-[2-hydroxy-1-methylethyl]-3,5-dimethyl-tetrahydro-pyran-2-one (232). Deprotection was performed according to the procedure of Paterson *et al.*[23] To a solution of the benzyl ether **231** (161 mg, 0.37 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added pH 7 phosphate buffer (3 mL) followed by DDQ (126 mg, 0.55 mmol) and the resultant slurry was stirred at 0 °C for 3 hours. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous $NaHCO_3$ (30 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/CH_2Cl_2) to give the alcohol **232** (106 mg, 92%) as a clear oil. $\mathbf{R}_f$ = 0.32 (30% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +21.1 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3332, 1733, 1456, 1386, 1316, 1240, 1196, 1107, 1064, 1039, 1009, 989, 879, 853, 747 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.61 (1H, dd, 10.8, 2.7 Hz, C*H*(O-)CH(CH_3)CH_2OH), 3.87 (1H, t, 3.6 Hz, C*H*OTES), 3.79 (1H, dd, 11.1, 5.1 Hz, C$H_A$$H_B$OH), 3.70 (1H, dd, 11.1, 4.2 Hz, C$H_A$$H_B$OH), 2.58 (1H, qd, 7.2, 3.6 Hz, CH(OTES)C*H*(CH_3)C=O), 2.20 (1H, br s, O*H*), 2.04-1.92 (2H, m, CH(OTES)C*H*(CH_3)CHO-, C*H*(CH)$_3$$CH_2$OH), 1.24 (3H, d, 7.2 Hz, CH(OTES)CH(C*H*$_3$)C=O), 0.97 (3H, d, 7.2 Hz, CH(OTES)CH(C*H*$_3$)CHO-), 0.95 (9H, t, 7.8 Hz, Si(CH_2C*H*$_3$)$_3$), 0.88 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH_2OH), 0.60 (6H, q, 7.8 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 173.4, 81.1, 73.8, 66.0, 37.1, 36.6, 35.8, 12.7, 12.6, 10.0, 6.8, 4.8; **HRESIMS** calculated for $C_{16}H_{32}O_4SiNa^+$ $[M+Na]^+$: 339.1962; found 339.1963; **EIMS** *m/z* (%): 269 (3), 257 (3), 231 (4), 213 (5), 199 (10), 187 (16), 173 (14), 167 (6), 159 (10), 143 (100), 115 (37), 103 (57), 96 (11), 87 (36), 75 (44), 69 (16), 59 (27), 47 (21).



(2*S*-[2*S*,3*R*,4*R*,5*R*])-2-(4-triethylsilyloxy-3,5-dimethyl-6-oxo-tetrahydro-pyran-2-yl)-propanal (205). Oxidation was performed according to the procedure of Dess and Martin.[22] To a solution of the lactone alcohol **232** (45 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added Dess-Martin Periodinane (91 mg, 0.22 mmol). The reaction mixture was stirred for 1 hour then diluted with Et_2O (15 mL) and quenched with a solution of $Na_2S_2O_3$ (364 mg) in saturated aqueous $NaHCO_3$ (10 mL). After stirring for several minutes the layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine (10 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave the lactone aldehyde **205** (45 mg, 99%) as a clear oil. $\mathbf{R_f}$ = 0.53 (10% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +37.3 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1732, 1457, 1392, 1317, 1247, 1194, 1144, 1118, 1087, 1065, 1040, 1012, 989, 977, 855, 747 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.85 (1H, d, 2.7 Hz, C*H*O), 4.94 (1H, dd, 10.8, 2.7 Hz, C*H*(O-)CH(CH_3)CHO), 3.90 (1H, t, 3.6 Hz, C*H*OTES), 2.67 (1H, dqd, 10.8, 7.2, 2.7 Hz, CH(O-)C*H*($CH)_3$CHO), 2.60 (1H, qd, 7.2, 3.6 Hz, CH(OTES)C*H*(CH_3)C=O), 1.98 (1H, qdd, 7.2, 3.6, 2.7 Hz, CH(OTES)C*H*(CH_3)CHO-), 1.24 (3H, d, 7.2 Hz, CH(OTES)CH(C*H*$_3$)C=O), 0.99 (6H, d, 7.2 Hz, CH(OTES)CH(C*H*$_3$)CHO-, CH(O-)CH(C*H*$_3$)CHO), 0.94 (9H, t, 8.1 Hz, Si(CH_2C*H*$_3)_3$), 0.60 (6H, q, 8.1 Hz, Si(C*H*$_2$$CH_3)_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 202.9, 172.7, 78.4, 73.5, 47.0, 37.1, 35.5, 12.7, 9.9, 9.8, 6.7, 4.8; **HRESIMS** calculated for $C_{16}H_{30}O_4SiNa^+$ $[M+Na]^+$: 337.1806; found 337.1809; **EIMS** *m/z* (%): 285 (2), 257 (4), 239 (2), 217 (3), 199 (28), 187 (9), 171 (20), 143 (100), 115 (38), 103 (44), 87 (25), 75 (25), 69 (12), 59 (22), 47 (13).

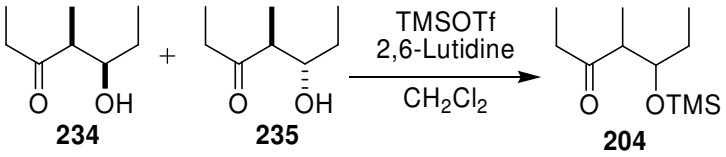


91 **234** **235**

5-hydroxy-4-methylheptan-3-one (234 and 235). The aldol addition was performed according to the procedure of Evans *et al.*[30] To pentan-3-one (**91**) (2.0 g, 23.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added $TiCl_4$ (27.9 mL of a 1 M solution in CH_2Cl_2, 27.9 mmol) dropwise and the resulting yellow solution was stirred for 30 minutes. $^{i}Pr_2NEt$ (5.66 mL, 32.5 mmol) was added dropwise giving a deep red solution, which was stirred for an additional 1 hour before being cooled to −90 °C and treated with propanal (3.35 mL, 46.4 mmol). The reaction mixture was stirred at −78 °C for 1 hour then warmed to 0 °C and quenched with the addition of pH 7 phosphate buffer (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (7% Et_2O/CH_2Cl_2) to give the adduct **234 and 235** (2.78 g, 83%) as a clear oil. $\mathbf{R}_f$ = 0.18 (7% Et_2O/CH_2Cl_2).

***syn*-isomer 234**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.80-3.74 (1H, m, C*H*OH), 2.84 (1H, d, 3.3 Hz, O*H*), 2.63-2.35 (3H, m, CH_3CH_2C=O, C*H*(CH_3)CHOH), 1.60-1.27 (2H, m, CH(OH)CH_2CH_3), 1.08 (3H, d, 6.9 Hz, CH(CH_3)CHOH), 1.01 (3H, t, 7.2 Hz, CH_3CH_2C=O), 0.91 (3H, t, 7.2 Hz, CH(OH)CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.5, 72.6, 49.4, 35.0, 26.9, 10.3, 9.9, 7.5.

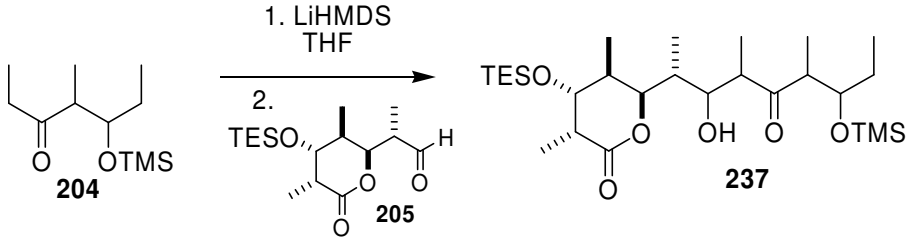
***anti*-isomer 235**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.62-3.53 (1H, m, C*H*OH), 2.72 (1H, d, 6.3 Hz, O*H*), 2.67-2.47 (3H, m, CH_3CH_2C=O, C*H*(CH_3)CHOH), 1.60-1.27 (2H, m, CH(OH)CH_2CH_3), 1.07 (3H, d, 7.2 Hz, CH(CH_3)CHOH), 1.00 (3H, t, 7.2 Hz, CH_3CH_2C=O), 0.93 (3H, t, 7.2 Hz, CH(OH)CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.6, 74.9, 50.6, 36.0, 27.5, 14.1, 9.7, 7.4.



4-methyl-5-trimethylsilyloxyheptan-3-one (204). To a solution of the β-hydroxy ketone **234 and 235** (2.78 g, 19.3 mmol) in CH_2Cl_2 (96 mL) at −90 °C was added 2,6-lutidine (4.5 mL, 38.6 mmol) followed by TMSOTf (5.23 mL, 28.9 mmol) and the resulting solution was stirred at −90 °C for 10 minutes before being quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 80 mL) and the combined extracts were dried ($MgSO_4$), concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give the silyl ether **204** (4.10 g, 98%) as a clear liquid. $\mathbf{R}_f$ = 0.44 (CH_2Cl_2).

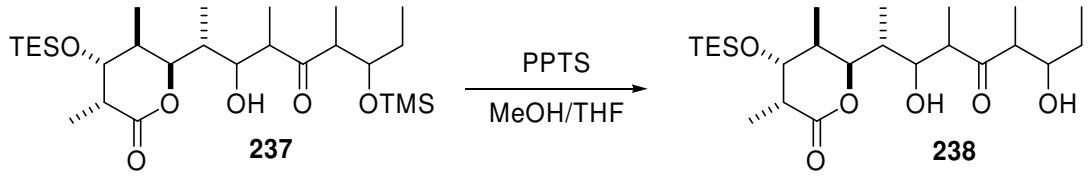
***syn*-isomer**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.79-3.73 (1H, m, C*H*OTMS), 2.53-2.35 (3H, m, CH_3CH_2C=O, C*H*(CH_3)CHOTMS), 1.53-1.20 (2H, m, CH(OTMS)C$H_2$$CH_3$), 1.03 (3H, d, 7.2 Hz, CH(CH_3)CHOTMS), 0.99 (3H, t, 7.2 Hz, C$H_3$$CH_2$C=O), 0.89 (3H, t, 7.2 Hz, CH(OTMS)CH_2CH_3), 0.08 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.1, 75.2, 51.3, 36.0, 27.7, 12.6, 10.1, 7.5, 0.4.

***anti*-isomer**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.83-3.79 (1H, m, C*H*OTMS), 2.73-2.55 (3H, m, CH_3CH_2C=O, C*H*(CH_3)CHOTMS), 1.53-1.20 (2H, m, CH(OTMS)C$H_2$$CH_3$), 0.99 (3H, t, 7.2 Hz, C$H_3$$CH_2$C=O), 0.91 (3H, d, 7.2 Hz, CH(CH_3)CHOTMS), 0.89 (3H, t, 7.2 Hz, CH(OTMS)CH_2CH_3), 0.03 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.1, 75.4, 50.7, 37.0, 26.6, 13.0, 8.5, 7.3, 0.2.



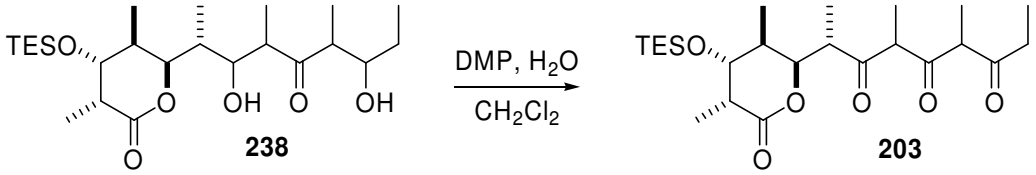
([1*R*]-3*R*,4*R*,5*R*,6*R*)-6-(2-hydroxy-1,3,5-trimethyl-4-oxo-6-trimethylsilyloxy-octyl)-4-triethylsilyloxy-3,5-dimethyl-pyran-2-one (237). To a solution of the

ketone **204** (62 mg, 0.29 mmol) in THF (572 μL) at −78 °C was added LiHMDS (315 μL of a 1.0 M solution in THF, 0.32 mmol) dropwise and the resulting yellow solution was stirred at −78 °C for 30 minutes and then at −50 °C for a further 30 minutes. The reaction was re-cooled to −78 °C and a solution of the aldehyde **205** (45 mg, 0.14 mmol) in THF (100 μL) was added *via* cannula. After 2 hours the reaction was diluted with Et_2O (10 mL) and quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL) then allowed to warm to 0 °C. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL), then the organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification of the crude product by column chromatography (10% Et_2O/CH_2Cl_2) gave an inseparable mixture of diastereomers **237** (62 mg, 83%) as a clear oil. $\mathbf{R}_f$ = 0.53-0.28 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.66 (1H, dd, 10.5, 2.7 Hz, CH(OTES)CH(CH_3)C*H*O-), 4.29-4.20 (1H, m, C*H*OTMS), 3.86 (1H, t, 3.6 Hz, C*H*OTES), 3.83-3.77 (1H, m, C*H*OH), 3.05-2.95 (1H, m, C*H*(CH_3)C=O), 2.88-2.76 (1H, m, C*H*(CH_3)C=O), 2.58-2.51 (1H, m, CH(OTES)C*H*(CH_3)C=O), 2.39 (1H, d, 5.1 Hz, O*H*), 2.03-1.93 (1H, m, CH(OTES)C*H*(CH_3)CHO-), 1.90-1.76 (1H, m, CH(O-)C*H*(CH_3)CHOH), 1.55-1.40 (1H, m, $CH_3CH_AH_BCHOTMS$), 1.37-1.27 (1H, m, $CH_3CH_AH_BCHOTMS$), 1.24-0.84 (27H, m, C*H*$_3$CH$_2$, CH(OH)CH(C*H*$_3$)C=O, CH(C*H*$_3$)CHOTMS, CH(O-)CH(C*H*$_3$)CHOH, CH(OTES)CH(C*H*$_3$)CHO-, CH(OTES)CH(C*H*$_3$)C=O, Si(CH$_2$C*H*$_3$)$_3$), 0.60 (6H, q, 8.0 Hz, Si(C*H*$_2$CH$_3$)$_3$), 0.11 (9H, s, Si(C*H*$_3$)$_3$).



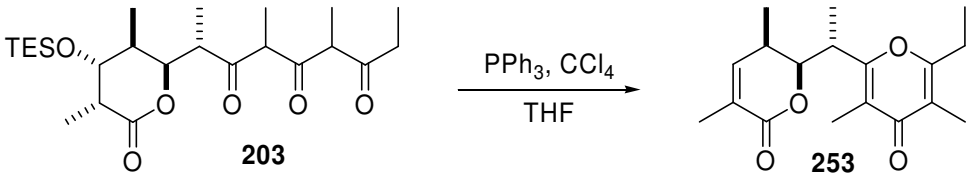
([1*R*]-3*R*,4*R*,5*R*,6*R*)-6-(2,6-dihydroxy-1,3,5-trimethyl-4-oxo-octyl)-4-triethylsilyloxy-3,5-dimethyl-pyran-2-one (238). To a solution of the aldol adduct **237** (50 mg, 94.2 μmol) in MeOH/THF (1 mL, 9:1) at ambient temperature was added a few crystals of PPTS and the resulting mixture was stirred for 45 minutes. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was

extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (50% Et_2O/CH_2Cl_2) gave the diol **238** as an inseparable mixture of diastereomers (42 mg, 97 %) as a clear oil. $\mathbf{R}_f$ = 0.50-0.26 (50% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.68-4.62 (1H, m, CH(OTES)CH(CH_3)C*H*O-), 4.28-4.19 (1H, m, CH_3CH_2CHOH), 3.86-3.85 (1H, m, C*H*OTES), 3.84-3.75 (1H, m, C*H*(OH)CH(CH_3)C=O), 3.09-2.95 (1H, m, C*H*(CH_3)C=O), 2.87-2.74 (1H, m, C*H*(CH_3)C=O), 2.58-2.50 (1H, m, CH(OTES)C*H*(CH_3)C=O), 2.00-1.92 (3H, m, O*H* x 2, CH(OTES)C*H*(CH_3)CHO-), 1.84-1.75 (1H, m, CH(O-)C*H*(CH_3)CHOH), 1.60-1.30 (2H, m, CH_3CH_2CHOH), 1.23-0.82 (27H, m, CH_3CH_2, CH(OH)CH(C*H*$_3$)C=O, CH(C*H*$_3$)CHOH, CH(O-)CH(C*H*$_3$)CHOH, CH(OTES)CH(C*H*$_3$)CHO-, CH(OTES)CH(C*H*$_3$)C=O, Si(CH_2CH_3)$_3$), 0.64-0.55 (6H, m, Si(CH_2CH_3)$_3$).

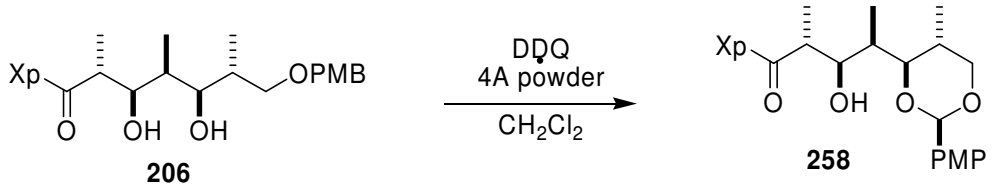


([1*R*]-3*R*,4*R*,5*R*,6*R*)-6-(-1,3,5-trimethyl-2,4,6-trioxo-octyl)-4-triethylsilyloxy-3,5-dimethyl-pyran-2-one (203). Oxidation was performed according to the procedure of Meyer and Schreiber.[34] To a solution of the diol **238** (71 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added Dess-Martin Periodinane (197 mg, 0.46 mmol). To the reaction mixture was added a solution of H_2O in CH_2Cl_2 (6 µL in 3 mL) at a rate of 250 µL every 5 minutes for 1 hour. After complete addition the reaction was diluted with Et_2O (15 mL) and quenched with a solution of $Na_2S_2O_3$ (800 mg) in saturated aqueous $NaHCO_3$ (15 mL). After stirring for several minutes the layers were separated and the organic phase was washed with in saturated aqueous $NaHCO_3$ and brine (15 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/CH_2Cl_2) gave the tri-ketone **203** as a mixture of keto-enol forms (69 mg, 99%) as a clear oil. $\mathbf{R}_f$ = 0.69-0.31 (20% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.00-4.714 (1H, m, CH(OTES)CH(CH_3)C*H*O-), 4.11-3.85 (3H, m, C*H*OTES, C*H*(CH_3)C=O x 2), 3.18-

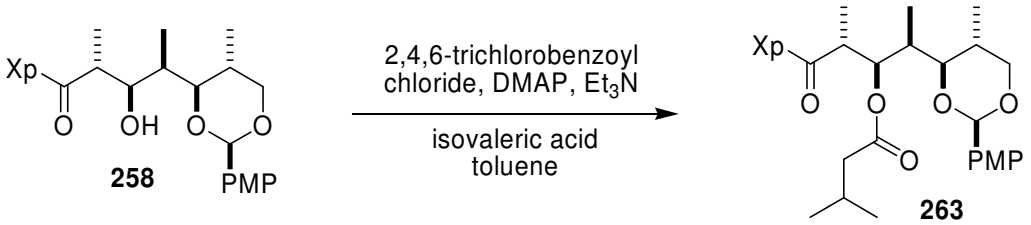
3.00 (1H, m, CH(O-)C*H*(CH_3)C=O), 2.77-2.39 (3H, m, $CH_3C\mathit{H}_2$, CH(OTES)C*H*(CH_3)C=O), 2.06-1.94 (1H, m, CH(OTES)C*H*(CH_3)CHO-), 1.36-0.89 (27H, m, $C\mathit{H}_3CH_2$, CH($C\mathit{H}_3$)C=O x 2, CH(O-)CH($C\mathit{H}_3$)C=O, CH(OTES)CH($C\mathit{H}_3$)CHO-, CH(OTES)CH($C\mathit{H}_3$)C=O, Si($CH_2C\mathit{H}_3$)$_3$), 0.65-0.55 (6H, m, Si($C\mathit{H}_2CH_3$)$_3$).



([1*S*,5*S*,6*S*])-2-[1-(3,5-dimethyl-4,5-dihydro-2*H*-pyran-2-one)-ethyl]-6-ethyl-3,5-dimethyl-pyran-4-one (253). Pyrone formation was performed according to the procedure of Arimoto *et al*.[35] To a solution of PPh_3 (199 mg, 0.76 mmol) and CCl_4 (73 μL, 0.76 mmol) in THF (2.5 mL) at ambient temperature was added a solution of the trione **203** (69 mg, 0.15 mmol) in THF (200 + 500 μL). The reaction mixture was stirred at ambient temperature for 3 days then poured into brine (10 mL) and extracted with EtAOc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (50 % Et_2O/CH_2Cl_2) to give the title compound **253** (32 mg, 70%) as a clear oil. $\mathbf{R}_f$ = 0.37 (50% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.70 (1H, dd, 3.3, 1.2 Hz, C*H*=C(CH_3)C=O), 4.58 (1H, dd, 10.5, 3.0 Hz, C*H*OC=O), 3.29 (1H, dq, 10.5, 6.9 Hz, CH(OC=O)C*H*(CH_3)-4-pyrone), 2.58 (2H, q, 7.5 Hz, $CH_3C\mathit{H}_2$), 2.49 (1H, qdd, 6.9, 3.3, 3.0, CHC*H*(CH_3)CHOC=O), 1.99 (3H, s, C=C($C\mathit{H}_3$)C=O), 1.92 (3H, s, C=C($C\mathit{H}_3$)C=O), 1.88 (3H, br s, CH=C($C\mathit{H}_3$)C=O), 1.18 (3H, d, 6.9 Hz, CH(OC=O)CH($C\mathit{H}_3$)-4-pyrone), 1.17 (3H, t, 7.5 Hz, $C\mathit{H}_3CH_2$), 1.08 (3H, d, 7.2 Hz, CHCH($C\mathit{H}_3$)CHOC=O); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 179.7, 165.2, 164.0, 162.0, 145.0, 127.4, 119.7, 118.1, 80.1, 36.5, 30.1, 24.7, 16.9 x2, 13.8, 11.2, 10.7, 9.5.

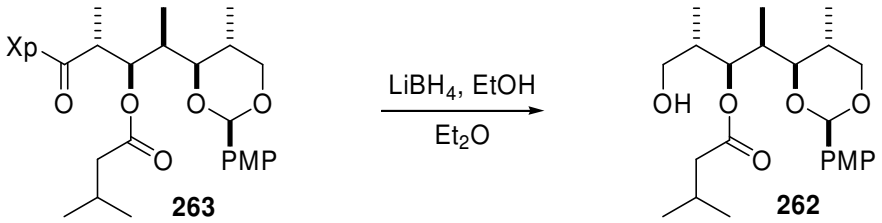


[[3-(2*R*,3*R*,4*S*-[2*R*]-,5*S*,6*R*)-4*R*]-3-{3-hydroxy-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methyl-pentanoyl}-4-(phenylmethyl)-2-oxazolidinone (258). PMB migration was performed according to the procedure of Paquette *et al*.[36] To a solution of the diol **206** (415 mg, 0.83 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added 4Å molecular sieves (2 g) followed by DDQ (229 mg, 1.01 mmol). The resulting slurry was stirred at 0 °C for 5 hours then filtered through a pad of celite. The filtrate washed with a 1 M solution of NaOH (15 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (buffered silica) (10% Et_2O/CH_2Cl_2) to give the benzylidene acetal **258** (330 mg, 80%) as a white foam. **m.p.** = 57-59 °C; $\mathbf{R}_f$ = 0.49 (10% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −102.4 (*c* 2.5, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3508, 1779, 1698, 1615, 1519, 1456, 1385, 1252, 1211, 1163, 1110, 1075, 1032, 1011, 831, 703 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.45 (2H, d, 8.7 Hz, Ar*H*), 7.07-6.98 (3H, m, Ar*H*), 6.90-6.87 (2H, m, Ar*H*), 6.69 (2H, d, 8.7 Hz, Ar*H*), 5.30 (1H, s, C*H*PMP), 4.64 (1H, dq, 9.0, 6.9 Hz, C(=O)C*H*(CH_3)CHOH), 4.40-4.29 (2H, m, C*H*OH, OCH_2CHN-), 3.82 (1H, dd, 11.1, 4.8 Hz, CH(CH_3)C$H_A$$H_B$OCHPMP), 3.77 (1H, d, 2.1 Hz, O*H*), 3.40 (1H, dd, 9.0, 2.1 Hz, OC$H_A$$H_B$CHN-), 3.36 (1H, dd, 10.2, 2.1 Hz, CH(CH_3)C*H*(OCHPMP)CH(CH_3)), 3.23 (3H, s, OCH_3), 3.15 (1H, t, 9.0 Hz, $OCH_A$$H_B$CHN-), 3.11 (1H, t, 11.1 Hz, CH(CH_3)$CH_A$$H_B$OCHPMP), 3.00 (1H, dd, 13.2, 3.0 Hz, CHC$H_A$$H_B$Ph), 2.42 (1H, dd, 13.2, 9.3 Hz, $CHCH_A$$H_B$Ph), 1.90-1.79 (2H, m, CH(OH)C*H*(CH_3)CHO-, CH(O)C*H*(CH_3)CH_2OCHPMP), 1.24 (3H, d, 6.9 Hz, C(=O)CH(CH_3)CHOH, 1.13 (3H, d, 6.9 Hz, CH(OH)CH(CH_3)CHO-), 0.27 (3H, d, 6.6 Hz, CH(O)CH(CH_3)CH_2OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 176.7, 160.5, 153.5, 136.1, 131.4, 129.6, 128.9, 127.2, 114.0, 101.3, 88.3, 79.7, 72.9, 65.5, 55.5, 54.7, 39.9, 38.0, 35.0, 30.5, 14.6, 11.5, 6.2; **HRESIMS** calculated for $C_{28}H_{35}NO_7Na^+$ $[M+Na]^+$: 520.2306; found 520.2311; **EIMS** *m/z* (%): 263 (12), 207 (5), 152 (12), 135 (100), 121 (6), 108 (12), 83 (12), 77 (11), 69 (5), 55 (16).



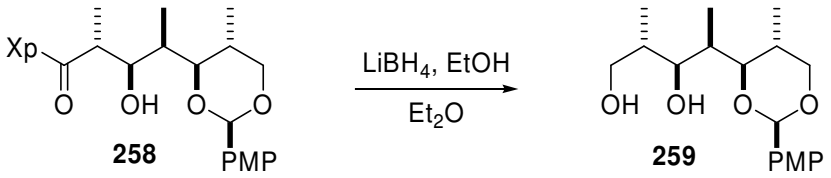
[[3-(2*R*,4*S*-[2*R*]-,5*S*,6*R*)-4*R*]-3-{3-[3-methyl-1-oxobutanyl]-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methyl-pentanoyl}-4-(phenylmethyl)-2-oxazolidinone (263). Yamaguchi esterification was attempted according to the procedure of Paterson *et al.*[28] 2,4,6-Trichlorobenzoyl chloride (667 μL, 4.27 mmol) was added to a solution of the alcohol **258** (250 mg, 0.50 mmol), isovaleric acid (277 μL, 2.51 mmol), DMAP (1.17 g, 9.55 mmol) and Et_3N (630 μL, 4.52 mmol) in toluene (50 mL) at −78 °C. After 15 mins the reaction was warmed to 0 °C and allowed to stir for a further 15 minutes before being warmed to room temperature and stirred for an additional 1 hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL), the layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow slurry. Purification by column chromatography (7.5% Et_2O/CH_2Cl_2, on buffered silica) gave the ester **263** (300 mg, 99%) as a white foam. $\mathbf{R}_f$ = 0.52 (7.5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −84.2 (*c* 0.9, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 1780, 1736, 1700, 1615, 1519, 1455, 1387, 1292, 1249, 1211, 1184, 1109, 1076, 1031, 967, 830 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.63 (2H, d, 8.7 Hz, Ar*H*), 7.07-6.99 (3H, m, Ar*H*), 6.89-6.85 (2H, m, Ar*H*), 6.79 (2H, d, 8.7 Hz, Ar*H*), 5.81 (1H, dd, 9.3, 2.4 Hz, C*H*OC(=O)CH_2CH(CH_3)CH_3), 5.51 (1H, s, C*H*PMP), 4.68 (1H, dq, 9.3, 6.9 Hz, C(=O)C*H*(CH_3)CH), 4.33-4.25 (1H, m, OCH_2C*H*N-), 3.89 (1H, dd, 11.1, 4.5 Hz, CH(CH_3)C$H_A$$H_B$OCHPMP), 3.75 (1H, d, 10.2 Hz, C*H*OCHPMP), 3.48 (1H, dd, 9.0, 2.4 Hz, OC$H_A$$H_B$CHN-), 3.28-3.18 (2H, m, OCH_AH_BCHN-, CH(CH_3)CH_AH_BOCHPMP), 3.26 (3H, s, OCH_3), 2.94 (1H, dd, 13.2, 3.0 Hz, CHC$H_A$$H_B$Ph), 2.30 (1H, dd, 13.2, 9.6 Hz, $CHCH_AH_B$Ph), 2.10-1.92 (3H, m, C*H*(CH_3)CHOCHPMP, C*H*(CH_3)CH_2OCHPMP, C*H*(CH_3)CH_3), 1.85 (1H, dd, 15.3, 7.5 Hz, C$H_A$$H_B$CH($CH_3$)$CH_3$), 1.79 (1H, dd, 15.3, 6.9 Hz, CH_AH_BCH(CH_3)CH_3), 1.23 (3H, d, 6.9 Hz, C(=O)CH(CH_3)CH, 1.17 (3H, d, 7.2 Hz,

CH(C*H*$_3$)CHOCHPMP), 0.78 (3H, d, 6.3 Hz, CH(C*H*$_3$)CH$_3$), 0.70 (3H, d, 6.6 Hz, CH(CH$_3$)C*H*$_3$), 0.33 (3H, d, 6.6 Hz, CH(C*H*$_3$)CH$_2$OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 174.6, 171.5, 160.4, 153.1, 135.7, 132.4, 129.6, 129.0, 128.4, 127.4, 113.7, 101.9, 85.2, 77.6, 73.1, 65.5, 55.4, 54.7, 43.6, 40.0, 37.8, 35.0, 30.7, 25.3, 22.5, 22.4, 14.9, 12.1, 7.7; **HRESIMS** calculated for $C_{33}H_{43}NO_8Na^+$ $[M+Na]^+$: 604.2881; found 604.2878; **EIMS** *m/z* (%): 581 (9), 405 (5), 327 (6), 247 (14), 233 (13), 207 (54), 178 (20), 150 (33), 135 (100), 121 (38), 85 (74), 57 (76).



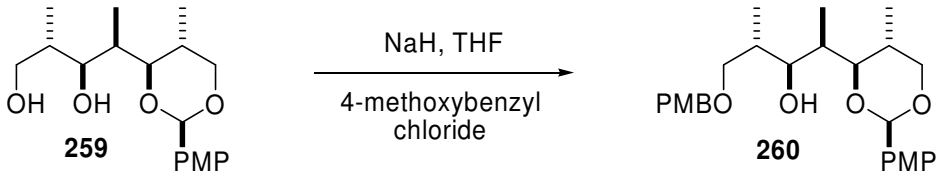
[2*S*,3*S*,4*S*[2*R*,5*R*,6*R*]]-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methyl-3-[3-methyl-1-oxobutanyl]-pentan-1-ol (262). Auxiliary cleavage was peformed according to the procedure of Penning *et al.*[3] To a solution of oxazolidinone **263** (285 mg, 0.49 mmol) in dry Et_2O (12 mL) at −10 °C was added anhydrous EtOH (34 μL, 0.59 mmol) and $LiBH_4$ (294 μL of a 2.0 M solution in THF, 0.59 mmol). The reaction mixture was stirred at −10 °C for 3.5 h and then quenched by the addition of a 1 M solution of Rochelle's salt (10 mL). The resulting cloudy solution was stirred for 30 minutes at 0 °C, then extracted with Et_2O (3 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 EtOAc/hexanes, on buffered silica) to give the alcohol **262** (140 mg, 70%) as a clear liquid and the diol **259** (characterised below) (40 mg, 20%) as a clear oil. $\mathbf{R_f}$ = 0.39 (1:1 EtOAc/hexanes); $\mathbf{[\alpha]^{20}_D}$ = −29.1 (*c* 1.6, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3488, 1731, 1616, 1519, 1463, 1371, 1297, 1251, 1189, 1171, 1118, 1072, 1034, 831 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.57 (2H, d, 8.7 Hz, Ar*H*), 6.78 (2H, d, 8.7 Hz, Ar*H*), 5.32 (1H, s, C*H*PMP), 5.26 (1H, dd, 8.4, 3.3 Hz, C*H*OC(=O)CH$_2$CH(CH$_3$)$_2$), 3.88 (1H, dd, 11.1, 4.5 Hz, C*H*$_A$H$_B$OCHPMP), 3.52 (1H, br d, 3.3 Hz, C*H*$_2$OH), 3.35 (1H, br d, 9.9 Hz, C*H*OCHPMP), 3.27 (3H, s, OC*H*$_3$), 3.17 (1H, t, 11.1 Hz, CH$_A$*H*$_B$OCHPMP), 2.20 (1H, br s, O*H*), 2.05-1.90 (2H, m, C*H*(CH$_3$)CHOCHPMP), C*H*(CH$_3$)CH$_3$), 1.89-

1.75 (2H, m, C*H*CH_2OCHPMP, CH_2(OH)C*H*(CH_3)CH), 1.83 (1H, dd, 15.6, 7.8 Hz, C$H_A$$H_B$CH($CH_3$)$CH_3$), 1.74 (1H, dd, 15.6, 6.6 Hz, $CH_A$$H_B$CH($CH_3$)$CH_3$), 1.04 (3H, d, 7.2 Hz, CH(CH_3)CHOCHPMP), 0.97 (3H, d, 6.9 Hz, CH_2(OH)CH(CH_3)CH), 0.80 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.72 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.32 (3H, d, 6.9 Hz, CH(CH_3)CH_2OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 173.5, 160.4, 132.2, 128.2, 113.7, 101.9, 86.3, 77.8, 73.0, 64.0, 54.7, 43.5, 37.5, 34.6, 30.8, 25.2, 22.5, 22.4, 14.6, 11.8, 7.7; **HRESIMS** calculated for $C_{23}H_{36}O_6Na^+$ $[M+Na]^+$: 431.2404; found 431.2402; **EIMS** *m/z* (%): 408 (5), 207 (23), 173 (23), 135 (44), 121 (14), 85 (83), 83 (100), 57 (27).



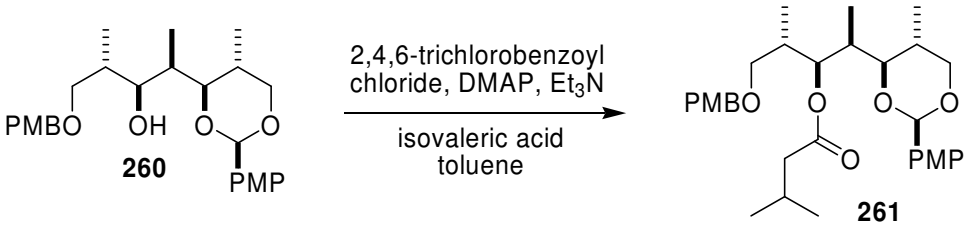
[2*S*,3*S*,4*R*-[2*R*,5*R*,6*R*]]-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methyl-pentan-1,3-diol (259). Auxiliary cleavage was peformed according to the procedure of Penning *et al*.[3] To a solution of oxazolidinone **258** (200 mg, 0.40 mmol) in dry Et_2O (10 mL) at −10 °C was added anhydrous EtOH (28 μL, 0.48 mmol) and $LiBH_4$ (241 μL of a 2.0 M solution in THF, 0.48 mmol). The reaction mixture was stirred at −10 °C for 3 hours and then quenched by the addition of a 1 M solution of NaOH (1 mL). The resulting cloudy solution was stirred for 15 minutes at 0 °C, then the mixture was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 EtOAc/hexanes, on buffered silica) to give the alcohol **259** (143 mg, 99%) as a white solid. **m.p.** 128-130 °C. **R_f** = 0.19 (1:1 EtOAc/hexanes); **$[\alpha]^{20}_D$** = −41.7 (*c* 1.9, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3455, 1615, 1519, 1461, 1386, 1302, 1251, 1163, 1114, 1071, 1033, 1010, 830 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.46 (2H, d, 8.7 Hz, Ar*H*), 6.75 (2H, d, 8.7 Hz, Ar*H*), 5.32 (1H, s, C*H*PMP), 3.83 (1H, dd, 11.1, 4.8 Hz, C$H_A$$H_B$OCHPMP), 3.82-3.79 (1H, m, CH_2OH), 3.68 (1H, d, 9.3 Hz, C*H*OH), 3.53 (2H, br s, O*H* x 2), 3.27 (1H, dd, 10.2, 2.4 Hz, C*H*OCHPMP), 3.26 (3H, s, OCH_3), 3.12 (1H, t, 11.1 Hz, $CH_A$$H_B$OCHPMP), 1.97-1.85 (1H, m, CH_2(OH)C*H*(CH_3)CHOH), 1.90-1.79 (1H, m,

C*H*CH_2OCHPMP), 1.72-1.65 (1H, m, C*H*(CH_3)CHOCHPMP), 0.97 (3H, d, 7.2 Hz, CH(C*H*$_3$)CHOCHPMP), 0.66 (3H, d, 6.6 Hz, CH_2(OH)CH(C*H*$_3$)CHOH), 0.25 (3H, d, 6.9 Hz, CH(C*H*$_3$)CH_2OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 160.6, 131.3, 127.6, 114.0, 101.5, 89.4, 82.4, 72.9, 68.2, 54.8, 38.0, 35.0, 30.6, 14.0, 11.4, 5.7; **HRESIMS** calculated for $C_{18}H_{28}O_5Na^+$ $[M+Na]^+$: 347.1829; found 347.1829; **EIMS** *m/z* (%): 324 (24), 265 (3), 236 (5), 207 (61), 171 (6), 153 (25), 137 (98), 135 (100), 121 (30), 109 (24), 94 (11), 77 (19), 69 (10), 55 (18).



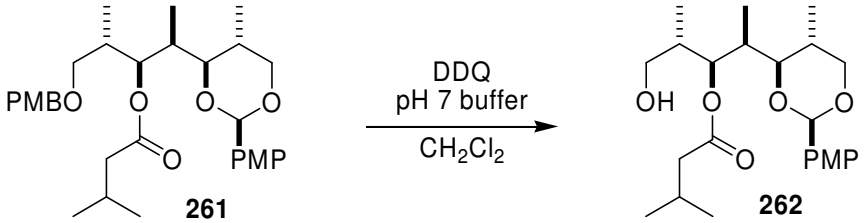
[2*S*,3*S*,4*R*-[2*R*,5*R*,6*R*]]-3-hydroxy-1-(4-methoxybexzyl)oxy-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-2-methyl-pentane (260). Protection was performed according to the procedure of Hikotam *et al*.[37] To a slurry of freshly washed (hexanes) NaH (17 mg, 0.69 mmol) in THF (200 μL) at room temperature was added the diol **259** (75 mg, 0.23 mmol) and stirring maintained for 2 hours. 4-Methoxybenzyl chloride (38 μL, 0.28 mmol) was then added and the mixture was stirred for 3 hours. Et_2NH was added and the mixture was poured into saturated aqueous NH_4Cl (10 mL), then extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$), then concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/CH_2Cl_2, on buffered silica) to give the mono-protected product **260** (85 mg, 83 %) as a clear oil. $\mathbf{R}_f$ = 0.50 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = −58.6 (*c* 1.3, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3514, 1614, 1587, 1515, 1462, 1422, 1386, 1302, 1249, 1171, 1111, 1072, 1034, 829 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.48 (2H, d, 8.7 Hz, Ar*H*), 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.78 (2H, d, 8.7 Hz, Ar*H*), 6.72 (2H, d, 8.7 Hz, Ar*H*), 5.31 (1H, s, C*H*PMP), 4.42 (2H, s, C*H*$_2$OPMP), 3.88-3.82 (2H, m, C*H*OH, C*H*$_A$H$_B$OCHPMP), 3.47 (1H, d, 1.5 Hz, O*H*), 3.55 (1H, dd, 10.2, 2.4 Hz, C*H*OCHPMP), 3.29 (3H, s, OC*H*$_3$), 3.24 (3H, s, OC*H*$_3$), 3.12 (1H, t, 11.1 Hz, CH$_A$*H*$_B$OCHPMP), 2.13-2.00 (1H, m, PMBOCH$_2$C*H*), 1.97-1.86 (1H, m, C*H*CH_2OCHPMP), 1.86-1.79 (1H, m, C*H*(CH_3)CHOCHPMP), 1.05 (6H, d, 6.9 Hz,

PMBOCH$_2$CH(C*H$_3$*), CH(C*H$_3$*)CHOCHPMP), 0.28 (3H, d, 6.9 Hz, CH(C*H$_3$*)CH$_2$OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 160.4, 159.6, 131.5, 131.5, 129.4, 127.6, 114.0, 113.9, 101.4, 88.8, 77.8, 73.2, 73.0, 72.8, 54.7, 54.7, 37.3, 35.1, 30.7, 14.8, 11.6, 6.2; **HRESIMS** calculated for $C_{26}H_{36}O_6Na^+$ $[M+Na]^+$: 467.2404; found 467.2401; **EIMS** *m/z* (%): 444 (1), 323 (3), 207 (8), 187 (8), 137 (590), 121 (100), 100 (15), 77 (16), 55 (6).

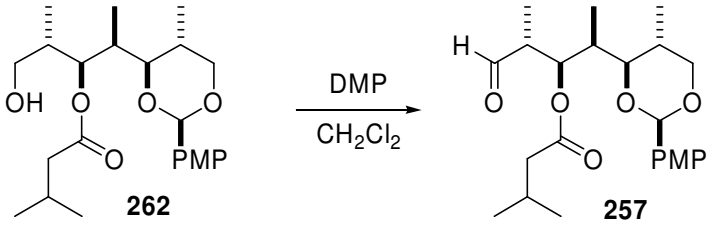


[2*S*,3*S*,4*S*-[2*R*,5*R*,6*R*]]-1-(4-methoxybexzyl)oxy-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(3-methyl-1-oxobutanyl)-2-methyl-pentane (261). Yamaguchi esterification was attempted according to the procedure of Paterson *et al*.[28] 2,4,6-Trichlorobenzoyl chloride (359 μL, 2.29 mmol) was added to a solution of the alcohol **260** (60 mg, 0.14 mmol), isovaleric acid (149 μL, 1.35 mmol), DMAP (627 mg, 5.13 mmol) and Et_3N (339 μL, 2.43 mmol) in toluene (14 mL) at −78 °C. After 15 mins the reaction was warmed to 0 °C and allowed to stir for a further 15 minutes before being warmed to room temperature and stirred for an additional 1 hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (15 mL), the layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow slurry. Purification by column chromatography (7.5% Et_2O/CH_2Cl_2, on buffered silica) gave the ester **261** (64 mg, 90 %) as a white foam. $\mathbf{R}_f$ = 0.57 (7.5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = −21.9 (*c* 1.3, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 1732, 1614, 1516, 1463, 1370, 1301, 1249, 1172, 1119, 1088, 1035, 829 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.60 (2H, d, 8.7 Hz, Ar*H*), 7.25 (2H, d, 8.7 Hz, Ar*H*), 6.79 (2H, d, 8.7 Hz, Ar*H*), 6.77 (2H, d, 8.7 Hz, Ar*H*), 5.48 (1H, t, 6.0 Hz, C*H*OC(=O)CH$_2$), 5.39 (1H, s, C*H*PMP), 4.38 (1H, d, 11.4 Hz, C*H$_A$*H$_B$PMP), 4.31 (1H, d, 11.4 Hz, CH$_A$*H$_B$*PMP), 3.88 (1H, dd, 11.1, 4.8 Hz, C*H$_A$*H$_B$OCHPMP), 3.60 (1H, dd, 10.2, 1.5 Hz, C*H*OCHPMP), 3.56 (1H, dd, 9.0, 4.8

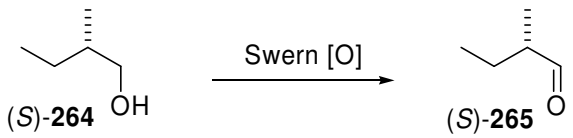
Hz, C*H*$_A$H$_B$OPMB), 3.31 (1H, dd, 9.0, 6.3 Hz, CH$_A$*H*$_B$OPMB), 3.29 (3H, s, OC*H*$_3$), 3.26 (3H, s, OC*H*$_3$), 3.21 (1H, t, 11.1 Hz, CH$_A$*H*$_B$OCHPMP), 2.34-2.21 (1H, m, PMBOCH$_2$C*H*), 2.10-1.95 (2H, m, C*H*(CH$_3$)CHOCHPMP, C*H*(CH$_3$)CH$_3$), 1.95-1.83 (3H, m, C*H*CH$_2$OCHPMP, C*H*$_2$CH(CH$_3$)CH$_3$), 1.08 (3H, d, 6.3 Hz, CH(C*H*$_3$)CHOCHPMP), 1.05 (3H, d, 6.3 Hz, PMBOCH$_2$CH(C*H*$_3$)), 0.84 (3H, d, 6.3 Hz, CH(C*H*$_3$)CH$_3$), 0.77 (3H, d, 6.6 Hz, CH(CH$_3$)C*H*$_3$), 0.30 (3H, d, 6.6 Hz, CH(C*H*$_3$)CH$_2$OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 172.2, 160.3, 159.7, 132.3, 131.1, 129.6, 128.1, 114.1, 113.7, 101.7, 85.0, 77.6, 73.2, 73.1, 71.8, 54.7, 54.7, 35.6, 35.2, 30.8, 25.3, 22.6, 22.5, 15.4, 11.7, 8.5; **HRESIMS** calculated for $C_{31}H_{44}O_7Na^+$ $[M+Na]^+$: 551.2979; found 551.2975; **EIMS** *m/z* (%): 479 (1), 271 (2), 217 (4), 207 (6), 190 (6), 169 (6), 137 (35), 121 (100), 109 (5), 85 (9), 57 (14).



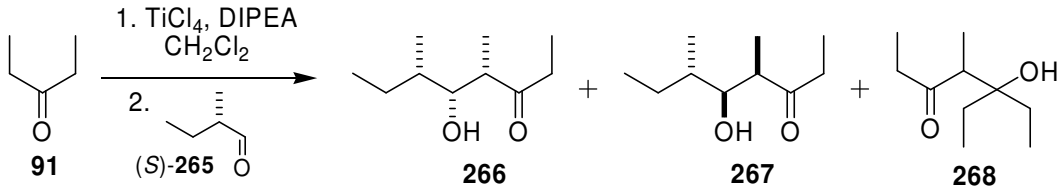
[2*S*,3*S*,4*S*-[2*R*,5*R*,6*R*]]-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(3-methyl-1-oxobutanyl)-2-methyl-pentan-1-ol (262). Deprotection was performed according to the procedure of Paterson *et al.*[23] To a solution of the benzyl ether **261** (60 mg, 0.11 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added pH 7 phosphate buffer (0.6 mL) followed by DDQ (31 mg, 0.14 mmol) and the resultant slurry was stirred at 0 °C for 3 hours. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (12% Et_2O/CH_2Cl_2, on buffered silica) to give the alcohol **262** (32 mg, 85% based on recovered starting material) as a clear oil. $\mathbf{R}_f$ = 0.20 (12% Et_2O/CH_2Cl_2); Spectral data is identical to that reported above.



[2*R*,3*R*,4*S*-[2*R*,5*R*,6*R*]]-4-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3-(3-methyl-1-oxobutanyl)-2-methyl-pentan-1-al (257). Oxidation was performed according to the procedure of Dess and Martin.[22] To a solution of the alcohol **262** (165 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) at room temperature was added Dess-Martin Periodinane (257 mg, 0.61 mmol). The reaction mixture was stirred for 1 hour then diluted with Et_2O (15 mL) and quenched with a solution of $Na_2S_2O_3$ (364 mg) in saturated aqueous $NaHCO_3$ (10 mL). After stirring for several minutes the layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine (10 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2, on buffered silica) gave the aldehyde **257** (155 mg, 94%) as a clear oil. $\mathbf{R}_f$ = 0.36 (CH_2Cl_2); $[\alpha]^{20}_D$ = −30.6 (*c* 1.6, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 1731, 1615, 1519, 1463, 1396, 1371, 1294, 1251, 1171, 1119, 1088, 1033, 984, 831 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 9.61 (1H, d, 2.0 Hz, C*H*O), 7.58 (2H, d, 8.8 Hz, Ar*H*), 6.77 (2H, d, 8.8 Hz, Ar*H*), 5.54 (1H, t, 7.6, 4.6 Hz, C*H*OC(=O)CH_2), 5.31 (1H, s, C*H*PMP), 3.83 (1H, dd, 11.2, 4.6 Hz, C$H_A$$H_B$OCHPMP), 3.40 (1H, dd, 10.0, 2.2 Hz, C*H*OCHPMP), 3.25 (3H, s, OCH_3), 3.14 (1H, t, 11.2 Hz, $CH_A$$H_B$OCHPMP), 2.60 (1H, dqd, 7.6, 7.0, 2.0 Hz, HC(=O)C*H*(CH_3)), 2.13-1.71 (5H, m, C*H*(CH_3)CHOCHPMP, C*H*(CH_3)CH_3, C*H*CH_2OCHPMP, CH_2CH(CH_3)CH_3), 0.99 (3H, d, 7.0 Hz, CH(CH_3)CHOCHPMP), 0.94 (3H, d, 7.0 Hz, HC(=O)CH(CH_3)), 0.81 (3H, d, 6.2 Hz, CH(CH_3)CH_3), 0.78 (3H, d, 6.2 Hz, CH(CH_3)CH_3), 0.29 (3H, d, 6.6 Hz, CH(CH_3)CH_2OCHPMP); **^{13}C NMR** (50 MHz, C_6D_6) δ 201.3, 171.9, 160.5, 131.8, 128.0, 113.8, 101.5, 82.9, 75.6, 72.9, 54.7, 48.8, 43.4, 35.6, 30.6, 25.6, 22.4, 22.4, 11.5, 10.1, 9.4; **HRESIMS** calculated for $C_{23}H_{34}O_6Na^+$ $[M+Na]^+$: 429.2248; found 429.2243; **EIMS** *m/z* (%): 405 (1), 304 (5), 207 (78), 152 (9), 135 (100), 121 (35), 109 (28), 8 (30), 77 (20), 57 (24).



(2*S*)-2-methylbutan-1-al [(*S*)-265]. Oxidation was performed according to the procedure of Swern and Mancuso.[5] To a solution of DMSO (4.83 mL, 68.1 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added oxalyl chloride (17.0 mL, 2 M in CH_2Cl_2, 34.0 mmol) over 5 mins. After 30 minutes, (2*S*)-2-methylbutan-1-ol [(*S*)-**264**] (4.22 g, 20.1 mmol) in CH_2Cl_2 (15 mL) was added *via* cannula and the resulting mixture stirred at −78 °C for 45 minutes. Triethylamine (19.0 mL, 136.0 mmol) was added over 5 minutes and the resulting white solution was stirred at −78 °C for 30 minutes then at 0 °C for 30 minutes. The reaction mixture was fractionally distilled (b.p. 50-65 °C) to give (2*S*)-2-methylbutan-1-al [(*S*)-**265**] as a solution in residual CH_2Cl_2. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.61 (1H, d, 1.8 Hz, C*H*O), 2.27 (1H, dqd, 13.8, 6.9, 1.8 Hz, C*H*(CH_3)CHO), 1.74 (1H, m, $CH_AH_BCH_3$), 1.43 (1H, m, $CH_AH_BCH_3$), 1.08 (3H, d, 6.9 Hz, CH(CH_3)CHO), 0.94 (3H, t, 7.5 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.4, 47.7, 23.5, 12.8. 11.3.



(4*R*,5*S*,6*S*)-5-hydroxy-4,6-dimethyloctan-3-one (267). The aldol addition was performed according to the procedure of Evans *et al*.[30] To a solution of pentan-3-one **91** (2.0 g, 23.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added $TiCl_4$ (27.9 mL of a 1 M solution in CH_2Cl_2, 27.9 mmol) dropwise and the resulting yellow solution was stirred for 30 minutes. ^{i}Pr$_2$NEt (5.66 mL, 32.5 mmol) was added dropwise giving a deep red solution which was stirred for an additional 1 hour before being cooled to −90 °C and treated with a solution of (2*S*)-2-methylbutan-1-al (*S*)-**265** (~ 2.97 mL, ~34.5 mmol) in residual CH_2Cl_2. The reaction mixture was stirred at −78 °C for 1 hour then warmed to 0 °C and quenched with the addition of pH 7 phosphate buffer (100 mL). The layers were separated and the aqueous phase was extracted with

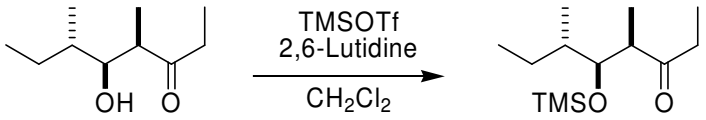
CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (10% Et_2O/CH_2Cl_2) to give first the self-condensation adduct **268** (160 mg, 5%), followed by the *anti*-Felkin adduct **267** (1.92 g, 60%) followed by the Felkin adduct **266** (480 mg, 15%) all as clear oils.

***anti*-Felkin isomer 267**: $\mathbf{R}_f$ = 0.41 (10% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +14.7 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3488, 1704, 1460, 1410, 1379, 1105, 1019, 972 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.59 (1H, dt, 9.0, 3.0 Hz, C*H*OH), 2.88 (1H, d, 3.0 Hz, O*H*), 2.71 (1H, qd, 7.2, 3.0 Hz, C*H*(CH_3)C=O), 2.56 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC$=O), 2.47 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC$=O), 1.83-1.70 (1H, m, $CH_3CH_2CH(CH_3)CHOH$), 1.50-1.36 (1H, m, $CH_3CH_AH_BCH(CH_3)CHOH$), 1.21-1.00 (1H, m, $CH_3CH_AH_BCH(CH_3)CHOH$), 1.09 (3H, d, 7.2 Hz, $CH(CH_3)C$=O), 1.04 (3H, t, 7.2 Hz, CH_3CH_2C=O), 0.88 (3H, t, 7.2 Hz, $CH_3CH_2CH(CH_3)CHOH$), 0.79 (3H, d, 6.9 Hz, $CH_3CH_2CH(CH_3)CHOH$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.0, 74.4, 46.9, 36.8, 34.8, 25.0, 14.8, 10.8, 9.1, 7.6.

Felkin isomer 266: $\mathbf{R}_f$ = 0.32 (10% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = −10.5 (*c* 2.3, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3480, 1705, 1460, 1410, 1378, 1148, 1103, 1025, 975 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.63 (1H, dt, 6.9, 4.2 Hz, C*H*OH), 2.74 (1H, qd, 7.2, 4.2 Hz, C*H*(CH_3)C=O), 2.56 (1H, d, 4.2 Hz, O*H*), 2.54 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC$=O), 2.46 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC$=O), 1.45-1.31 (2H, m, $CH_3CH_2CH(CH_3)CHOH$, $CH_3CH_AH_BCH(CH_3)CHOH$), 1.15-1.05 (1H, m, $CH_3CH_AH_BCH(CH_3)CHOH$), 1.11 (3H, d, 7.2 Hz, $CH(CH_3)C$=O), 1.03 (3H, t, 7.2 Hz, CH_3CH_2C=O), 0.94 (3H, d, 6.6 Hz, $CH_3CH_2CH(CH_3)CHOH$), 0.87 (3H, t, 7.2 Hz, $CH_3CH_2CH(CH_3)CHOH$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.3, 74.6, 47.7, 37.0, 35.0, 25.7, 14.3, 11.0, 10.7, 7.6.

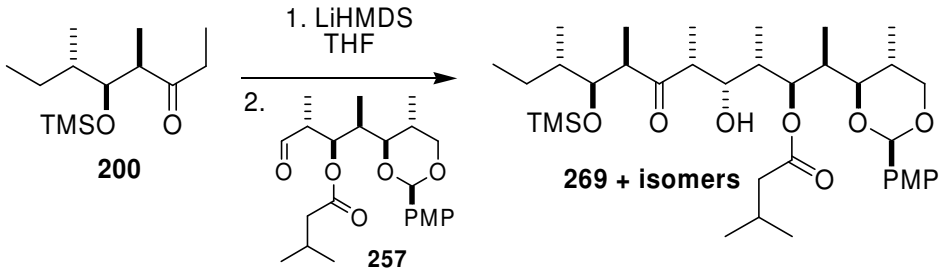
5-ethyl-5-hydroxyheptan-3-one 268. $\mathbf{R}_f$ = 0.49 (10% Et_2O/CH_2Cl_2); **IR** ($CHCl_3$, FT, film): 3489, 1697, 1460, 1406, 1377, 1355, 1140, 1115, 1100, 957 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.64 (1H, s, O*H*), 2.69 (1H, q, 7.2 Hz, C*H*(CH_3)C=O), 2.61 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC$=O), 2.44 (1H, dq, 18.0, 7.2 Hz,

$CH_3CH_AH_BC{=}O$), 1.54 (H, dq, 14.1, 7.5 Hz, $CH_3CH_AH_BCOH$), 1.41 (1H, q, 7.5 Hz, CH_3CH_2COH), 1.38 (1H, dq, 14.1, 7.5Hz, $CH_3CH_AH_BCOH$), 1.09 (3H, d, 7.2 Hz, $CH(CH_3)C{=}O$), 1.03 (3H, t, 7.2 Hz, $CH_3CH_2C{=}O$), 0.84 (3H, t, 7.5 Hz, CH_3CH_2COH), 0.78 (3H, t, 7.5 Hz, CH_3CH_2COH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 219.4, 75.5, 49.2, 37.4, 29.7, 26.4, 11.5, 7.8, 7.5, 7.4.



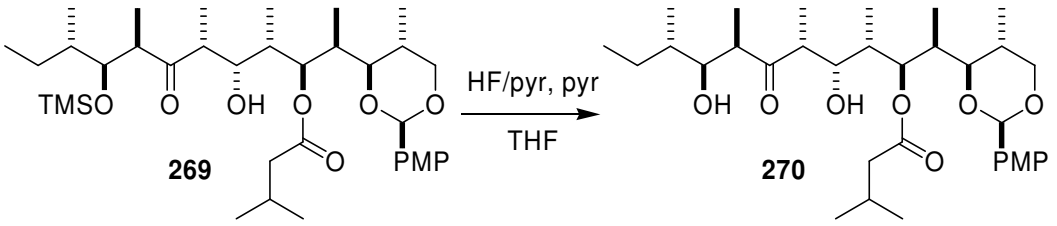
267 **200**

(4*R*,5*S*,6*S*)-4,6-dimethyl-5-trimethylsilyloxyoctan-3-one (200). To a solution of the β-hydroxy ketone **267** (170 mg, 0.99 mmol) in CH_2Cl_2 (10 mL) at −90 °C was added 2,6-lutidine (228 μL, 1.97 mmol) followed by TMSOTf (268 μL, 1.48 mmol) and the resulting solution was stirred at −90 °C for 10 minutes before being quenched with the addition of saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified by column chromatography (1:1 CH_2Cl_2/hexanes) to give the silyl ether **200** (219 mg, 91%) as a clear liquid. $\mathbf{R}_f$ = 0.41 (1:1 CH_2Cl_2/hexanes); $[\alpha]^{20}_D$ = −13.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1714, 1461, 1380, 1250, 1102, 1057, 885, 840, 750 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.78 (1H, t, 5.1 Hz, C*H*OTMS), 2.69 (1H, qn, 7.2 Hz, $CH(CH_3)C{=}O$), 2.46 (2H, q, 7.2 Hz, $CH_3CH_2C{=}O$), 1.56-1.43 (1H, m, $CH_3CH_AH_BCH(CH_3)CHOTMS$), 1.38-1.24 (1H, m, $CH_3CH_2CH(CH_3)CHOTMS$), 1.09-0.95 (1H, m, $CH_3CH_AH_BCH(CH_3)CHOTMS$), 1.06 (3H, d, 7.2 Hz, $CH(CH_3)C{=}O$), 1.02 (3H, t, 7.2 Hz, $CH_3CH_2C{=}O$), 0.85 (3H, t, 7.2 Hz, $CH_3CH_2CH(CH_3)CHOTMS$), 0.84 (3H, d, 6.6 Hz, $CH_3CH_2CH(CH_3)CHOTMS$), 0.07 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.2, 77.8, 49.4, 39.3, 35.3, 24.2, 16.2, 12.8, 11.8, 7.6, 0.6.



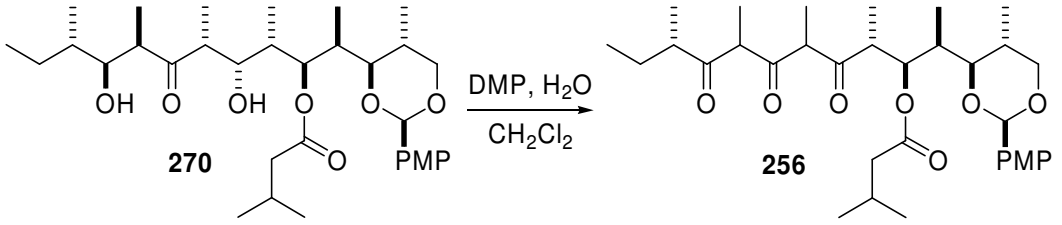
[3*S*,4*S*,5*R*,7*R*,8*S*,9*S*,10*R*,11*S*-[2*R*,5*R*,6*R*]]-8-hydroxy-11-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3,5,7,9-tetramethyl-10-[3-methyl-1-oxobutanyl]-4-trimethylsilyloxydodeca-6-one (269). To a solution of the ketone **200** (180 mg, 0.74 mmol) in THF (740 μL) at −78 °C was added LiHMDS (812 μLof a 1.0 M solution in THF, 0.81 mmol) dropwise and the resulting yellow solution was stirred at −78 °C for 30 minutes and then at −50 °C for a further 30 minutes. The reaction was re-cooled to −78 °C and the aldehyde **257** (150 mg, 0.37 mmol) as a solution in THF (300 μL) was added *via* cannula. After 2 hours the reaction was diluted with Et_2O (15 mL) and quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL) then allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL) then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification of the crude product by column chromatography (5% Et_2O/CH_2Cl_2, on buffered silica) gave a partially separable mixture of diastereomers (229 mg, 92%, >85% ds) as a colourless oil. $\mathbf{R}_f$ = 0.26-0.47 (5% Et_2O/CH_2Cl_2); **Major diastereomer 269**: $[\alpha]^{20}_D$ = +2.6 (*c* 1.2, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3502, 1733, 1703, 1616, 1520, 1464, 1456, 1373, 1298, 1250, 1171, 1117, 983, 836 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.58 (2H, d, 8.7 Hz, Ar*H*), 6.77 (2H, d, 8.7 Hz, Ar*H*), 5.44 (1H, s, C*H*PMP), 5.37 (1H, dd, 7.5, 4.2 Hz, C*H*OC(=O)$CH_2CH(CH_3)_2$), 4.12 (1H, dd, 9.6, 2.1 Hz, C*H*OH), 3.99 (1H, dd, 6.6, 3.9 Hz, C*H*OTMS), 3.92 (1H, dd, 11.1, 4.8 Hz, CH_AH_BOCHPMP), 3.52 (1H, dd, 9.9, 1.8 Hz, C*H*OCHPMP), 3.42 (1H, t, 11.1 Hz, CH_AH_BOCHPMP), 3.26 (3H, s, OCH_3), 3.05 (1H, d, 3.6 Hz, O*H*), 2.86 (1H, dq, 9.6, 6.9 Hz, C(=O)C*H*(CH_3)CHOH), 2.74 (1H, qn, 7.2 Hz, CH(OTMS)C*H*(CH_3)C=O), 2.10-1.83 (4H, m, CH(OH)C*H*(CH_3)CHO-, C*H*(CH_3)CHOCHPMP, C*H*CH_2OCHPMP, C*H*(CH_3)CH_3), 1.91 (1H, dd, 15.3, 7.5 Hz, CH_AH_BCH(CH_3)CH_3), 1.77 (1H, dd, 15.3, 6.6 Hz, CH_AH_BCH(CH_3)CH_3), 1.63-

1.50 (1H, m, $CH_3CH_AH_BCH$), 1.43-1.33 (1H, m, CH_3CH_2CH), 1.30 (3H d, 6.9 Hz, C(=O)CH(CH_3)CHOH), 1.22-1.09 (1H, m, $CH_3CH_AH_BCH$), 1.09 (3H, d, 6.6 Hz, CH(CH_3)CHOCHPMP), 1.07 (3H, d, 7.2 Hz, CH(OTMS)CH(CH_3)C=O), 1.03 (3H, d, 6.9 Hz, CH(OH)CH(CH_3)CO-), 0.86 (3H, t, 7.2, CH_3CH_2), 0.86 3H, d, 6.9 Hz, $CH_3CH_2CH(CH_3)$), 0.82 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.76 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.43 (3H, d, 6.6 Hz, CH(CH_3)CH_2OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 215.7, 173.8, 160.4, 132.1, 128.1, 113.7, 101.8, 85.4, 79.3, 76.9, 73.1, 70.8, 54.7, 49.2, 48.7, 43.5, 39.7, 37.0, 35.0, 30.9, 25.3, 24.0, 22.4, 22.4, 17.1, 15.4, 13.8, 12.1, 11.7, 10.5, 8.2, 0.9; **HRESIMS** calculated for $C_{36}H_{62}O_8SiNa^+$ $[M+Na]^+$: 673.4106; found 673.4105; **EIMS** *m/z* (%): 304 (60), 207 (57), 176 (6), 152 (5), 137 (100), 135 (91), 121 (30), 109 (24), 94 (8), 77 (15), 71 (9), 55 (7).



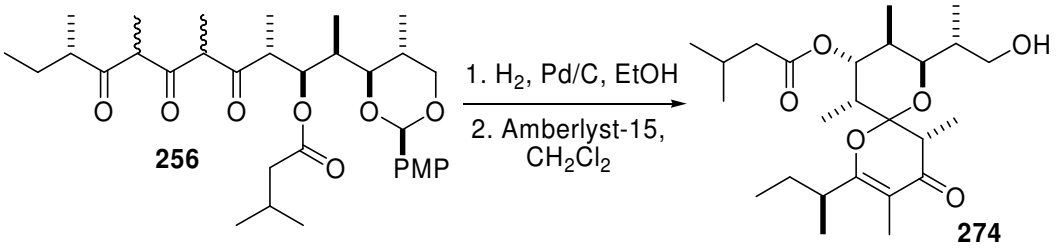
[3*S*,4*S*,5*R*,7*R*,8*S*,9*S*,10*R*,11*S*-[2*R*,5*R*,6*R*]]-4,8-dihydroxy-11-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3,5,7,9-tetramethyl-10-[3-methyl-1-oxobutanyl]-dodeca-6-one (270). To a solution of the major aldol adduct **269** (65 mg, 0.10 mmol) in THF (2 mL) at 0 °C was added buffered pyridinium hydrofluoride (0.5 mL) (stock solution prepared from dry THF (10 mL), pyridine (5 mL) and 30% pyridinium hydrofluoride (2.1 g)). The resulting solution was warmed to ambient temperature and stirred for 45 minutes then diluted with Et_2O (15 mL) and washed with saturated aqueous $CuSO_4$ (3 x 5 mL), saturated aqueous $NaHCO_3$ (2 x 5 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (20% Et_2O/CH_2Cl_2, on buffered silica) to give the diol **270** (55.5 mg, 96%) as a colourless oil. $\mathbf{R}_f$ = 0.38 (20% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +10.8 (*c* 1.1, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3508, 1702, 1616, 1519, 1461, 1372, 1300, 1251, 1171, 1117, 1034, 1006, 983, 831 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.59 (2H, d, 8.7 Hz, Ar*H*), 6.77 (2H, d, 8.7 Hz, Ar*H*), 5.43 (1H, s, C*H*PMP), 5.35 (1H, dd, 7.2, 4.5 Hz, C*H*OC(=O)$CH_2CH(CH_3)_2$), 4.13 (1H, dd, 9.3, 3.0 Hz,

C(=O)CH(CH_3)C*H*OH), 3.92 (1H, dd, 11.1, 4.8 Hz, C$H_A$$H_B$OCHPMP), 3.60 (1H, dt, 8.7, 3.0 Hz, CH_3CH_2CH(CH_3)C*H*OH), 3.47 (1H, dd, 9.9, 2.1 Hz, C*H*OCHPMP), 3.32 (1H, t, 11.1 Hz, $CH_A$$H_B$OCHPMP), 3.25 (3H, s, OC$H_3$), 2.99 (1H, t, 3.0 Hz, O*H* x 2), 2.84 (1H, dq, 9.3, 6.9 Hz, C(=O)C*H*(CH_3)CHOH), 2.60 (1H, qd, 6.9, 3.0 Hz, CH_3CH_2CH(CH_3)CH(OH)C*H*(CH_3)C=O), 2.11-1.97 (2H, m, C*H*(CH_3)CHOCHPMP, C*H*(CH_3)CH_3), 1.96-1.83 (3H, m, C*H*CH_2OCHPMP, CH(OH)C*H*(CH_3)CHO-, CH_3C$H_A$$H_B$CH($CH_3$)CHOH), 1.91 (1H, dd, 15.6, 7.8 Hz, C$H_A$$H_B$CH($CH_3$)$CH_3$), 1.77 (1H, dd, 15.6, 6.6 Hz, $CH_A$$H_B$CH($CH_3$)$CH_3$), 1.48-1.34 (1H, m, CH_3CH_2C*H*(CH_3)CHOH), 1.26 (3H d, 6.9 Hz, C(=O)CH(CH_3)CHOH), 1.25-1.14 (1H, m, $CH_3CH_A$$H_B$CH($CH_3$)CHOH), 1.06 (3H, d, 6.9 Hz, CH(CH_3)CHOCHPMP), 1.01 (3H, d, 6.6 Hz, CH(OH)CH(CH_3)CHO-), 0.99 (3H, d, 6.9 Hz, CH_3CH_2CH(CH_3)CH(OH)CH(CH_3)C=O), 0.90 (3H, t, 7.5, CH_3CH_2), 0.83 3H, d, 6.3 Hz, CH(CH_3)CH_3), 0.77 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.65 (3H, d, 6.6 Hz, CH_3CH_2CH(CH_3)CHOH), 0.43 (3H, d, 6.6 Hz, CH(CH_3)CH_2OCHPMP); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 219.3, 173.8, 160.4, 132.1, 128.1, 113.7, 101.9, 85.3, 79.4, 74.8, 73.1, 70.7, 54.7, 49.0, 46.6, 43.5, 37.2, 34.9, 30.9, 25.3, 25.3, 22.4, 22.3, 15.5, 15.0, 11.6, 11.1, 10.4, 9.1, 8.3; **HRESIMS** calculated for $C_{33}H_{54}O_8Na^+$ $[M+Na]^+$: 601.3711; found 601.3718; **EIMS** *m/z* (%): 304 (6), 207 (60), 176 (7), 152 (5), 137 (100), 135 (93), 121 (30), 109 (24), 94 (8), 77 (15), 71 (9), 55 (7).



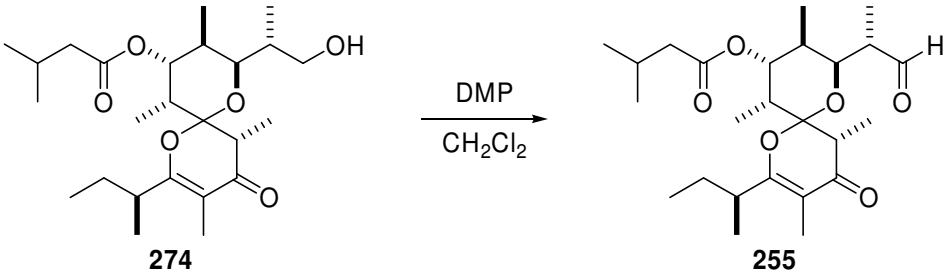
[3*S*,9*R*,10*R*,11*S*-[2*R*,5*R*,6*R*]]-11-[2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-3,5,7,9-tetramethyl-10-[3-methyl-1-oxobutanyl]-dodeca-4,6,8-trione 256. Oxidation was performed according to the procedure of Meyer and Schreiber.[34] To a solution of the diol **270** (177 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) at room temperature was added Dess-Martin Periodinane (389 mg, 0.92 mmol). To the reaction mixture was added a solution of H_2O in CH_2Cl_2 (12 μL in 6 mL) at a rate of 500 μL every 5 minutes for 1 hour. After complete addition the reaction was diluted with Et_2O (15

mL) and quenched with a solution of $Na_2S_2O_3$ (1.6 g) in saturated aqueous $NaHCO_3$ (15 mL). After stirring for several minutes the layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine (15 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O/CH_2Cl_2, on buffered silica) gave the tri-ketone as a mixture of keto-enol forms **256** (176 mg, 99%) as a clear oil. $\mathbf{R_f}$ = 0.65-0.53 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, C_6D_6) δ 7.61-7.55 (2H, m, Ar*H*), 6.81-6.737 (2H, m, Ar*H*), 5.75-5.54 (1H, m, C*H*OC(=O)CH_2CH(CH_3)$_2$), 5.45-5.39 (1H, m, C*H*PMP), 3.93-3.54 (5H, m, C*H*(CH_3)C=O x 2, CH_2OCHPMP, C*H*OCHPMP), 3.26-3.32 (3H, m, OCH_3), 2.50-2.23 (1H, m, C(=O)C*H*(CH_3)C(OC=O)), 2.02-1.72 (5H, m, C*H*(CH_3)CHOCHPMP, C*H*(CH_3)CH_3, CH_2CH(CH_3)CH_3, CH_3CH_2C*H*(CH_3)C), 1.67-1.49 (1H, m, C*H*CH_2OCHPMP), 1.37-0.27 (29H CH_3CH_2, CH_3CH_2, CH_3CH_2CH(CH_3)C=O, CH(CH_3)C(=O) x 2, C(=O)CH(CH_3)CHO-, CH(CH_3)CHOCHPMP, CH(CH_3)CH_3), CH(CH_3)CH_3, CH(CH_3)CH_2OCHPMP); **HRESIMS** calculated for $C_{33}H_{50}O_8Na^+$ $[M+Na]^+$: 597.3398; found 597.3397; **EIMS** *m/z* (%): 405 (1), 237 (6), 207 (99), 137 (74), 121 (44), 109 (26), 85 (49), 57 (100).



(2*R*-(1*R*),3*S*,4*R*,5*R*,8-(1*S*),11*R*)-8-(1-methylpropyl)-2-(2-hydroxy-1-methylethyl)-3,5,9,11-tetramethyl-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-4-yl (3-methyl)-butanoate (274). 1) To a solution of β-triketone **256** (215 mg, 0.37 mmol) in EtOH (3.75 mL) at room temperature was added Pd/C (150 mg). The reaction vessel was sealed and purged with H_2 and then maintained under 1 atmosphere of H_2 (balloon) for 30 minutes. The reaction mixture was filtered through a pad of celite (Et_2O) and then concentrated *in vacuo*. The residue was purified by column chromatography (20% Et_2O/CH_2Cl_2) to give the diol **271** (143 mg, 87%) as a clear oil which was used in the next step without characterisation.

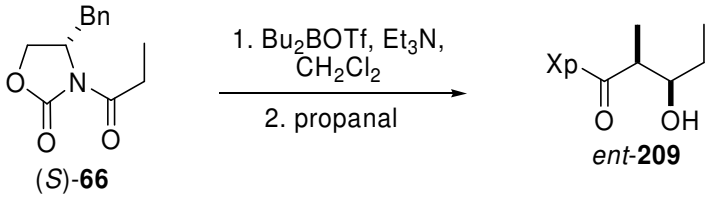
2) To a solution of the diol **271** (70 mg, 0.15 mmol) in CH_2Cl_2 (1.6 mL) at −50 °C was added Amberlyst-15 (30 mg) resin and the reaction mixture was stirred at this temperature for 30 minutes before being wrmed to 0 °C and stirred for a further 2 hours and finally warmed to room temperature and stirred for an additional 2 hours. After this time the reaction mixture was filtered through $NaHCO_3$ with rinsing (EtOAc) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (80% Et_2O/hexanes, on buffered silica) afforded the spiroacetal-dihydropyrone **274** (42 mg, 63%) as a clear oil. $\mathbf{R}_f$ = 0.25 (15% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +107.5 (*c* 0.4, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3478, 1732, 1669, 1624, 1462, 1387, 1371, 1294, 1166, 1095, 1058, 1038, 1010, 986, 918 cm^{-1}; **^{1}H NMR** (600 MHz, C_6D_6) δ 4.93 (1H, t, 3.6 Hz, C*H*OC(=O)CH$(CH_3)_2$), 3.83 (1H, dd, 10.2, 2.4 Hz, C*H*(O-)CH$(CH_3)CH_2OH$), 3.49 (1H, dd, 10.8, 5.4 Hz, CH_AH$_B$OH), 3.35 (1H, dd, 10.8, 6.6 Hz, CH$_A$$H_B$OH), 2.50-2.44 (1H, m, $CH_3CH_2CH(CH_3)C$), 2.43 (1H, q, 6.6 Hz, C*H*(CH_3)C=O), 2.20-2.13 (3H, m, CH_2CH$(CH_3)CH_3$, C*H*$(CH_3)CH_3$), 1.89 (3H, s, C=C(CH_3)C=O), 1.87 (1H, qd, 7.2, 3.6 Hz, CH(OC=O)C*H*(CH_3)C(O-)O-), 1.81-1.73 (2H, m, $CH_3C$$H_AH_B$CH, C*H*$(CH_3)$CH(O-)CH$(CH_3)CH_2OH$), 1.61-1.55 (1H, m, CH(O-)C*H*$(CH_3)CH_2OH$), 1.54-1.40 (2H, m, CH_3CH_2CH$_A$$H_B$CH, O*H*), 1.14 (3H, d, 6.6 Hz, CH(CH_3)C=O), 1.06 (3H, d, 6.6 Hz, $CH_3CH_2CH(CH_3)C$), 0.89 (3H, d, 6.0 Hz, CH(CH_3)CH_3), 0.88 (3H, t, 7.8 Hz, CH_3CH_2), 0.88 (3H, d, 6.0 Hz, $CH(CH_3)CH_3$), 0.80 (3H, d, 7.2 Hz, CH(OC=O)CH(CH_3)C(O-)O-), 0.67 (3H, d, 7.2 Hz, CH(CH_3)CH(O-)CH(CH_3)CH_2OH), 0.56 (3H, d, 7.2 Hz, CH(CH_3)CH_2OH); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 192.8, 172.0, 167.3, 108.0, 105.3, 75.1, 71.8, 66.6, 44.6, 44.0, 37.7, 36.6, 34.2, 31.9, 27.4, 26.3, 22.4, 22.3, 16.6, 12.6, 12.4, 12.0, 10.0, 9.4, 8.0; **HRESIMS** calculated for $C_{25}H_{42}O_6Na^+$ $[M+Na]^+$: 461.2874; found 461.2879; **EIMS** *m/z* (%): 197 (15), 149 (22), 111 (17), 97 (30), 85 (55), 83 (67), 72 (51), 70 (59), 57 (100), 55 (71).



274 **255**

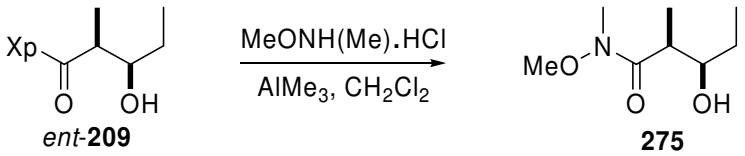
(2*R*-(1*R*),3*S*,4*R*,5*R*,8-(1*S*),11*R*)-8-(1-methylpropyl)-2-(1-methylethan-2-al)-3,5,9,11-tetramethyl-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-4-yl (3-methyl)-butanoate (255). Oxidation was performed according to the procedure of Dess and Martin.[22] To a solution of the alcohol **274** (60 mg, 0.14 mmol) in CH_2Cl_2 (1.6 mL) at room temperature was added Dess-Martin Periodinane (100 mg, 0.24 mmol). The reaction mixture was stirred for 1 hour then diluted with Et_2O (10 mL) and quenched with a solution of $Na_2S_2O_3$ (400 mg) in saturated aqueous $NaHCO_3$ (5 mL). After stirring for several minutes the layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL), then the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine (10 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (8% Et_2O/CH_2Cl_2, on buffered silica) gave the aldehyde **255** (54.1 mg, 91%) as a clear oil. $\mathbf{R}_f$ = 0.50 (8% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +150.0 (*c* 0.4, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 1731, 1671, 1627, 1461, 1386, 1372, 1293, 1166, 1093, 1058, 1009, 986, 919 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 9.67 (1H, d, 1.5 Hz, C*H*O), 4.91 (1H, t, 3.3 Hz, C*H*OC(=O)CH_2CH(CH_3)CH_3), 4.06 (1H, dd, 10.5, 2.1 Hz, C*H*(O-)CH(CH_3)CHO), 2.52-2.38 (1H, m, $CH_3CH_2CH(CH_3)C$), 2.40 (1H, q, 6.9 Hz, C*H*(CH_3)C=O), 2.24-2.08 (3H, m, CH_2CH(CH_3)CH_3, C*H*(CH_3)CH_3), 2.06-1.94 (1H, m, CH(O-)C*H*(CH_3)CHO), 1.90-1.81 (1H, m, CH(OC=O)C*H*(CH_3)C(O-)O-), 1.85 (3H, s, C=C(CH_3)C=O), 1.79-1.60 (2H, m, $CH_3CH_AH_BCH$, C*H*(CH_3)CH(O-)CH(CH_3)CHO), 1.48-1.35 (1H, m, $CH_3CH_AH_BCH$), 1.16 (3H, d, 6.9 Hz, CH(CH_3)C=O), 1.03 (3H, d, 6.9 Hz, $CH_3CH_2CH(CH_3)C$), 0.87 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.87 (3H, d, 6.6 Hz, CH(CH_3)CH_3), 0.83 (3H, t, 7.2 Hz, CH_3CH_2), 0.78 (3H, d, 6.9 Hz, CH(OC=O)CH(CH_3)C(O-)O-), 0.58 (3H, d, 7.2 Hz, CH(CH_3)CH(O-)CH(CH_3)CHO), 0.55 (3H, d, 6.9 Hz, CH(O-)CH(CH_3)CHO); **^{13}C NMR** (75.5 MHz, C_6D_6) δ 202.8, 192.3, 172.0, 166.7, 108.4, 105.1, 74.8, 70.0, 46.3,

44.5, 43.9, 37.7, 34.2, 32.0, 27.3, 26.3, 22.4, 22.3, 16.7, 12.4, 12.0, 9.6, 9.3, 8.9, 8.0; **HRESIMS** calculated for $C_{25}H_{40}O_6Na^+$ $[M+Na]^+$: 459.2725; found 459.2717; **EIMS** *m/z* (%): 430 (2), 337 (2), 197 (5), 165 (6), 149 (6), 111 (17), 97 (37), 85 (53), 83 (70), 69 (66), 57 (100).



(*S*)-**66** *ent*-**209**

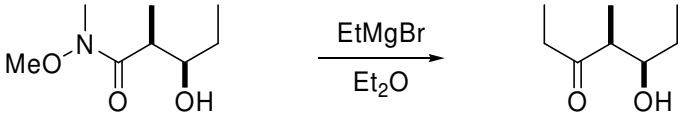
[[3-(2*S*,3*R*)-4*S*]-3-(3-hydroxy-2-methyl-1-oxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (*ent*-209). The previous procedure[30] used for the preparation of **209** was followed with (4*S*)-3-(1-oxo-propyl)-4-(phenylmethyl)-2-oxazolidinone **209** (2.00 g, 8.57 mmol), $(Bu)_2BOTf$ (10.3 mL of a 1.0 M solution in CH_2Cl_2, 10.3 mmol), Et_3N (1.55 mL, 11.2 mmol) and propanal (1.23 mL, 17.2 mmol) in CH_2Cl_2 (20 mL). Standard oxidative work-up preceeded purification by flash chromatography (20% Et_2O/CH_2Cl_2) to afford the aldol adduct *ent*-**209** (2.17 g, 88%) as a white solid. All spectral data was identical to that reported for compound **209** except optical rotation which had the opposite sign.



ent-**209** **275**

(2*S*,3*R*)-3-hydroxy-2-methyl-*N*-methoxy-*N*-methylheptionamide (275). Transamidation was performed according to the procedure of Evans *et al.*[38] To a solution of the Wienreb salt (1.53 g, 15.7 mmol) in CH_2Cl_2 (54 mL) at 0 °C was added $AlMe_3$ (7.86 mL of a 2.0 M solution in hexanes, 15.7 mmol) dropwise and the resulting solution was warmed to ambient temperature and stirred for 30 minutes. The reaction mixture was cooled to −15 °C and a solution of the aldol adduct *ent*-**209** (2.29 g, 7.86 mmol) in CH_2Cl_2 (23 mL) was added *via* cannula, then stirred for 30 minutes before being allowed to warm to room temperature, with stirring, overnight. The reaction was quenched by transferring it, *via* cannula, into a rapidly stirring 1.0

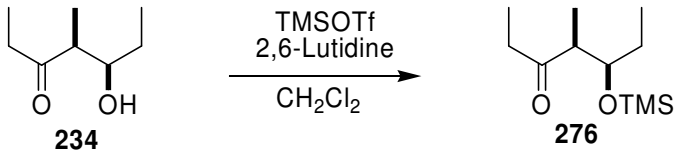
M solution of Rochelle's salt (85mL) and stirring maintained until the solution became clear. The product was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were washed with brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (80% Et_2O/hexanes) gave the Weinreb amide **275** (1.26 g, 99%) as a clear oil. $\mathbf{R}_f$ = 0.18 (80% Et_2O/hexanes); $\mathbf{[\alpha]^{20}_D}$ = +13.1 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3447, 1638, 1460, 1421, 1388, 1179, 1149, 1113, 1042, 1027, 994, 979 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.72 (1H, ddd, 8.1, 5.4, 2.7 Hz, C*H*OH), 3.67 (3H, s, OC*H*$_3$), 3.16 (3H, s, NC*H*$_3$), 2.94-2.82 (1H, br m, C*H*(CH_3)CHOH), 1.61-1.47 (1H, m, $CH_3CH_AH_BCHOH$), 1.43-1.30 (1H, m, $CH_3CH_AH_BCHOH$), 1.12 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOH), 0.93 (3H, t, 7.5 Hz, C*H*$_3$$CH_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 178.3, 73.0, 61.4, 38.1, 31.8, 26.7, 10.3, 10.0; **HRESIMS** calculated for $C_8H_{17}NO_3Na^+$ $[M+Na]^+$: 198.1101; found 198.1102; **EIMS** *m/z* (%): 146 (3), 117 (13), 98 (11), 84 (15), 69 (25), 61 (100), 59 (62), 57 (14).



275 **234**

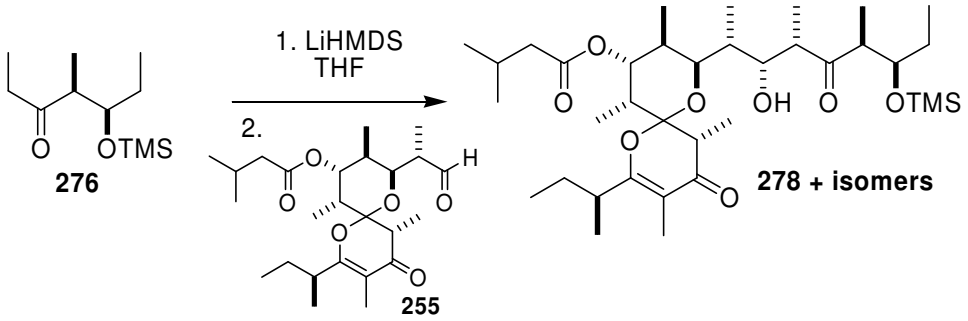
(4*S*,5*R*)-5-hydroxy-4-methyl-heptan-3-one (234). Grignard addition was performed according to the procedure of Evans *et al*.[38] To a solution of the Weinreb amide **275** (1.20 g, 6.85 mmol) in Et_2O (69 mL) at 0 °C was added EtMgBr (21 mL of a 1.0 M solution in THF, 20.5 mmol) dropwise and the resulting solution was warmed to room temperature and stirred overnight. The reaction was quenched with the addition of saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$), then concentrated *in vacuo*. The residue was purified by column chromatography (7% Et_2O/CH_2Cl_2) to give the β-hydroxyketone **234** (864 mg, 88%) as a clear oil. $\mathbf{R}_f$ = 0.49 (7% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = −26.5 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 3451, 1705, 1460, 1411, 1377, 1150, 1101, 1031, 972 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.79 (1H, ddd, 8.1, 5.1, 3.0 Hz, C*H*OH), 2.64 (1H, br s, O*H*), 2.58 (1H, qd, 7.2, 3.0 Hz, C*H*(CH_3)CHOH), 2.54 (1H, dq, 18.0, 7.2 Hz,

$CH_3CH_AH_BC{=}O$), 2.46 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC{=}O$), 1.56-1.40 (1H, m, $CH_3CH_AH_BCHOH$), 1.42-1.28 (1H, m, $CH_3CH_AH_BCHOH$), 1.10 (3H, d, 7.2 Hz, $CH(CH_3)CHOH$), 1.03 (3H, t, 7.2 Hz, $CH_3CH_2C{=}O$), 0.92 (3H, t, 7.5 Hz, CH_3CH_2CHOH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.5, 72.6, 49.4, 35.0, 26.9, 10.3, 9.9, 7.5; **HRESIMS** calculated for $C_8H_{18}O_2Na^+$ $[M+Na]^+$: 167.1043; found 167.1049; **EIMS** *m/z* (%): 126 (8), 86 (46), 70 (16), 57 (100).



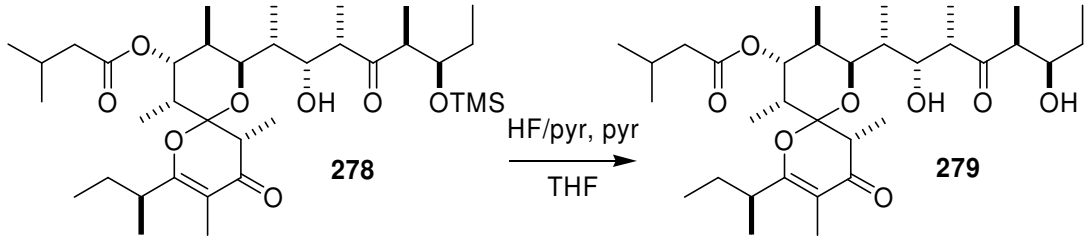
234 **276**

(4*S*,5*R*)-4-methyl-5-trimethylsilyloxyheptan-3-one (276). To a solution of the β-hydroxy ketone **234** (860 mg, 5.96 mmol) in CH_2Cl_2 (60 mL) at −90 °C was added 2,6-lutidine (1.39 mL, 11.9 mmol) follwed by TMSOTf (1.62 mL, 8.95 mmol) and the resulting solution was stirred at this temperature for 30 minutes. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (50 mL), the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2) to give the silane **276** (1.1 g, 85%) as a clear oil. $\mathbf{R}_f$ = 0.44 (CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +38.9 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, FT, film): 1713, 1460, 1378, 1252, 1101, 1056, 1016, 974, 887, 841, 751 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.78 (1H, ddd, 7.2, 6.0, 4.8 Hz, C*H*OTMS), 2.63 (1H, qd, 7.2, 6.0 Hz, $CH(CH_3)CHOTMS$), 2.53 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC{=}O$), 2.44 (1H, dq, 18.0, 7.2 Hz, $CH_3CH_AH_BC{=}O$), 1.52-1.40 (1H, m, $CH_3CH_AH_BCHOTMS$), 1.38-1.24 (1H, m, $CH_3CH_AH_BCHOTMS$), 1.05 (3H, d, 7.2 Hz, $CH(CH_3)CHOTMS$), 1.02 (3H, t, 7.2 Hz, $CH_3CH_2C{=}O$), 0.86 (3H, t, 7.2 Hz, $CH_3CH_2CHOTMS$), 0.10 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.2, 75.3, 51.3, 36.0, 27.8, 12.7, 10.1, 7.6, 0.4; **HRESIMS** calculated for $C_{11}H_{24}O_2SiNa^+$ $[M+Na]^+$: 239.1438; found 239.1440; **EIMS** *m/z* (%): 201 (51), 187 (31), 158 (25), 143 (62), 131 (100), 115 (14), 97 (11), 75 (41), 73 (75), 57 (45).



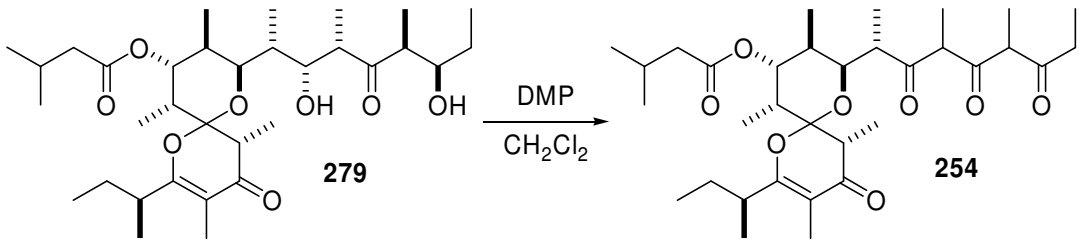
(2*R*-(1*R*),3*S*,4*R*,5*R*,8-(1*S*),11*R*)-8-(1-methylpropyl)-2-(2-hydroxy-1,3,5-trimethyl-6-trimethylsilyloxy-4-oxo-octyl)-3,5,9,11-tetramethyl-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-4-yl (3-methyl)-butanoate (278). To a solution of the ketone **276** (258 mg, 1.19 mmol) in THF (2.4 mL) at −78 °C was added LiHMDS (1.21 mL of a 1.0 M solution in THF, 1.21 mmol) dropwise and the resulting yellow solution was stirred at −78 °C for 30 minutes and then at −50 °C for a further 30 minutes. The reaction was re-cooled to −78 °C and the aldehyde **255** (54 mg, 0.15 mmol) as a solution in THF (100 μL) was added *via* cannula. After 1 hour the reaction was diluted with Et_2O (10 mL) and quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL) then allowed to warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL) then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification of the crude product by column chromatography (30% Et_2O/hexanes, on buffered silica) gave an inseparable mixture of two diastereomers (76.0 mg, 94%, 88% d.s. by NMR) as a colourless oil. Further purification by column chromatography (5% Et_2O/CH_2Cl_2) resulted in separation of the two diastereomers, with the data for the major isomer **278** presented below. $\mathbf{R}_f$ = 0.39 (5% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +95.1 (*c* 0.4, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3517, 1734, 1702, 1625, 1459, 1387, 1372, 1345, 1294, 1252, 1166, 1120, 1095, 1059, 1009, 987, 964, 918, 888, 840, 750 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6) δ 4.98 (1H, t, 3.6 Hz, C*H*OC=OCH_2CH(CH_3)$_2$), 4.18-4.15 (1H, m, C*H*OH), 4.02 (1H, dd, 10.2, 2.1 Hz, C*H*(O-)CH(CH_3)CHOH), 3.90 (1H, ddd, 6.9, 6.9, 4.2 Hz, C*H*OTMS), 2.69 (1H, qn, 6.9 Hz, C*H*(CH_3)CHOTMS), 2.61 (1H, d, 3.3 Hz, O*H*), 2.54 (1H, qd, 7.2, 3.9 Hz, CH(OH)C*H*(CH_3)C=O, 2.50-2.44 (1H, m, CH_3CH_2C*H*(CH_3)C), 2.41 (1H, q, 6.9 Hz, C(O_2)C*H*(CH_3)C=O), 2.27-2.16 (3H, m,

C*H*$_2$CH(CH$_3$)$_2$, C*H*(CH$_3$)$_2$), 2.02-1.85 (3H, m, CH$_3$C*H*$_A$H$_B$CH(CH$_3$)C, CH(OC=O)C*H*(CH$_3$)C(O$_2$), C*H*(CH$_3$)CH(O-)CH(CH$_3$)CHOH), 1.88 (3H, s, C=C(C*H*$_3$)C=O), 1.68-1.30 (4H, m, CH$_3$CH$_A$*H*$_B$CH(CH$_3$)C, CH(O-)C*H*(CH$_3$)CHOH, CH$_3$C*H*$_A$H$_B$OTMS, CH$_3$CH$_A$*H*$_B$OTMS), 1.24 (3H, d, 6.9 Hz, CH(C*H*$_3$)CHOTMS), 1.14 (3H, d, 6.9 Hz, C(O$_2$)CH(C*H*$_3$)C=O), 1.09 (3H, d, 7.2 Hz, CH(OH)CH(C*H*$_3$)C=O), 1.08 (3H, d, 6.9 Hz, CH$_3$CH$_2$CH(C*H*$_3$)C), 0.95 (3H, t, 7.5 Hz, C*H*$_3$CH$_2$CH(CH$_3$)C), 0.91 (6H, d, 6.3 Hz, CH(C*H*$_3$)CH$_3$, CH(CH$_3$)C*H*$_3$), 0.89 (3H, t, 7.2 Hz, C*H*$_3$CH$_2$OTMS), 0.81 (6H, d, 6.9 Hz, CH(O-)CH(C*H*$_3$)CHOH, CH(C*H*$_3$)CH(O-)CH(CH$_3$)CHOH), 0.76 (3H, d, 6.9 Hz, CH(OC=O)CH(C*H*$_3$)C(O$_2$), 0.14 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 218.0, 192.7, 172.1, 167.8, 107.5, 105.4, 75.3, 75.1, 70.2, 69.0, 51.2, 50.6, 44.6, 44.0, 38.1, 37.8, 34.2, 32.1, 28.4, 27.1, 26.3, 22.5, 22.4, 16.6, 14.3, 12.4, 12.0, 11.2, 10.4, 10.0, 9.9, 8.0, 0.6; **HRESIMS** calculated for $C_{36}H_{64}O_8SiNa^+$ $[M+Na]^+$: 675.4263; found 675.4271; **EIMS** *m/z* (%): 197 (70), 168 (14), 141 (20), 131 (55), 109 (20), 85 (65), 83 (79), 57 (100).



(2*R*-(1*R*),3*S*,4*R*,5*R*,8-(1*S*),11*R*)-8-(1-methylpropyl)- 2-(2,6-dihydroxy-1,3,5-trimethyl-4-oxo-octyl)-3,5,9,11-tetramethyl-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-4-yl (3-methyl)-butanoate (279). To a solution of the diastereomeric aldol adducts **278 + isomers** (11 mg, 16.9 μmol) in THF (1 mL) at 0 °C was added buffered pyridinium hydrofluoride (0.25 mL) (stock solution prepared from dry THF (10 mL), pyridine (5 mL) and 30% pyridinium hydrofluoride (2.1 g)). The resulting solution was warmed to ambient temperature and stirred for 45 minutes then diluted with Et_2O (10 mL) and washed with saturated aqueous $CuSO_4$ (3 x 2 mL), saturated aqueous $NaHCO_3$ (2 x 2 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (20% Et_2O/CH_2Cl_2, on buffered silica) to give the separated diastereomers (total mass, 9.8 mg, 99%) as

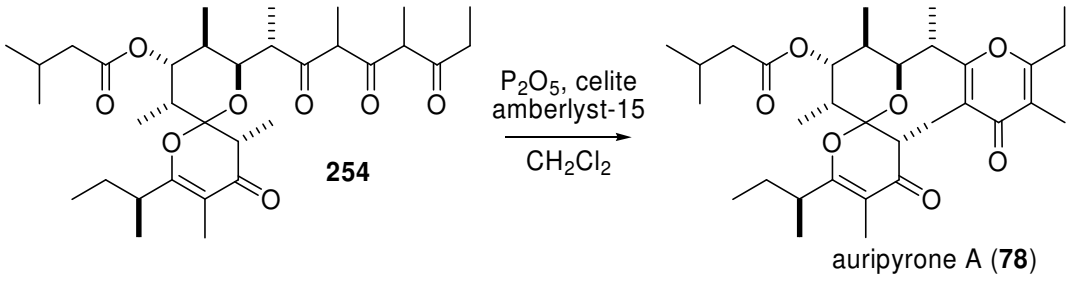
colourless oils. The data below is for the major diastereomer **279**. $\mathbf{R}_f$ = 0.26 (20% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +76.9 (*c* 0.4, CH_2Cl_2); **IR** (CH_2Cl_2, FT, film): 3505, 1734, 1670, 1620, 1459, 1388, 1373, 1346, 1294, 1254, 1212, 1166, 1120, 1094, 1058, 1009, 986, 964, 918 cm^{-1}; **^{1}H NMR** (600 MHz, C_6D_6) δ 4.96 (1H, t, 3.6 Hz, C*H*OC=OCH_2CH(CH_3)$_2$), 4.15 (1H, br s, CH(O-)CH(CH_3)C*H*OH), 3.98 (1H, dd, 10.2, 1.8 Hz, C*H*(O-)CH(CH_3)CHOH), 3.77 (1H, br m, C*H*(OH)CH_2CH_3), 2.81 (1H, br s, O*H*), 2.63 (1H, qd, 7.2, 4.2 Hz, CH(O-)CH(CH_3)CH(OH)C*H*(CH_3)C=O), 2.53-2.43 (3H, m, CH(OH)C*H*(CH_3)CH_2CH_3, CH_3CH_2C*H*(CH_3)C, O*H*), 2.39 (1H, q, 6.6 Hz, C(O_2)C*H*(CH_3)C=O), 2.24-2.16 (3H, m, C*H*$_2$CH(CH_3)$_2$, C*H*(CH_3)$_2$), 1.95-1.84 (3H, m, $CH_3CH_AH_BCH(CH_3)C$, CH(OC=O)C*H*(CH_3)C(O_2), C*H*(CH_3)CH(O-)CH(CH_3)CHOH), 1.84 (3H, s, C=C(C*H*$_3$)C=O), 1.61-1.55 (1H, m, $CH_3CH_AH_BCH(CH_3)C$), 1.55-1.50 (1H, m, CH(O-)C*H*(CH_3)CHOH), 1.49-1.43 (1H, m, $CH_3CH_AH_BOH$), 1.37-1.31 (1H, m, $CH_3CH_AH_BOH$), 1.14 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH(OH)CH_2CH_3), 1.08 (3H, d, 6.6 Hz, C(O_2)CH(C*H*$_3$)C=O), 1.07 (3H, d, 6.6 Hz, CH_3CH_2CH(C*H*$_3$)C), 1.03 (3H, d, 7.2 Hz, CH(O-)CH(CH_3)CH(OH)CH(C*H*$_3$)C=O), 0.99 (3H, t, 7.2 Hz, C*H*$_3CH_2OH$), 0.94 (3H, t, 7.2 Hz, C*H*$_3CH_2$CH(CH_3)C), 0.92 (3H, d, 6.0 Hz, CH(C*H*$_3$)CH_3), 0.91 (3H, d, 6.0 Hz, CH(CH_3)C*H*$_3$), 0.80 (3H, d, 6.6 Hz, CH(OC=O)CH(C*H*$_3$)C(O_2), 0.76 (3H, d, 6.6 Hz, CH(O-)CH(C*H*$_3$)CHOH), 0.76 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH(O-)CH(CH_3)CHOH); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 220.2, 194.0, 172.1, 168.4, 107.5, 105.5, 75.2, 73.8, 70.3, 68.8, 50.5, 49.6, 44.5, 44.0, 38.2, 37.9, 34.1, 32.0, 27.6, 27.1, 26.3, 22.5, 22.4, 16.6, 12.4, 12.0, 11.0, 10.9, 10.7, 9.9, 9.8, 9.3, 7.9; **HRESIMS** calculated for $C_{33}H_{56}O_8Na^+$ $[M+Na]^+$: 603.3867; found 603.3863; **EIMS** *m/z* (%): 197 (52), 168 (9), 139 (14), 109 (15), 85 (24), 57 (100).



279 **254**

(2*R*-(1*R*),3*S*,4*R*,5*R*,8-(1*S*),11*R*)-8-(1-methylpropyl)-2-(1,3,5-trimethyl-2,4,6-trioxo-octyl)-3,5,9,11-tetramethyl-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-4-yl (3-

methyl)-butanoate (254). Oxidation was performed according to the procedure of Dess and Martin.[22] To a solution of the diol **279 + isomers** (14.0 mg, 24.1 μmol) in CH_2Cl_2 (500 μL) at room temperature was added Dess-Martin Periodinane (41 mg, 96.4 μmol) and the resulting white suspension was stirred at ambient temperature for 1 hour. The reaction was diluted with Et_2O (15 mL) and quenched with the addition of a solution of $Na_2S_2O_3$ (164 mg) in saturated aqueous $NaHCO_3$ (2 mL). After stirring for several minutes the layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine (5 mL each), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% Et_2O/CH_2Cl_2) gave the tri-ketone as a mixture of keto-enol forms **254** (12.1 mg, 87%) as a clear oil. $\mathbf{R_f}$ = 0.44 (10% Et_2O/CH_2Cl_2); **^{1}H NMR** (300 MHz, C_6D_6) δ 4.98-4.92 (1H, m, C*H*OC=O$CH_2CH(CH_3)_2$), 4.15-3.88 (3H, m, C*H*(CH_3)C=O x 2, C*H*(O-)$CH(CH_3)$C=O), 2.68-2.08 (8H, m, CH_3CH_2C=O, CH_3CH_2C*H*(CH_3)C, C(=O)C*H*$_2CH(CH_3)_2$, C*H*$(CH_3)_2$, C(O_2)C*H*(CH_3)C=O, CH(O-)C*H*(CH_3)C=O), 1.99-1.72 (3H, m, C=C(C*H*$_3$)C=O), 1.68-1.22 (4H, m, CH_3C*H*$_2CH(CH_3)$C, CH(OC=O)C*H*(CH_3)CHO-, CH(OC=O)C*H*$(CH_3)C(O_2)$, 1.19-0.54 (33H, C*H*$_3CH_2$C=O, CH(C*H*$_3$)C=O x 2, CH(O-)CH(C*H*$_3$)C=O, CH(OC=O)CH(C*H*$_3$)CHO-, CH(OC=O)CH(C*H*$_3$)C(O_2), C(O_2)CH(C*H*$_3$)C=O, C*H*$_3CH_2CH(CH_3)$C, CH_3CH_2CH(C*H*$_3$)C, CH(C*H*$_3$)CH_3, CH(CH_3)C*H*$_3$); **HRESIMS** calculated for $C_{33}H_{52}O_8Na^+$ $[M+Na]^+$: 599.3554; found 599.3553; **EIMS** *m/z* (%): 576 (M^+, 6), 475 (4), 379 (12), 279 (22), 197 (37), 193 (45), 168 (11), 141 (11), 137 (18), 109 (16), 85 (21), 83 (14), 57 (100), 55 (11).



Auripyrone A (78). Pyrone formation was performed by modification of the procedure of Jeffery and Perkins.[39] To a solution of the tri-ketone **254** (20.0 mg, 34.7

μmol) in CH_2Cl_2 (1.3 mL) at −50 °C was added Amberlyst-15 resin (10 mg) and the resulting mixture was stirred for five minutes. Meanwhile, a mixture of P_2O_5 (20 mg, 139 μmol) and celite (60 mg) was stirred to homogeneity at ambient temperature. The cold bath was removed from the reaction mixture and the P_2O_5/celite was added in one portion. The resulting suspension was stirred at ambient temperature for 24 hours before being filtered through a plug of celite with rinsing (MeOH). The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (50% Et_2O/CH_2Cl_2, on buffered silica) to give auripyrone A (**78**) (4.0 mg, 39% based on 9.0 mg of recovered starting material) as a white solid. **m.p.** 171-173 °C (lit. 172-176 °C)[40]; $\mathbf{R}_f$ = 0.27 (50% Et_2O/CH_2Cl_2); $\mathbf{[\alpha]^{20}_D}$ = +33.3 (*c* 0.2, $CHCl_3$) (lit. +28)[40]; **IR** ($CHCl_3$, FT, film): 1729, 1656, 1626, 1618, 1459, 1419, 1386, 1374, 1291, 1251, 1166, 1091, 1058, 1010, 984, 963, 919 cm^{-1}; **UV/Vis** (MeOH) λ_{max} 260 (ε 18,200), 220 (ε 10,100) nm; **^{1}H NMR** (600 MHz, C_6D_6) δ 4.92 (1H, t, 3.3 Hz, C*H*OC=OCH_2CH(CH_3)$_2$), 3.98 (1H, dd, 10.2, 2.1 Hz, C*H*(O-)CH(CH_3)C(O-)=C), 2.76 (1H, dq, 10.2, 7.2 Hz, CH(O-)C*H*(CH_3)C(O-)=C), 2.32 (1H, q, 6.6 Hz, C(O_2)C*H*(CH_3)C=O), 2.31 (1H, dq, 15.0, 7.5 Hz, CCH_AH$_B$$CH_3$), 2.26 (1H, dqd, 7.2, 7.2, 3.6 Hz, CH_3CH_2C*H*(CH_3)C), 2.21-2.16 (1H, m, C*H*(CH_3)$_2$), 2.18-2.11 (2H, m, CH_2CH(CH_3)$_2$), 2.10 (1H, dq, 15.0, 7.5 Hz, CCH$_A$$H_B$$CH_3$), 2.03 (3H, s, CH($CH_3$)C(O-)=C(C*H*$_3$)C=O), 1.98 (3H, s, CH_3CH_2C(O-)=C(C*H*$_3$)C=O), 1.85 (1H, qd, 7.2, 3.6 Hz, CHC*H*(CH_3)C(O_2)), 1.83-1.80 (1H, m, C*H*(CH_3)CH(O-)CH(CH_3)C), 1.64 (3H, s, CH(CH_3)C(O-)=C(C*H*$_3$)=O), 1.56-1.48 (1H, m, CH_3CH_AH$_B$CH(CH_3)C), 1.41-1.34 (1H, m, CH_3CH$_A$$H_B$CH($CH_3$)C), 1.12 (3H, d, 6.6 Hz, C(O_2)CH(C*H*$_3$)C=O), 0.99 (3H, d, 7.2 Hz, CH_3CH_2CH(C*H*$_3$)C), 0.91 (3H, d, 6.0 Hz, CH(C*H*$_3$)CH_3), 0.90 (3H, d, 6.6 Hz, CH(CH_3)C*H*$_3$), 0.90 (3H, t, 7.5 Hz, CCH_2C*H*$_3$), 0.84 (3H, t, 7.5 Hz, C*H*$_3$$CH_2$CH), 0.78 (3H, d, 7.2 Hz, CHCH(C*H*$_3$)C(O_2)), 0.74 (3H, d, 7.2 Hz, CH(O-)CH(C*H*$_3$)C(O-)=C), 0.65 (3H, d, 7.2 Hz, CH(C*H*$_3$)CH(O-)CH(CH_3)C); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.8, 178.5, 172.0, 166.2, 162.1, 161.6, 121.3, 118.1, 107.8, 105.0, 75.2, 70.6, 44.5, 44.0, 37.2, 36.7, 34.1, 31.7, 26.4, 26.3, 24.7, 22.5, 22.3, 16.0, 12.1, 12.0, 11.9, 11.0, 10.7, 9.7, 9.5, 8.9, 8.1; **HRESIMS** calculated for $C_{33}H_{50}O_7Na^+$ $[M+Na]^+$: 581.3449; found 581.3448; **EIMS** *m/z* (%): 558 (M^+, 43), 501 (9), 457 (11), 391 (6), 317 (20), 261 (12), 221 (31), 193 (100), 180 (43), 151 (11), 137 (18), 85 (17), 83 (22), 57 (68), 55 (15).

5.5 References

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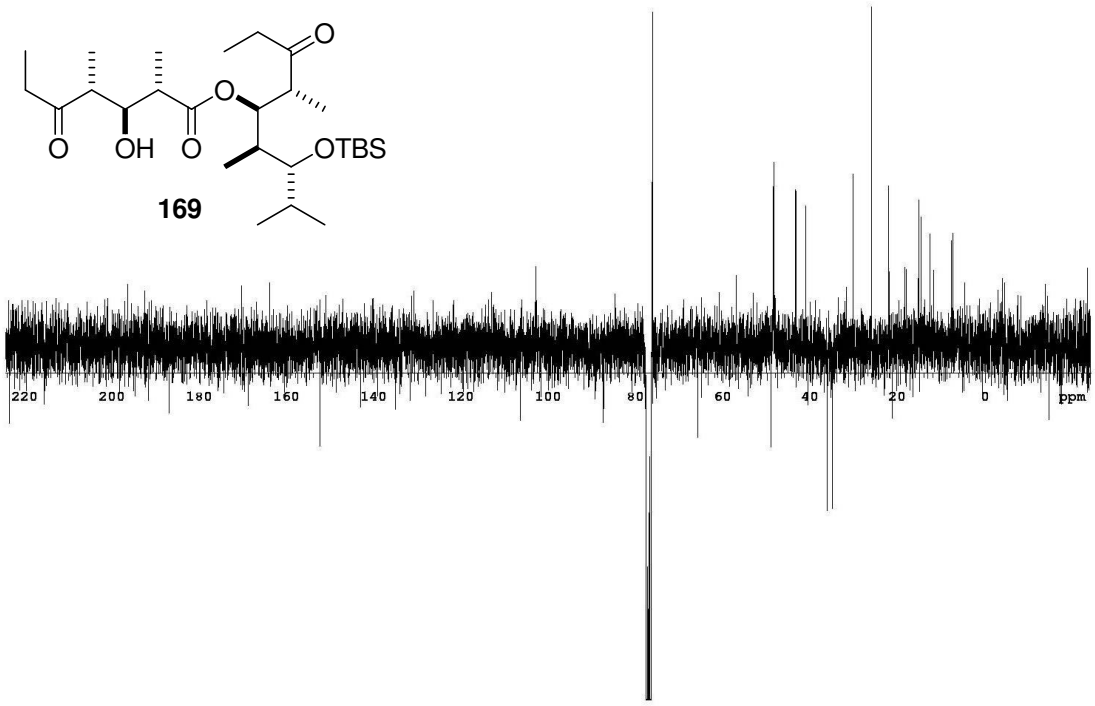
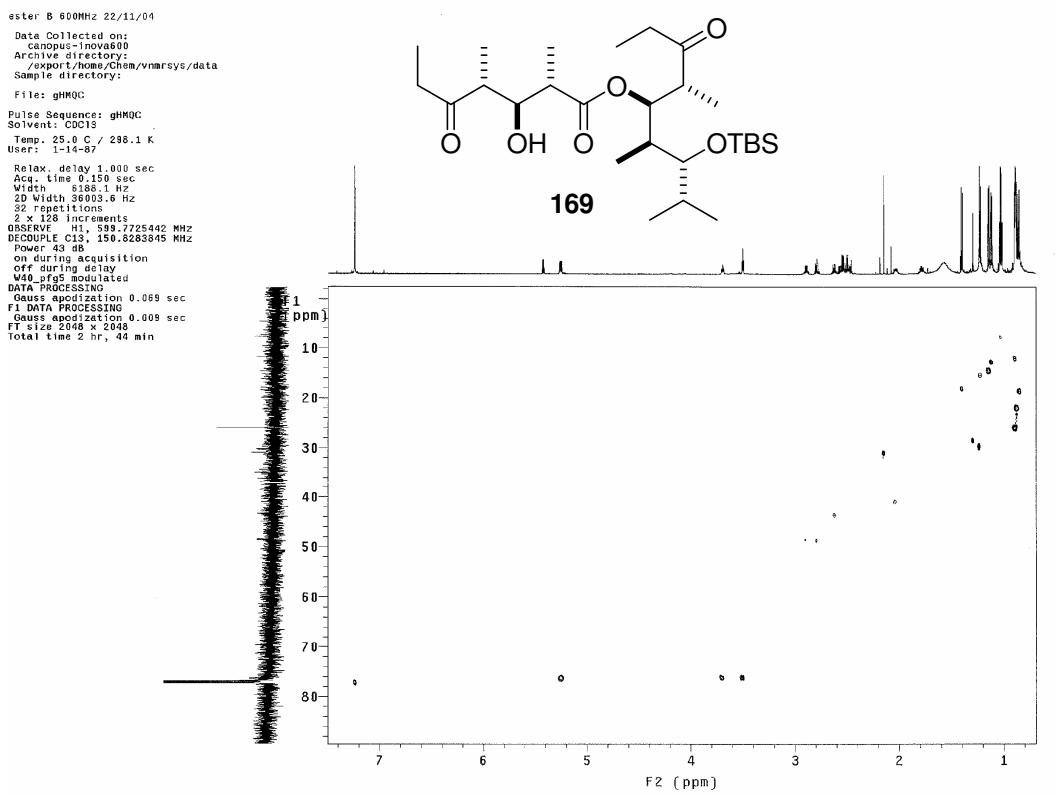
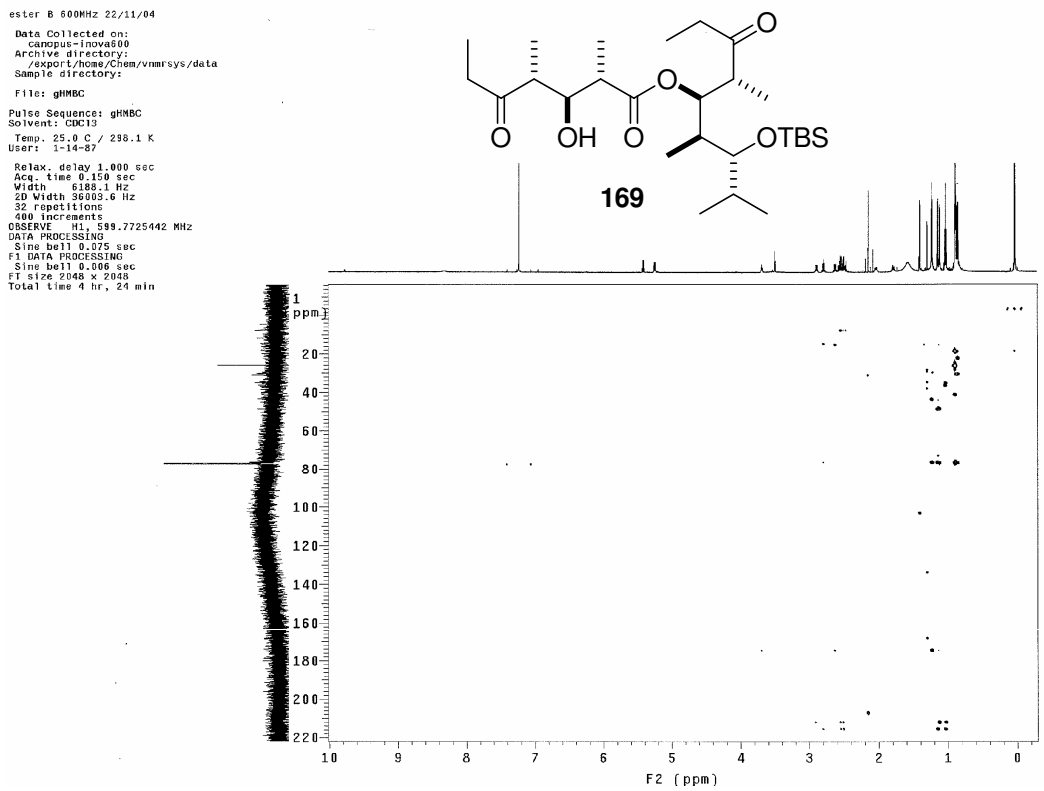


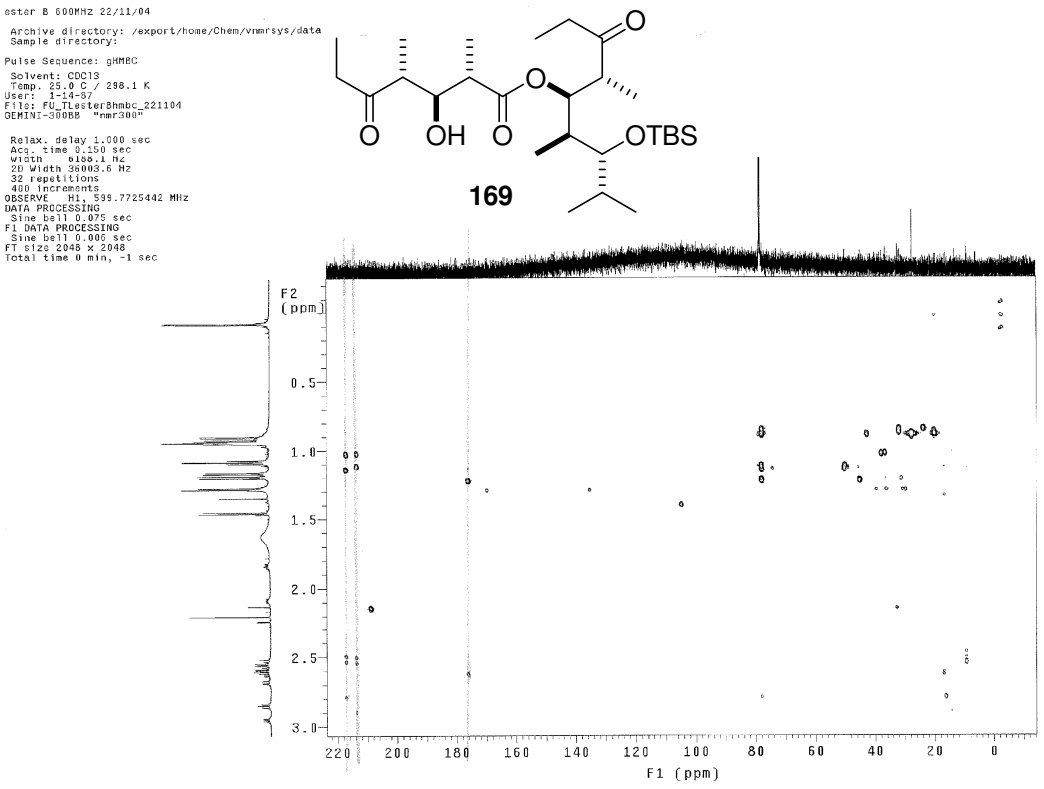
*75.5 MHz ^{13}C APT spectrum of ester (**169**).*



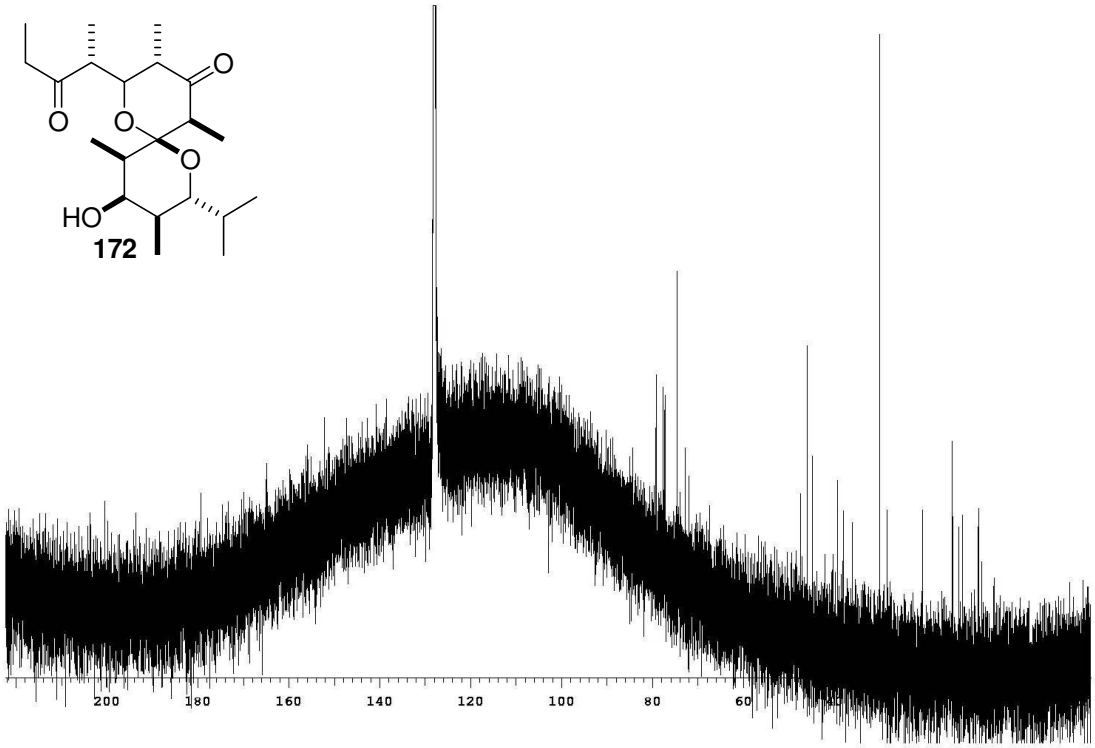
*600 MHz gHMQC spectrum of ester (**169**).*



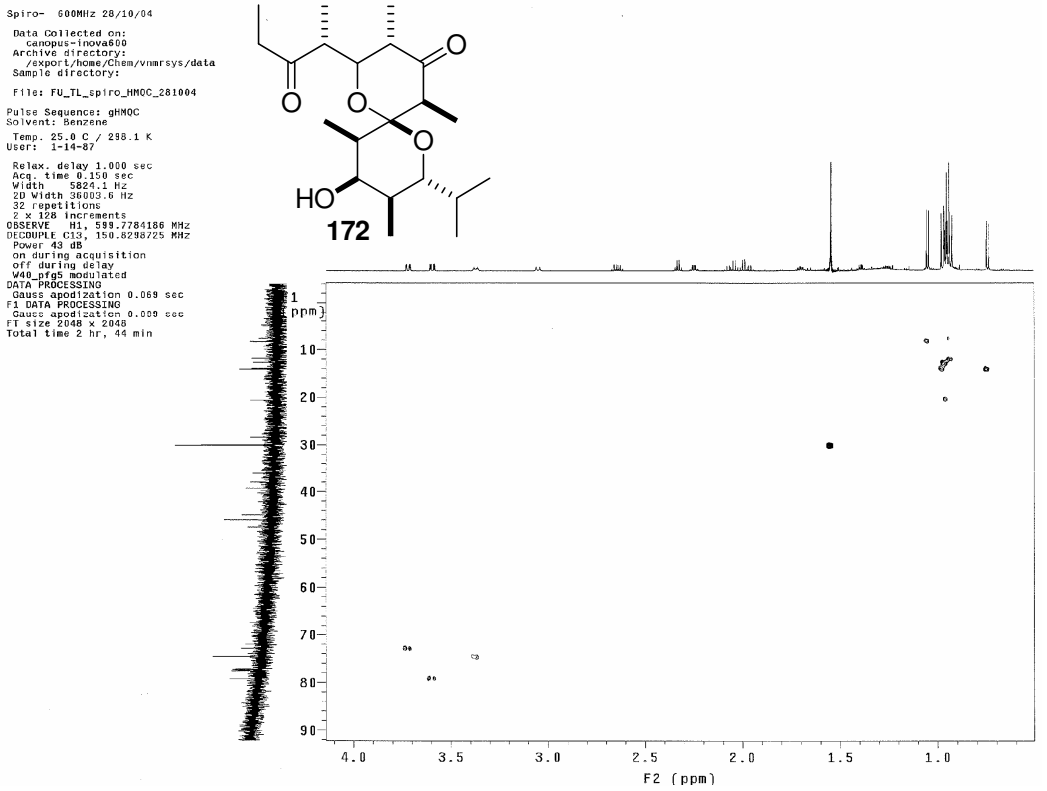
*600 MHz gHMBC spectrum of ester (**169**).*



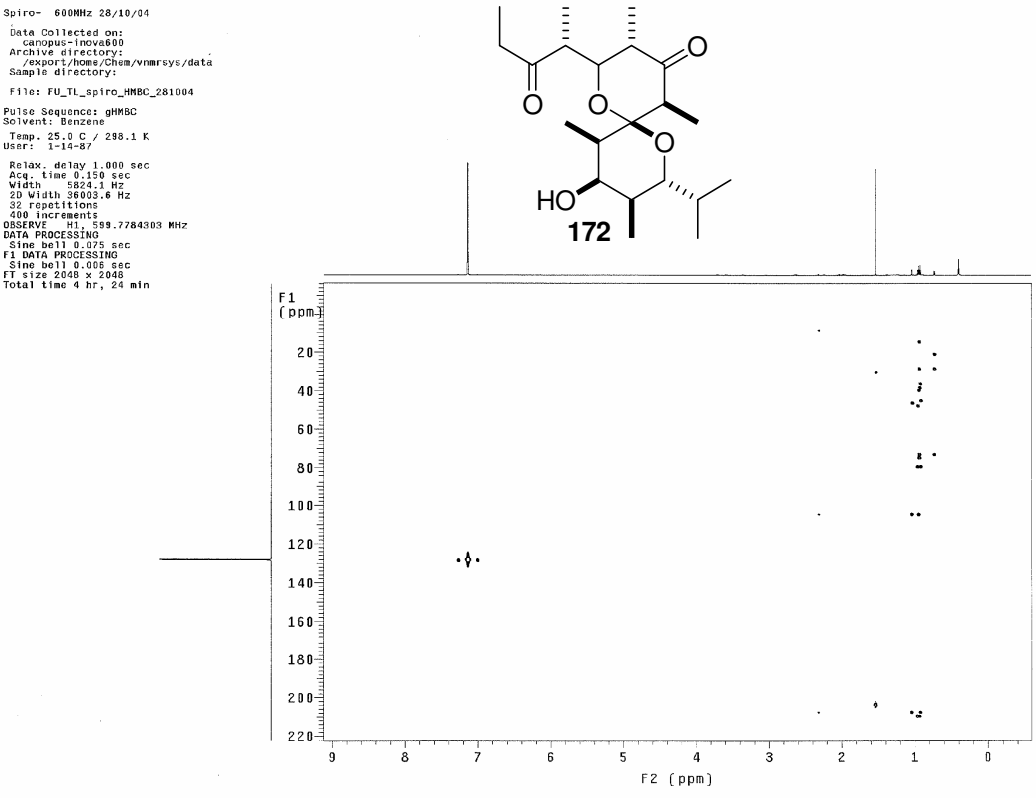
*600 MHz gHMBC spectrum of ester (**169**).*



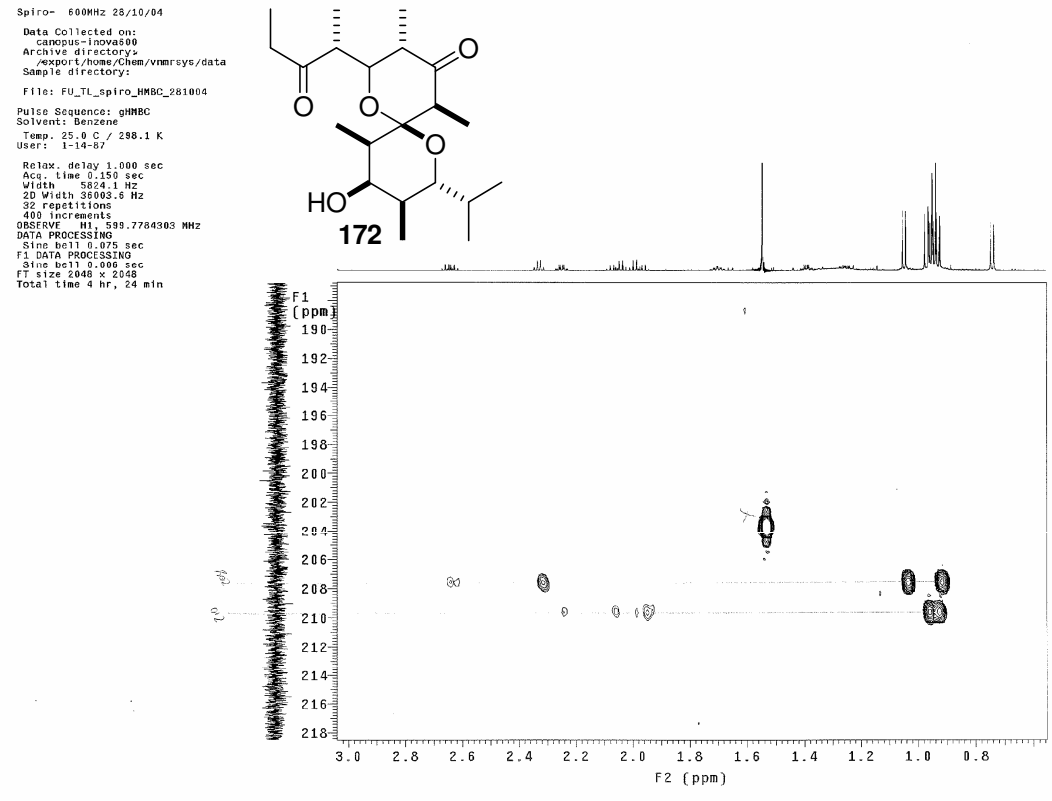
*151 MHz ^{13}C NMR spectrum of spiroacetal (**172**).*



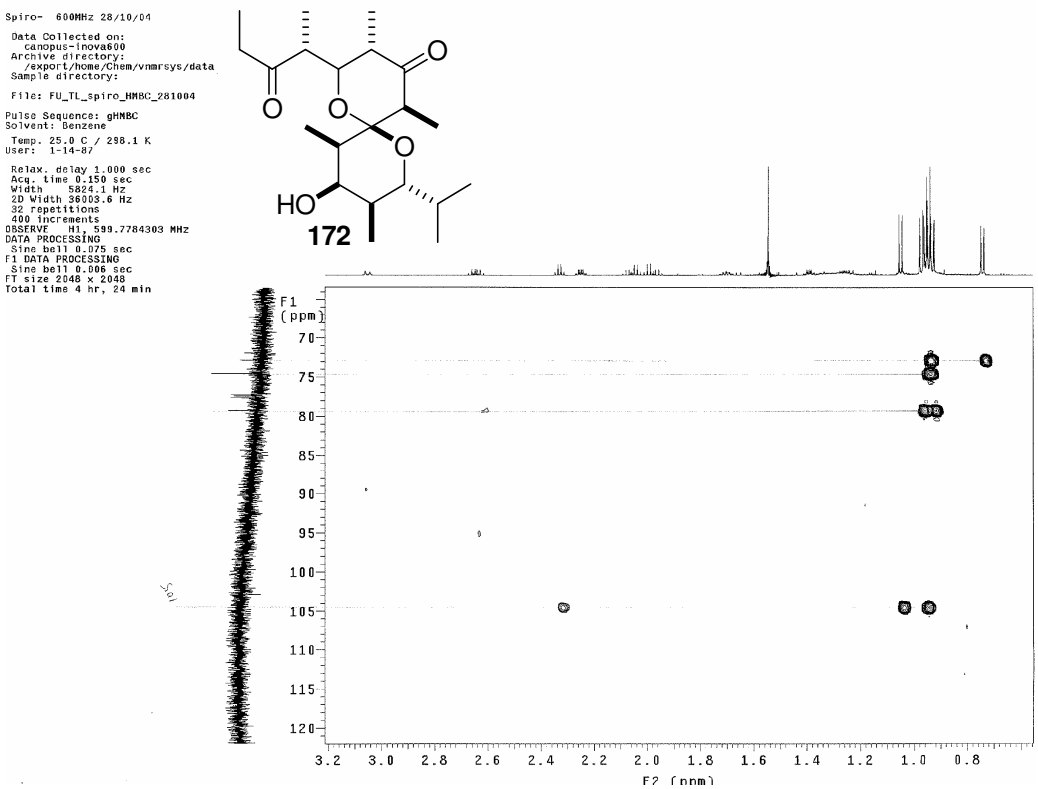
*600 MHz gHMQC spectrum of spiroacetal (**172**).*



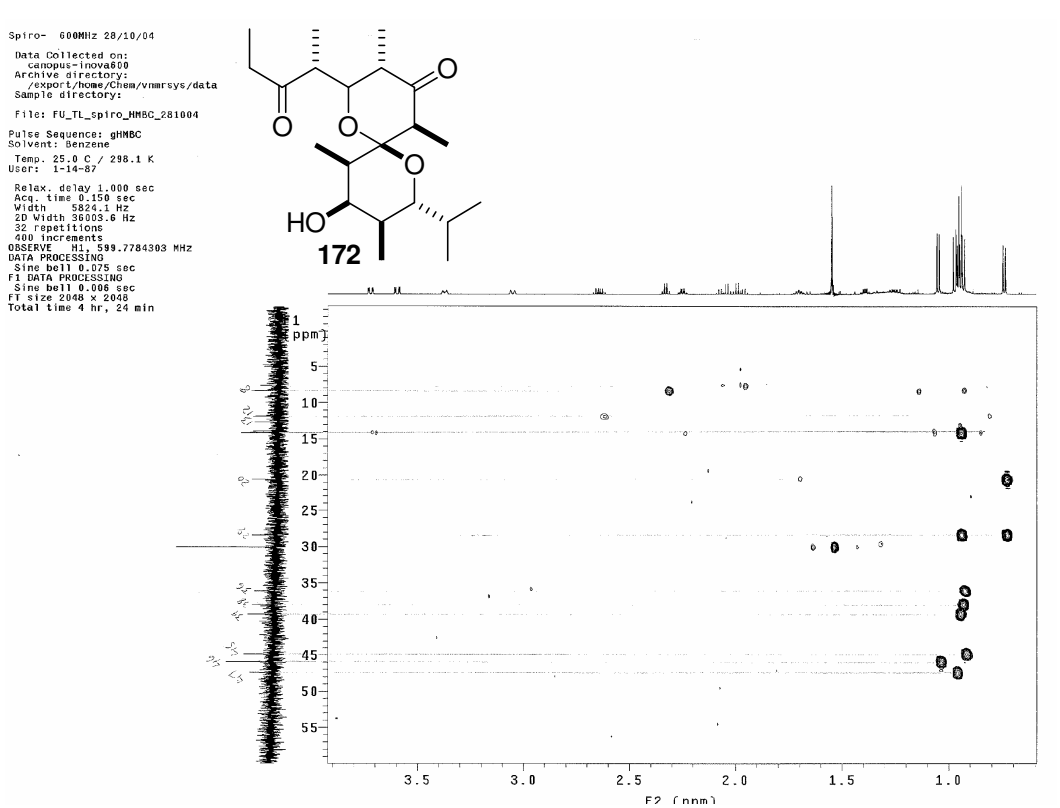
*600 MHz gHMBC spectrum of spiroacetal (**172**).*



*600 MHz gHMBC spectrum of spiroacetal (**172**).*



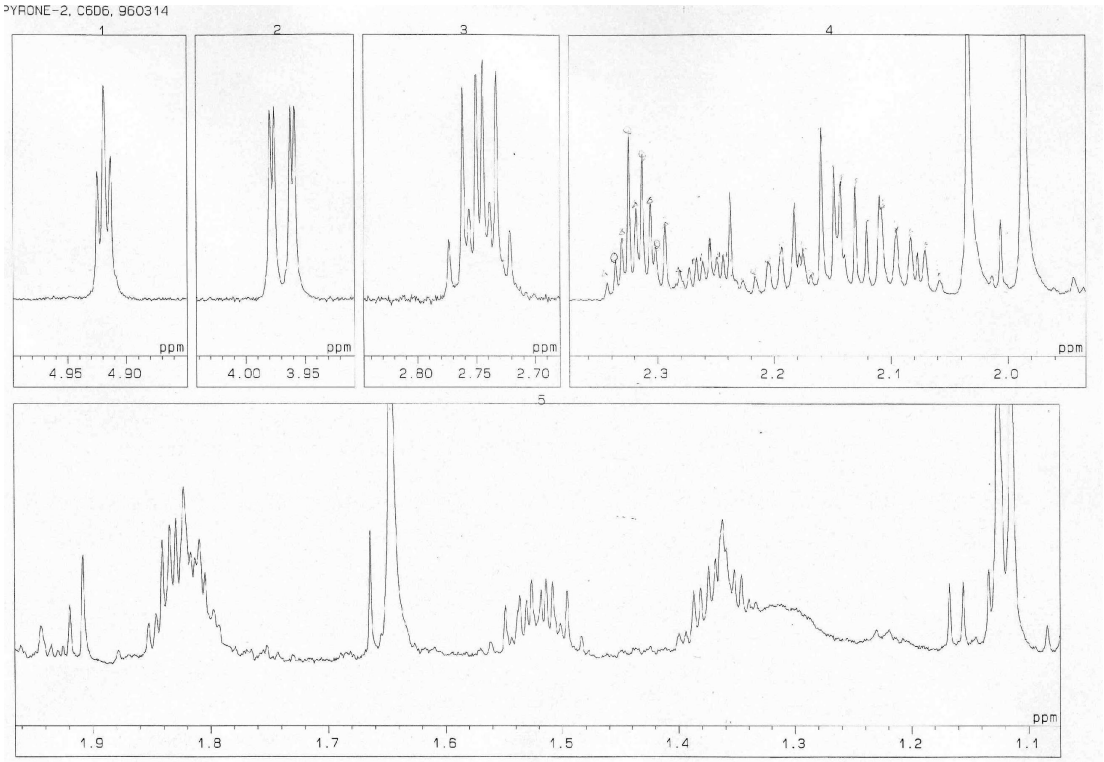
*600 MHz gHMBC spectrum of spiroacetal (**172**).*



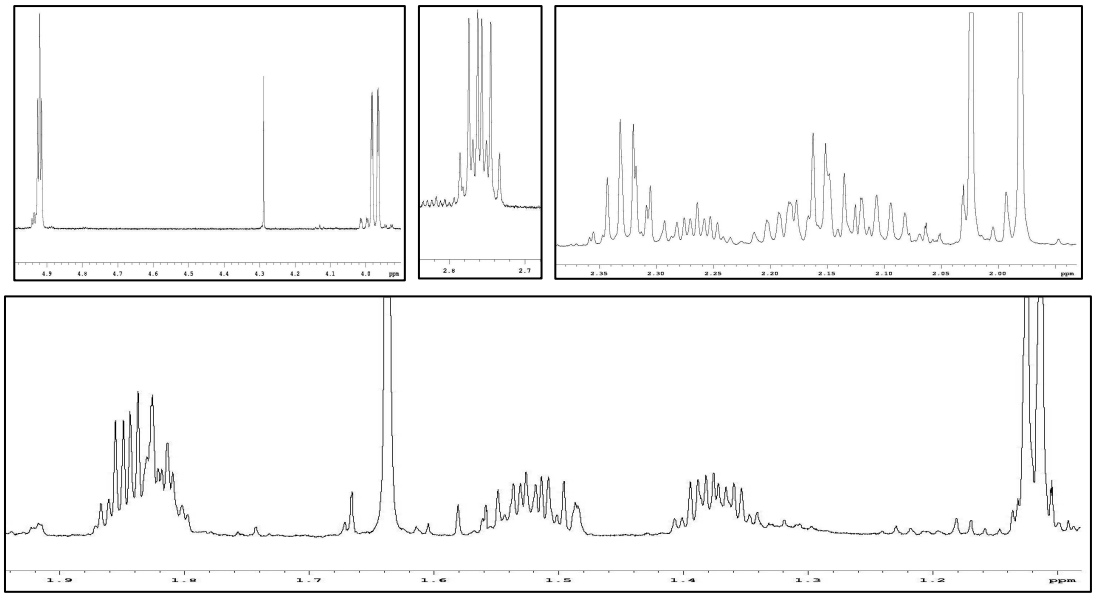
*600 MHz gHMBC spectrum of spiroacetal (**172**).*

	Authentic auripyrone A		Synthetic auripyrone A	
C	δ^1H^a m ^3J (Hz)[a]	$\delta\ ^{13}C^a$	δ^1H^b m ^3J (Hz)[d]	$\delta\ ^{13}C^c$
1	0.89 t (7.3)	11.0	0.90 t (7.5)	11.0
2a	2.31 dq (15.0, 7.3)	24.7	2.31 dq (15.0, 7.5)	24.7
2b	2.09 dq (15.0, 7.3)		2.10 dq (15.0, 7.5)	
3		162.0		162.1
4		118.1		118.1
5		178.4		178.5
6		121.3		121.3
7		161.5		161.6
8	2.75 dq (10.2, 7.0)	36.7	2.76 dq (10.2, 7.2)	36.7
9	3.98 dd (10.2, 2.2)	70.5	3.98 dd (10.2, 2.1)	70.6
10	1.81 m	34.1	1.83-1.80 m	34.1
11	4.92 dd (3.3, 3.3)	75.2	4.92 dd (3.3, 3.3)	75.2
12	1.83 m	31.7	1.85 qd (7.2, 3.6)	31.7
13		105.0		105.0
14	2.32 q (7.0)	44.5	2.32 q (6.6)	44.5
15		191.7		191.8
16		107.8		107.8
17		166.2		166.2
18	2.26 dqd (6.6, 6.6, 3.7)	37.2	2.26 dqd (7.2, 7.2, 3.6)	37.2
19a	1.52 m	26.3	1.56-1.48 m	26.3
19b	1.36 m		1.41-1.34 m	
20	0.84 t (7.3)	12.0	0.84 t (7.5)	12.0
21	1.99 s	9.7	1.98 s	9.7
22	2.03 s	10.7	2.03 s	10.7
23	0.73 d (7.0)	12.1	0.74 d (7.2)	12.1
24	0.63 d (7.0)	9.5	0.65 d (7.2)	9.5
25	0.77 d (7.0)	11.9	0.78 d (7.2)	11.9
26	1.12 d (7.0)	8.1	1.12 d (6.6)	8.1
27	1.65 s	9.0	1.64 s	8.9
28	0.99 d (6.6)	16.0	0.99 d (7.2)	16.0
1`		172.0		172.0
2`	2.18-2.10 m	44.0	2.18-2.11 m	44.0
3`	2.19 m	26.4	2.21-2.16 m	26.4
4`	0.91 d (6.2)	22.3	0.91 d (6.0)	22.5
5`	0.90 d (6.6)	22.3	0.90 d (6.6)	22.3

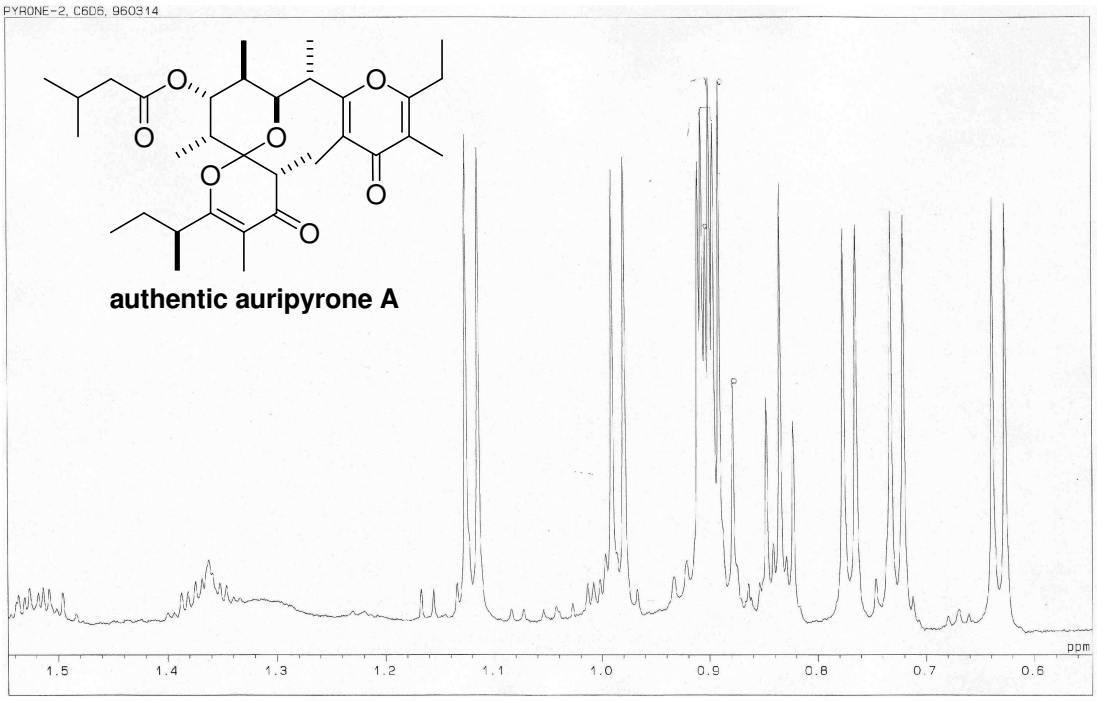
[a] Chemical shifts and coupling constants as reported in ref 13 (Chapter 4). [b] Recorded at 600 MHz (Varian Inova). Referenced to C_6HD_5 at δ 7.16. [c] Recorded at 151.1 MHz (Varian Inova). Referenced to C_6D_6 at δ 128.0. [d] Chemical shifts in ppm.



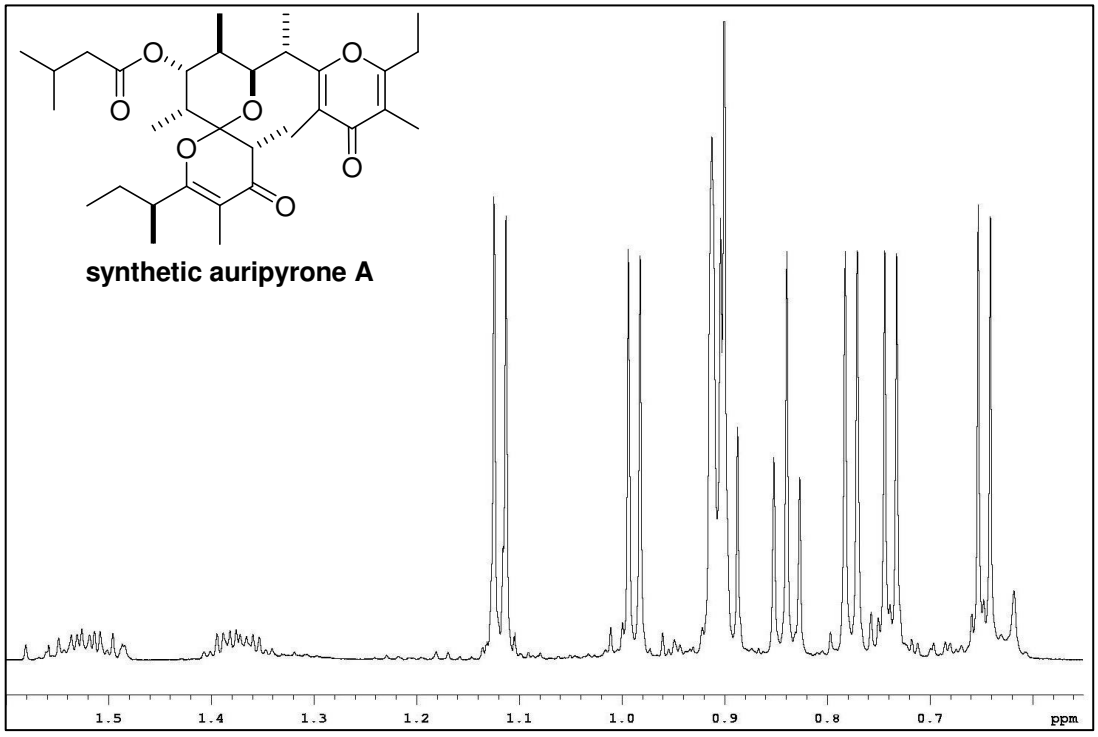
Expansions of ^{1}H NMR spectrum of authentic auripyrone A.



Expansions of ^{1}H NMR spectrum of synthetic auripyrone A.



Expansions of ^{1}H NMR spectrum of authentic auripyrone A.



Expansions of ^{1}H NMR spectrum of synthetic auripyrone A.

Publications

The list below represents publications that have resulted from research outlined in this thesis. The following pages of this appendix present reprints and/or preprints of the listed publications.

1. Total Synthesis of a Hemiacetal Polypropionate from Siphonaria australis.
   Lister, T.; Perkins, M.V. *Aust. J. Chem.* **2004**, 57(8), 787-797.

2. Total Synthesis of Auripyrone A
   Lister, T.; Perkins, M.V. *Agnew. Chem. Int. Ed.* **2006**, 45(16), 2560-2564.

3. A retro-Claisen Approach to Dolabriferol
   Lister, T.; Perkins, M.V. *Org. Lett.* **2006**, 8(9), 1827-1830.