Biomimetic Approaches to the Synthesis of Polyketide Derived Marine Natural Products; (-)-Maurenone and the Spiculoic Acids

A Thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

Julia S. Crossman

B.Sc. (Hons), B.Tech. (Forensic and Analytical Chemistry)

at

Flinders University

The Faculty of Science and Engineering

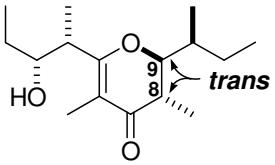
School of Chemistry, Physics and Earth Sciences

September 2007

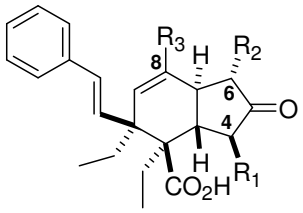
Contents

Abstract

This thesis describes the total synthesis of the polyketide derived marine natural product (-)-maurenone (**14**) and synthetic studies of a model system for the marine polyketides, the spiculoic acids (**20, 22-24**). A biomimetic approach involving cyclisation of linear polyketide precursors to install the complex chemical frameworks was employed.

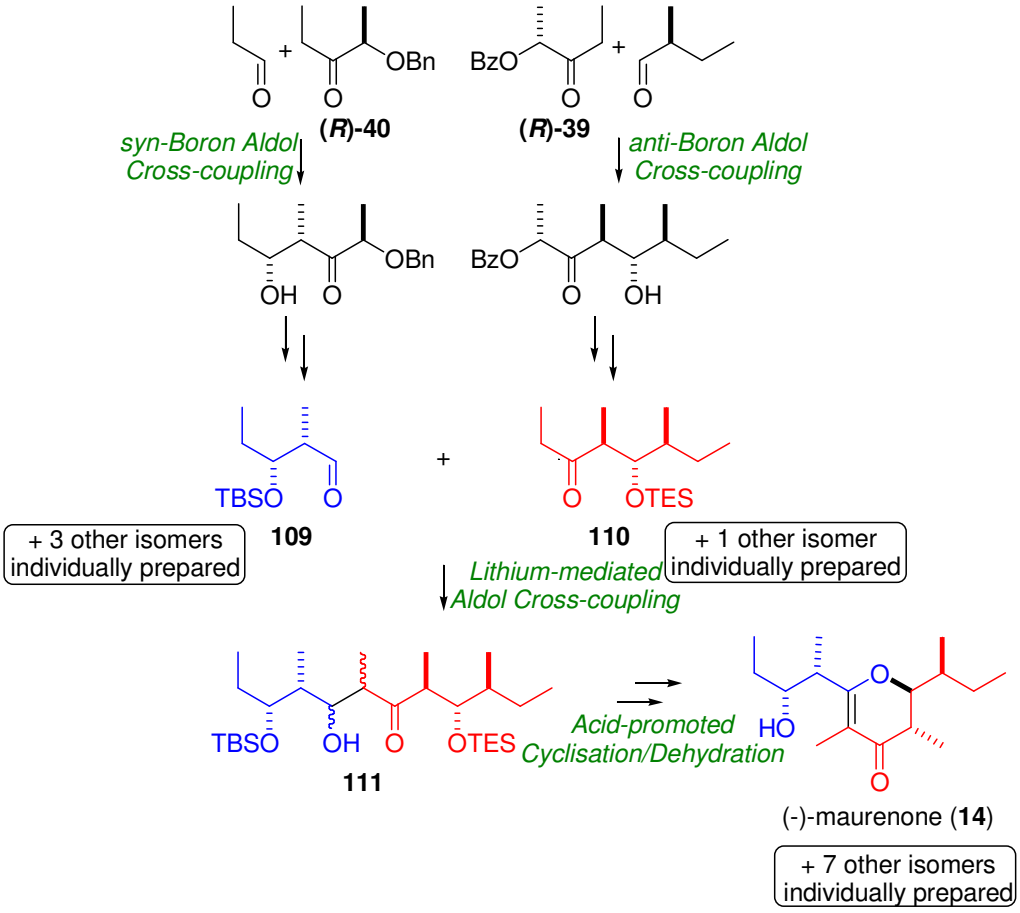


(-)-maurenone **(14)**

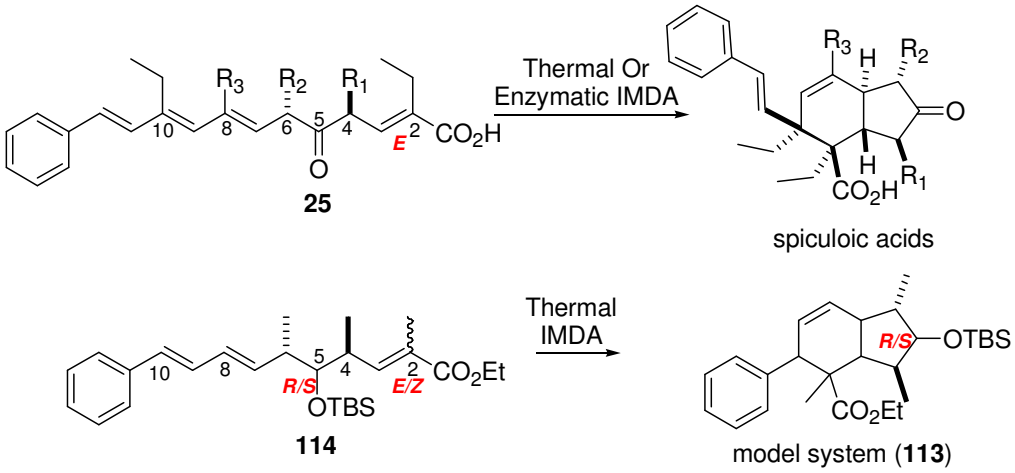


spiculoic acid A (**20**), R_1 = Et, R_2 = Me, R_3 = Et
isospiculoic acid A (**22**), R_1 = Me, R_2 = Et, R_3 = Et
nor-spiculoic acid A (**23**), R_1 = Me, R_2 = Et, R_3 = Me
dinor-spiculoic acid A (**24**), R_1 = Me, R_2 = Me, R_3 = Me

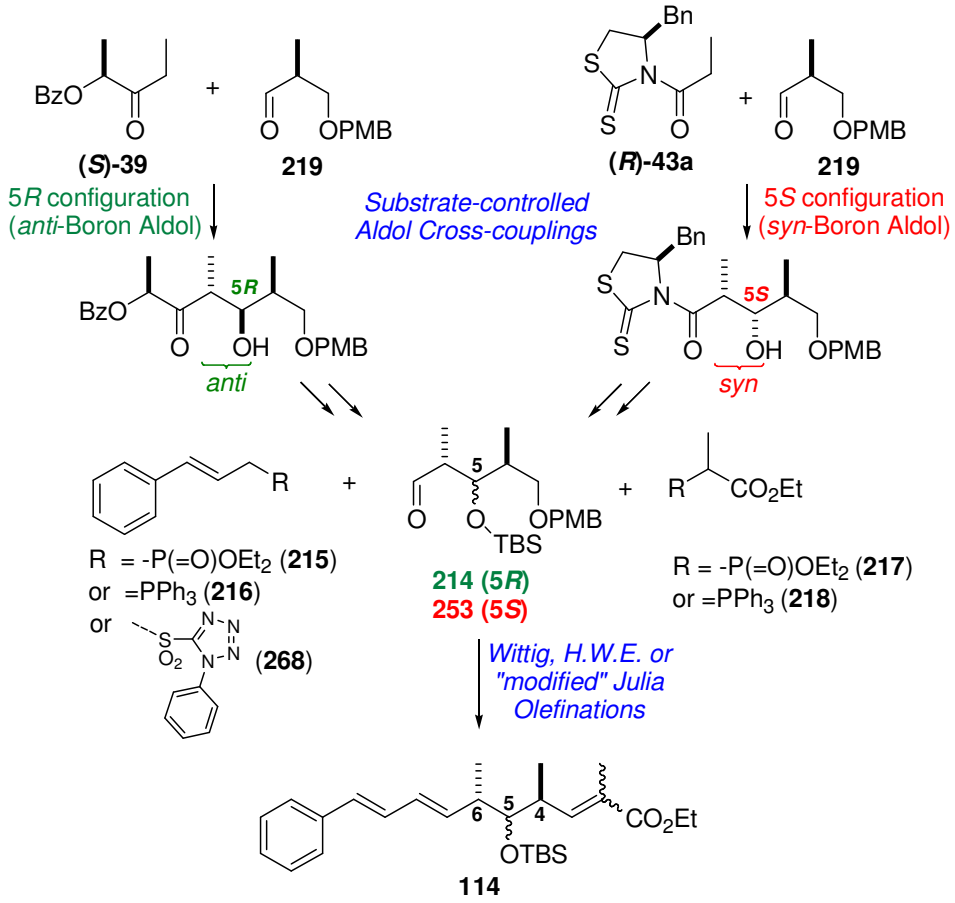
Maurenone is a polypropionate derived metabolite isolated from pulmonate molluscs collected off the coast of Costa Rica. While structural assignment following isolation revealed a relatively uncommon tetra-substituted dihydropyrone moiety the only stereochemical information deduced was the *trans*-relative relationship between the C8 and C9 protons. The total synthesis of a series of eight stereoisomeric putative structures was achieved in order to assign the stereochemistry of (-)-maurenone (**14**), as that depicted above. A time and cost efficient strategy was developed utilising common intermediates providing access to the eight stereoisomeric structures in a convergent manner. Six key fragments, four aldehydes (**109**) and two ketones (**110**), were synthesised using highly diastereoselective *syn*- and *anti*-boron aldol reactions and were coupled using a lithium-mediated aldol reaction. Trifluoroacetic acid-promoted cyclisation/dehydration enabled installation the γ-dihydropyrone ring. All eight isomers of one enantiomeric series were synthesised by coupling two ketones with each of four aldehydes. By comparison of the NMR data for the eight isomers with that reported for the natural product, the relative stereochemistry was established as shown. The (-)-enantiomer of maurenone was synthesised in nine linear steps (13 % overall yield) from (*R*)-2-benzylpentan-3-one ((***R*)-40**) and (*R*)-2-benzoyloxypentan-3-one ((***R*)-39**).



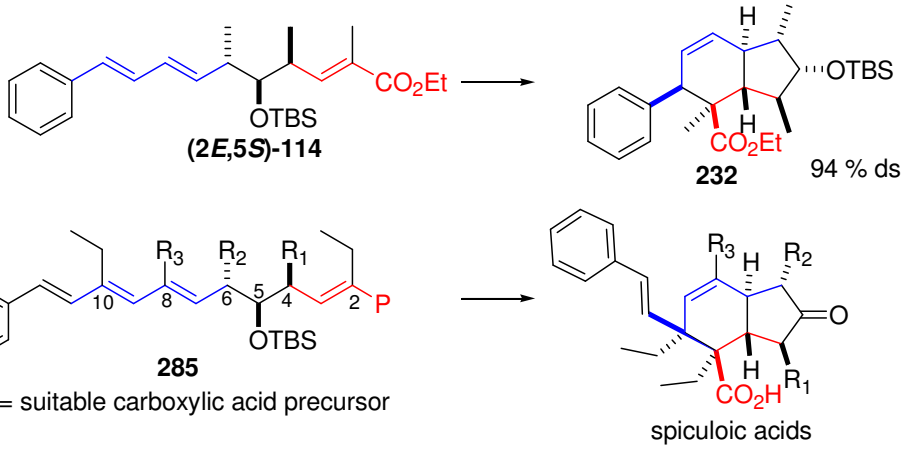
The spiculoic acid family of polyketide derived natural products, isolated from *plakortis* sponges, possess a unique [4.3.0]-bicyclic core which is proposed to be formed *via* an enzyme catalysed Intramolecular Diels-Alder (IMDA) cycloaddition reaction of linear polyene precursors **25**. Model linear precursors (**114**), possessing various olefin geometries at C2 and both stereochemical orientations of the C5 stereocentre, were synthesised in order to examine stereoselectivity of the thermally induced IMDA cycloaddition reaction.



The two alternative C4-C6 stereotriads of the linear precursors **114** were achieved by employing highly diastereoselective substrate-controlled aldol reactions; an *anti*-boron aldol reaction, controlled by the facial preference of (*R*)-2-benzoyloxypentan-3-one ((***R*)-39**), and a *syn*-titanium aldol reaction, under the control of chiral N-acylthiazolidinethione ((***R*)-43a**). The diene and dienophile moieties were installed using either standard Wittig, H.W.E. or "modified" Julia olefination reactions.



A thorough stereochemical assignment of the cycloadducts of the thermally induced IMDA reaction of each linear precursor was accomplished employing 2D NMR techniques. Comparison of the stereochemistry of each of the cycloadducts with the spiculoic acids revealed that the linear precursor **(2*E*,5*S*)-114** produced a cycloadduct **232** with stereochemistry analogous to the natural products in 94 % diastereoselectivity. Thus, a synthetic approach to the spiculoic acids *via* synthesis of a linear precursor **285** possessing a TBS ether at C5 in the *S* configuration was proposed. Unfortunately, problems encountered in the synthesis of the proposed linear precursors to the spiculoic acids ultimately prevented the total synthesis from being achieved.


CO2Et
OTBS
(2E,5S)-114
H
OTBS
H
CO2Et
232
94 % ds
R3
R2
R1
10
8
6
5
4
2
P
OTBS
285
P = suitable carboxylic acid precursor
R3
H
R2
O
H
R1
CO2H
spiculoic acids

Declaration

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

Julia S. Crossman

24th September, 2007

Acknowledgements

I would like to acknowledge the support and guidance provided by my supervisor, Dr. Michael Perkins, throughout my research projects. His advice, suggestions and unyielding enthusiasm were much appreciated, reigniting my passion in the wake of setbacks and keeping me focused on the targets.

The efforts of the academic and technical staff in the School of Chemistry, Physics and Earth Sciences at Flinders University in keeping the equipment in working order and laboratories stocked with chemicals and glassware cannot be overlooked. The staff of the chemical store deserve individual mention for placing extra orders when I required chemicals urgently. Dr. Martin Johnston and Mr. Phil Clements (University of Adelaide) also warrant special mention for their tireless efforts in maintaining the NMR spectrometers and for their assistance in acquiring the large numbers of spectra of all of my isomers!

The long and bumpy road towards a PhD would have been longer, bumpier and much less enjoyable without the support and friendship of my fellow students over the years. In particular thanks to my lab partners; Milena Kasprzyk, Helen Wray and Claire Gregg who made our lab an enjoyable place to come to work in each day. Thanks also to Rachel Brown, David Jeffery, Troy Lister, Eric Dennis, Simon Mathew, Dani Lyons and Jozef Hodel for their friendly faces, willingness to share chemicals, equipment and advice and for their idiosyncrasies which made the department an entertaining and unique place to work.

For financial support, I would like acknowledge the Australian Government for providing me with an Australian Postgraduate Award, the Australian Research Council for project funding and Flinders University for an Elaine Martin Fund Travel Scholarship.

Finally, I am indebted to my family and Damian for their endless love and support during this arduous journey. Their unwavering belief in my abilities kept me on track and helped me to survive the rollercoaster ride that is a PhD. Thank you for knowing intuitively when to provide distractions, laughs or a shoulder to cry on.

Publications and Presentations

The following is a list of publications that have resulted from research outlined in this thesis and presentations that were delivered at various symposia.

Publications

Total Synthesis and Structural Elucidation of (-)-Maurenone, Crossman, J.S. and Perkins, M.V. *Journal of Organic Chemistry* **2006**, 71 (1) 117-124.

Synthesis of a Model of the Spiculoic Acids by an Intramolecular Diels-Alder Reaction, Crossman, J.S. and Perkins, M.V. *Tetrahedron* **2008**, accepted for publication in a *Symposium in Print* on "Reseach in Natural Product Synthesis – A Vital and Dynamic Global Enterprise".

Presentations

Investigations of the Diels-Alder Reaction Towards the Synthesis of the Spiculoic Acids. Oral presentation delivered at the RACI Organic and Physical Chemistry Conference, Adelaide, S.A., January 2007.

Investigations of the Diels-Alder Reaction Towards the Synthesis of the Spiculoic Acids. Poster presentation delivered at the ICOB-5 and ISCNP IUPAC International Conference on Biodiversity and Natural Products, Kyoto, Japan, July 2006.

Total Synthesis and Structural Elucidation of (-)-Maurenone. Oral presentation delivered at the Adelaide Organic Synthesis Symposium, Adelaide, S.A., December 2005.

Total Synthesis and Structural Elucidation of (-)-Maurenone. Poster presentation delivered at the RACI Connect 2005 Conference, Sydney, N.S.W., July 2005.
(Awarded the IUPAC Poster Prize and the Geoffrey I. Feutrill Award for best student poster.)

Abbreviations

Δ	heat
AcCl	acetyl chloride
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
apt	apparent
9-BBN	9-borabicyclo[3.3.1]nonane
$BF_3.OEt_2$	boron trifluoride-diethyl ether complex
$BH_3.SMe_2$	borane-dimethyl sulfide complex
BHT	butylated hydroxytoluene
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	boiling point
Bn	benzyl
BT	benzothiazole-2-yl
Bu_2BOTf	dibutylboron triflate
^{n}BuLi	butyllithium
^{t}BuLi	*tert*-butyllithium
Bz	benzoyl
c	concentration (g/100 mL)
cat.	catalytic
CH_2Cl_2	dichloromethane
COSY	homonuclear COrrelation SpectroscopY
Cp_2ZrCl_2	bis(cyclopentadienyl)zirconium(IV) dichloride
m-CPBA	*meta*-chloroperbenzoic acid
CuBr.DMS	copper(1) bromide dimethylsulfide complex
δ	chemical shift
dba	dibenzylidineacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanno-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-(N,N-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone

DMSO	dimethylsulfoxide
dppe	diphenylphosphino ethane
dppf	diphenylphosphino ferrocene
ds	diastereoselectivity
EI	electron impact
EIMS	electron impact mass spectroscopy (spectrum)
eq.	equivalent (s)
ESI	electrospray ionisation
Et	ethyl
EtCOCl	propionyl chloride
Et_2O	diethyl ether
$(EtO)_2CO$	diethyl carbonate
EtOH	ethanol
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	Highest Occupied Molecular Orbital
HRMS	high resolution mass spectroscopy (spectrum)
Hz	hertz
Icp	isopinocamphenyl
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	Lowest Unoccupied Molecular Orbital
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
mmol	millimole
mol	mole
m.p.	melting point

MPM	methoxyphenylmethyl
m/z	mass-to-charge ratio
NIS	N-iodosuccinimide
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser and Exchange SpectroscopY
OAc	acetate
OTf	trifluoromethanesulfonate (triflate)
Ph	phenyl
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
PPTS	pyridinium *para*-toluenesulfonic acid
ppm	parts per million
^{i}PrOH	isopropanol
PT	1-phenyl-1H-tetrazole-5-yl
Pyr	pyridine
PYR	pyridin-2-yl
R_f	retention factor
ROESY	Rotating frame Overhauser Effect SpectroscopY
R.T. or RT	room temperature
sat.	saturated
SM	starting material
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBATFA	tetrabutylammonium trifluoroacetate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TBT	*tert*-butyl-1H-tetrazole-5-yl
TES	triethylsilyl
TESOTF	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	trimethylethylenediamine
TMS	trimethylsilyl
TOCSY	TOtal Correlation SpectroscopY
TPAP	tetrapropylammonium perruthenate
p-TsOH	*para*-toluenesulfonic acid

CHAPTER 1 INTRODUCTION

1.1 Marine Natural Products

The greatest biodiversity on Earth is found in the world's oceans, which cover greater than 70% of Earth's surface.[1] They contain more than 300 000 described plants and animals[2] which represents approximately 75% of all living organisms,[1] with 34 of the 36 phyla of life present. These plant and animal species are found in all of the regions of the ocean from polar to temperate to tropical areas which helps to account for the vast biodiversity. Ecological pressures, some of which are unique to the marine environment, such as competition for space, fouling of the surface, predation and successfully reproducing have required these species to develop chemical defence systems in addition to various physical defence systems they possess. As a result a multitude of unique secondary metabolites exhibiting various biological activities have evolved. The oceans potential to provide useful bioactive compounds has been largely under utilised and it is only in the last 40 years that natural products chemistry has shifted its focus from the terrestrial to the marine environment. It is estimated that 1 in 10 000 compounds isolated from the terrestrial sources and screened for *anti*-tumour activity yield candidates for drug development, while closer to 1 in 100 screened compounds isolated from marine sources yield potential drug candidates.[1]

Marine organisms have provided a varied array of novel structures since the launch of Marine Natural Products chemistry in the late 1960's - 1970's. The catalyst for the search for pharmaceutical products from the ocean came in 1969 when Weinheimer and Spraggins[3] discovered large quantities of the prostaglandins, in the gorgonian coral *Plexaura homomalla*. Interest in the search for "drugs from the sea" was stimulated because the prostaglandins had previously been identified as important mediators involved in managing inflammatory diseases, pain and fever. Following this discovery three dominant areas of research quickly emerged in marine natural products chemistry; marine toxins, marine biomedicinals and marine chemical ecology, which will each be discussed.

1.1.1 Marine Toxins

The majority of marine toxins have large polyether structures which have been described as "ladder-like", for example brevetoxin B, illustrated in Figure 1.1. Some of these toxins pose a significant risk to human health. Paralytic and diarrhetic toxins accumulate in the flesh of filter feeders and in some tropical fish when they feed on dinoflaggelates which produce the toxins. Amnesic shellfish poisoning is a serious condition arising when shellfish contaminated with diatoms are ingested.[4] An example of such a poison is domoic acid, produced by the diatom *Pseudonitzschia pungens* forma *multiseries,* which causes gastrointestinal symptoms and in more severe cases of poisoning, neurological disorders, coma or even death.

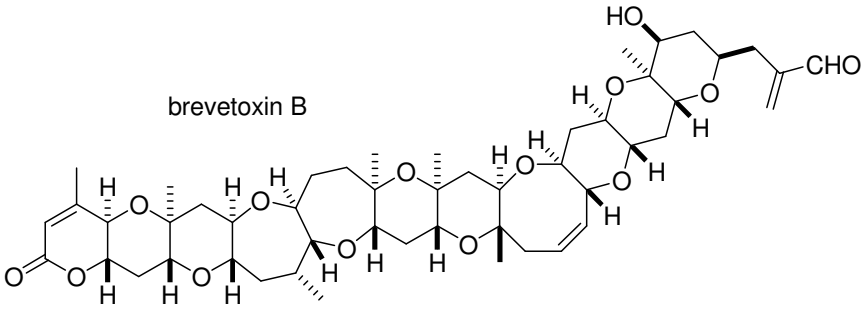


Figure 1.1 Brevetoxin B, a marine toxin with a large "ladder-like" polyether structure.

1.1.2 Marine Biomedicinals

The focus of research on marine natural products over the past 30 years has been in the search for bioactive compounds. A large number of marine-derived natural products have progressed to preclinical and clinical trials for assessment in treating a range of conditions such as cancer, pain, neuropathic pain, epilepsy, inflammation and asthma. However, many do not progress to development as commercial drugs due to formulation problems, undesirable side effects or inactivity. The journey of a potential drug target from identification/structural elucidation through to clinical trials can be extremely long so there are a significant number of compounds currently under investigation as potential pharmaceutical drugs. Table 1.1 and Figure 1.2 contain a small snapshot of compounds under clinical trial, for a comprehensive, up to date list several reviews are available.[5,6]

Table 1.1 Examples of marine-derived natural products currently under clinical trials. [5,6]

Name	Source	Status (disease)
bryostatin 1	*Bugula neritina*	Phase II (cancer)
ILX 651, synthatodin	Synthetic derivative of dolastatin	Phase II (cancer)
aplidine	*Aplidium albicans*	Phase II (cancer)
discodermolide	*Discodermia dissoluta*	Phase I (cancer)
squalamine	*Squalus acanthias*	Phase II (cancer)
laulimalide	*Cacospongia mycofijiensis*	preclinical (cancer)
salicylihalamide A	*Haliclona sp.*	preclinical (cancer)
IPL-576,092 (aka HMR-4011A)	*Petrosia contegnata*	Phase II (antiasthmatic)
ziconotide (aka prialt) (25 residue peptide)	*Conus magus*	Phase III (neuropathic pain)
χ-conotoxin (peptide)	*Conus sp.*	preclinical (pain)

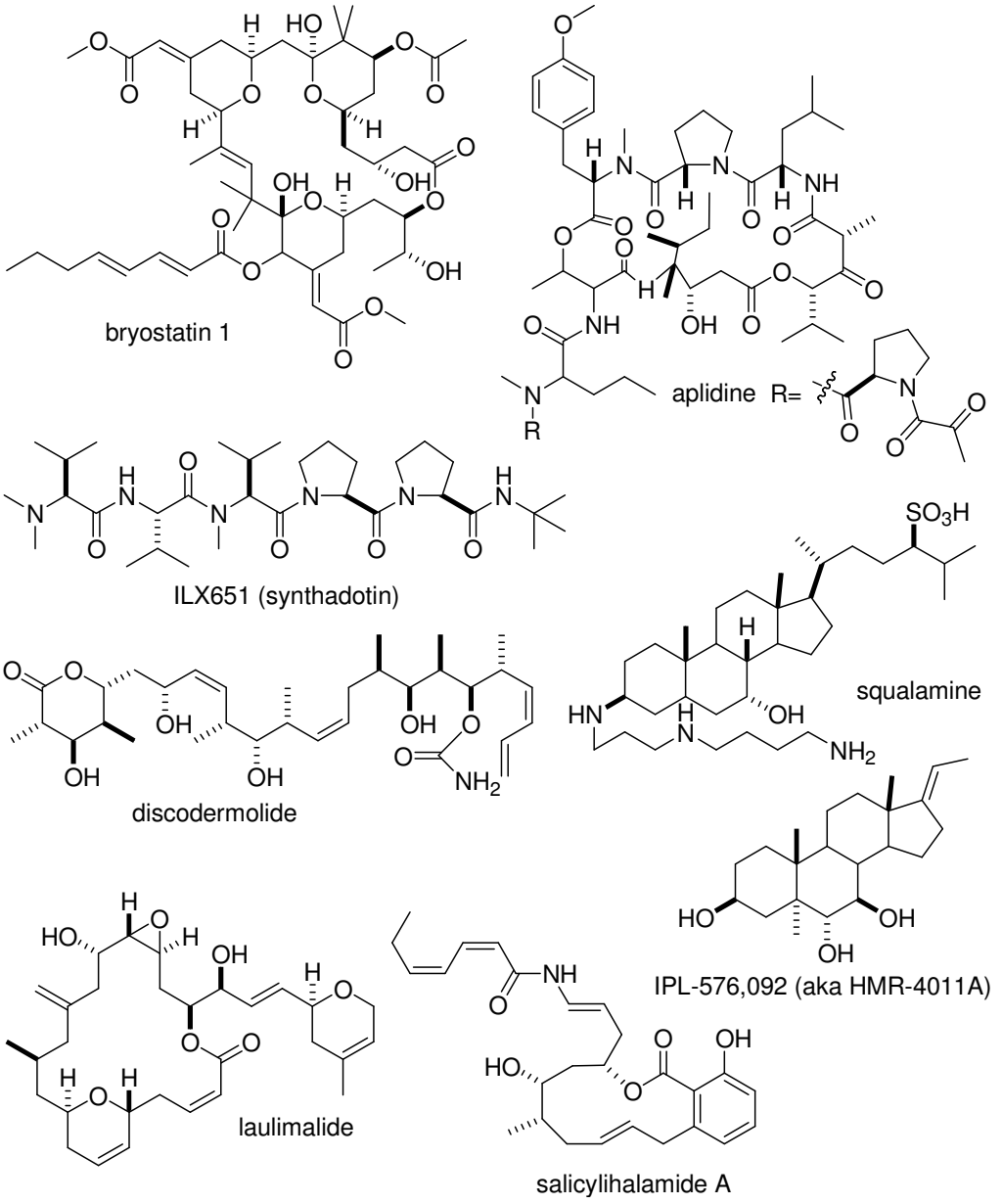


Figure 1.2 Drugs currently under investigation in clinical trials for the treatment of cancer, pain and asthma. [5,6]

In addition to pharmaceutical development, marine natural products have also been used by the cosmetics, agricultural and biological industries. An additive used in cosmetic products is the partially purified extract of the gorgonian coral *Pseudopterogorgia elisabethae*. Cellular biology uses many compounds isolated from marine organisms for a variety of purposes, such as disrupting or acting on cellular mechanisms, some examples are represented in Figure 1.3; jaspamide, acts on actin, ilimaquinone causes vesiculation of the Golgi, and adociasulfate 2 inhibits motor proteins.

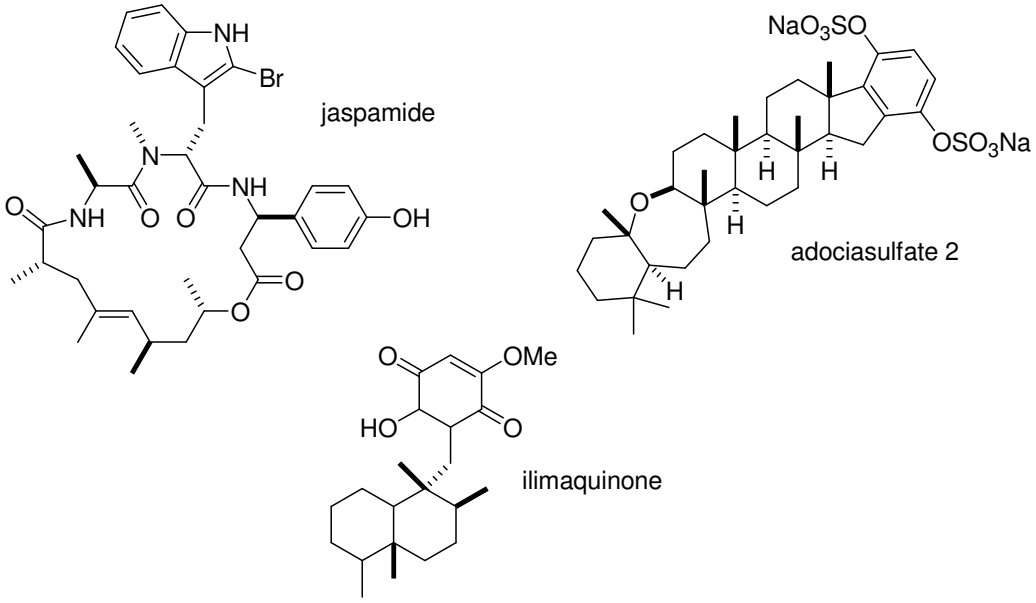


Figure 1.3 Marine-derived natural products used in cellular biology.

Anti-tumour pharmacological studies[7] were conducted in the year 2000 on 19 marine natural products to define or clarify the mechanisms of action. A further 124 novel compounds were found to have *invitro* cytotoxicity however the mechanisms of action are yet to be determined. It is therefore evident that marine natural products are currently at the cutting edge of pharmaceutical research and development.[7] While research on bioactive compounds isolated from marine organisms has been a major focus in the past 30 years, marine natural products have not yet been implemented by the pharmaceuticals industry to any great extent.[8] Typically low yields ($< 10^{-6}$ % of the wet weight) of the natural products obtained from the organisms means that synthesis is required to attain large quantities. However, the lengthy and expensive syntheses required to generate such complex chemical structures with stereochemical purity are presently limiting their integration into the pharmaceuticals industry. Partial synthetic routes offer a more commercially viable approach, for example the

structurally complex ET-743, in Figure 1.4, is synthesised from the biotechnologically available cyanosafracin B.[9,10]

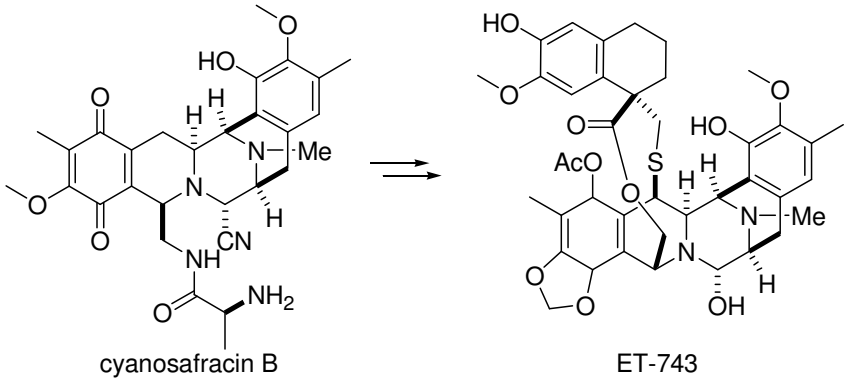


Figure 1.4 A *semi*-synthesis of ET-743 from the biotechnologically available cyanoasafracin B.

Unless synthesis of the marine natural products, or their derivatives, is relatively simple and time efficient (for example incorporating common fragments into the synthesis), cost effective, amenable to large scale synthesis and involving benign reagents and by-products they are unlikely to be integrated into pharmaceutical products.[4]

1.1.3 Chemical Ecology

Studies on marine chemical ecology comprise the remaining area of research in marine natural products chemistry. A large proportion of bioactive products are isolated from soft-bodied, sessile or slow moving marine invertebrates which lack physical defence systems such as shells or spines. For this reason biosynthesis or bio-accumulation of bioactive compounds can enhance the survival of the producing organism. Some algal metabolites use chemical defence to combat predation. Shell-less molluscs were able to evolve from their shelled counterparts due to their ability to store defensive chemicals biosynthesised by the organisms ingested. In sessile organisms metabolites are also thought to act as *anti*-fouling agents. The chemical defensive agents employed by marine organisms are highly potent perhaps accounting for the significant number of these compounds entering clinical trials. Upon excretion by the organism these agents are heavily diluted by sea-water, thus their elevated potency overcomes this problem.[5] The generally accepted reason for the presence of such a variety of bioactive compounds within marine organisms is chemical defence. However, relatively little is known about the exact mode of action of these compounds or their biosynthesis/bioaccumulation within the organism. Thus

marine ecology remains as area for future investigation.

Each of these three dominant areas of marine natural products chemistry which emerged in the 1960's and 1970's remain to be significant areas of interest today. Numerous reviews of research in each of these areas, in particular marine biomedicinals, have been, and continue to be, published each year.

1.2 Polyketides

Polyketides are a class of compounds biosynthesised by bacteria, fungi, plants and marine organisms using an enzyme system called polyketide synthase (PKS) which condenses simple carboxylic acids (such as acetate, propionate and less commonly butyrate) into long polyketide chains. This occurs in a very similar mechanism to the biosynthesis of fatty acids.[11,12] A simple schematic of the catalytic cycle[12] of PKS is shown in Figure 1.5. In both polyketide and fatty acid biosynthesis the first step is a Claisen-type condensation of a coenzyme A thioester of a short chain carboxylic acid "starter unit" (eg. acetate or propionate) and occasionally larger "starter units" (eg. cinnamate, benzoate or fatty acids derivatives) with a thioester of an "extender unit". These extender units, typically malonate or methyl malonate, undergo decarboxylation providing the driving force for the reaction. In fatty acid biosynthesis the β-carbonyl is reduced to the methylene while in polyketide biosynthesis it may be retained as the carbonyl or reduced or the alcohol, olefinic or methylene functionalities by various enzymes.

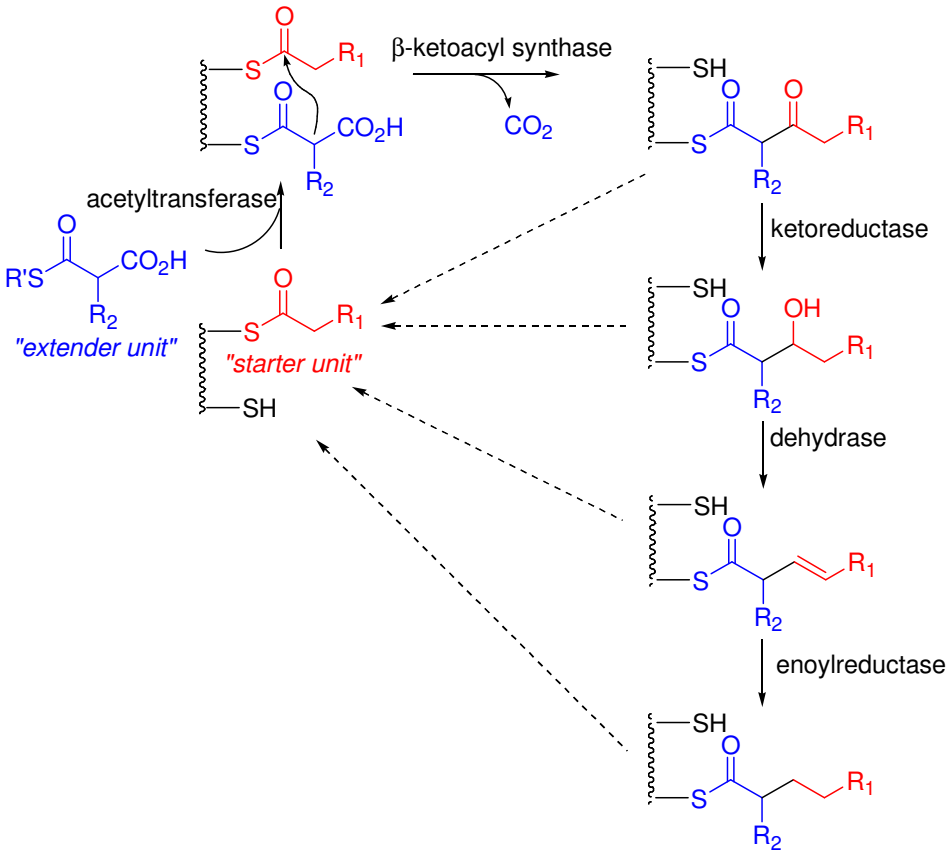


Figure 1.5 A schematic of the PKS facilitated biosynthetic pathway of polyketides.

The decarboxylative condensation, followed in some cases by modifications to the β-keto functionality, is repeated until the chain is the desired length. The reactive polyketomethylene chains are stabilised by H-bonding or metal chelation within the active site of the enzyme. The PKS system is responsible for control of the stereochemistry, chain length, the level of keto-reduction after each condensation event and the initial cyclisation pattern of the full-length polyketide chain.[12] The polyketides, being highly functionalised are much more reactive than the fatty acids possessing combinations of active methylene, olefinic, hydroxyl and carbonyl groups. As a result, intramolecular reactions such as Claisen and crotonic condensation and lactonisation reactions are common, in addition etherification reactions are occasionally observed. These cyclisation reactions can occur following biosynthesis of the polyketide chain, within the PKS enzyme which facilitates the cyclisation, or after release of the polyketide from the active site, in which case the cyclisation is driven by favourable thermodynamics. It is common for two or more intramolecular reactions to take place forming polycyclic systems. Further discussion of cyclisation modes of polyketides post-release from the active site is available in Section 1.2.1. Figure 1.6 illustrates several examples of cyclisation events which are known to occur within the active site generating derivatives containing benzene or pyrone rings which are found in a variety of natural products.[11]

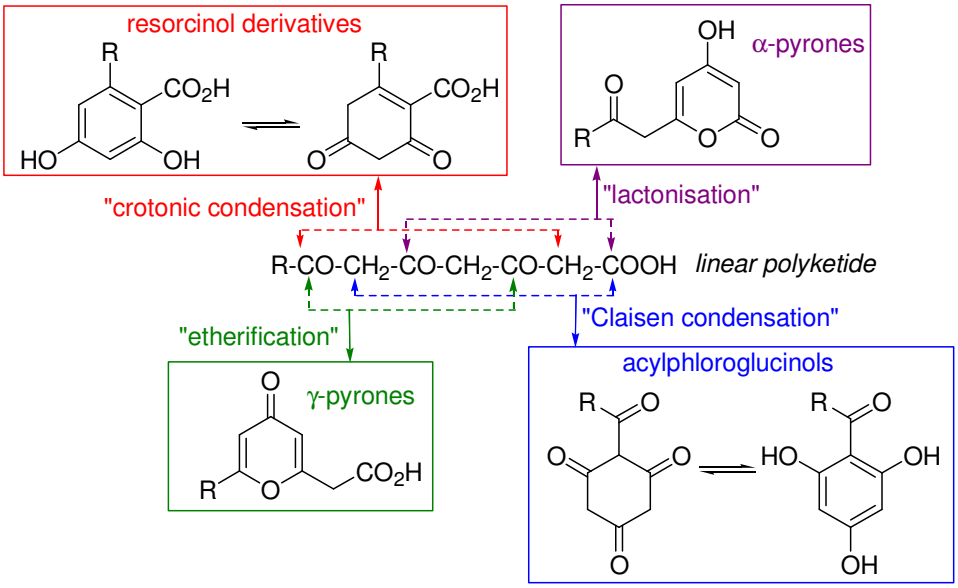


Figure 1.6 Cyclisation reactions of polyketides, known to occur within the active site of enzymes during biosynthesis.

The high degree of functionality present in the linear polyketides leads to a vast number of potential cyclisation modes resulting in a structurally diverse class of

compounds. This structural diversity means that polyketides exhibit a broad range of biological activities. There are between 5 000 and 10 000 known polyketides, of which 1 % have demonstrated drug activity.[13] This is five times the average of all natural products combined[13] making polyketides attractive isolation, characterisation and synthetic targets. Polyketides are often characterised by multiple contiguous stereocentres requiring stereocontrolled syntheses. A variety of pharmaceutical products containing polyketides are available including antibiotics, cancer chemotherapeutics, cholesterol lowering agents and *anti*-fungals. Polyether antibiotics are commercially important in agrochemical applications for example in preventing poultry infections.[14] The current and future economic value of polyketide metabolites to the pharmaceutical industry is enormous with sales exceeding 15 billion dollars (USA).[13]

A pharmaceutically important sub-class of polyketides are the polypropionates which as the name suggests, are biosynthesised by condensation of multiple propionate units. As a result of their biosynthesis, polypropionates typically possess a hydrocarbon backbone with oxygenation and methylation at alternate carbons. Some of these have had notable commercial value in clinical and agrochemical applications.[14] Examples include antibiotics, erythromycin and rifamycin B; immunosuppressants, FK506 and rapamycin; and *anti*-tumour agents, doxorubicin and mithramycin illustrated in Figure 1.7.[15]

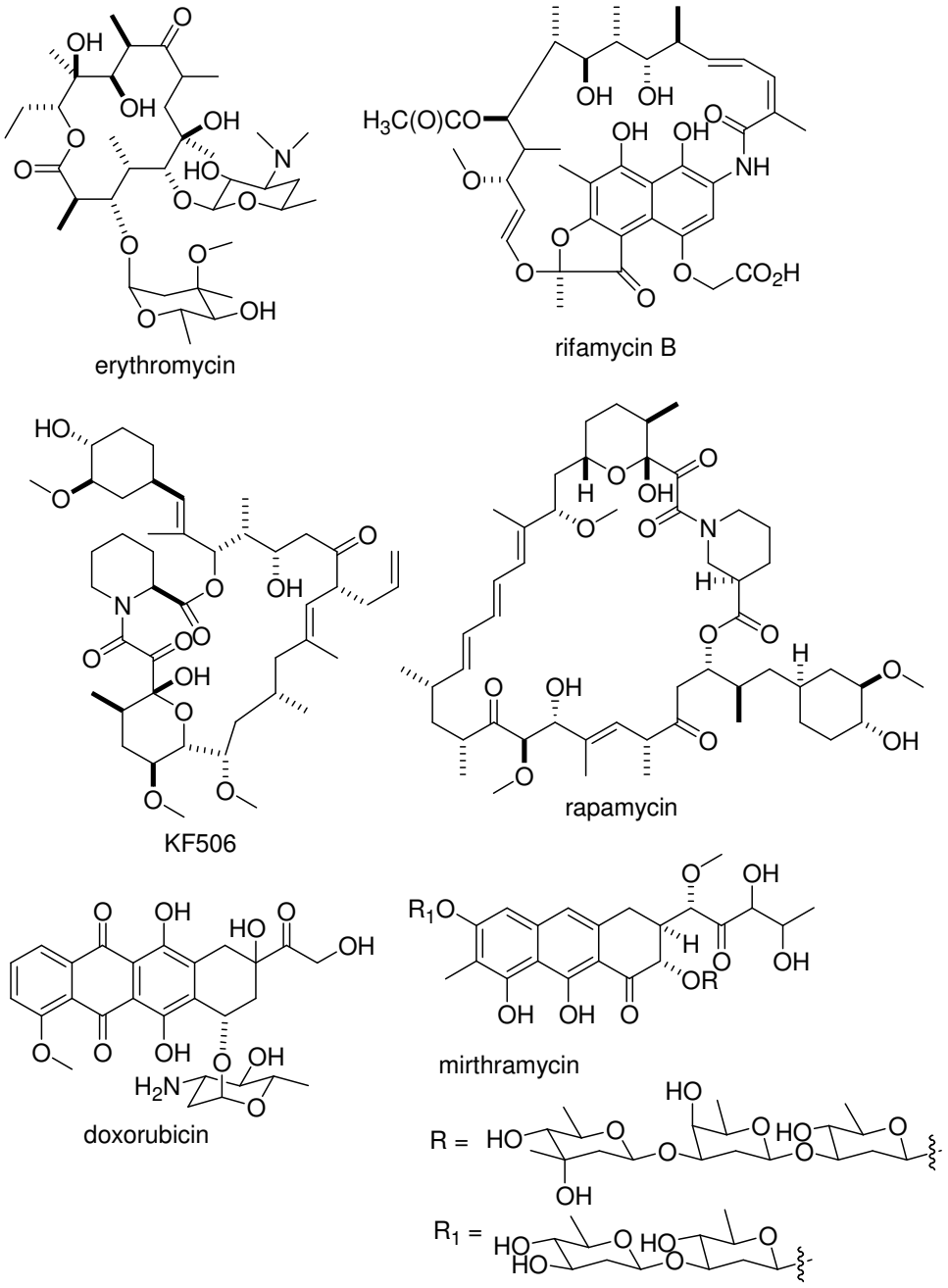


Figure 1.7 Commercially important polypropionate metabolites.

During the past 40 years marine organisms have become a major focus in the discovery of polypropionate metabolites.[4] These metabolites have been isolated from a diverse range of marine organisms from bacteria to sponges, however the family Mollusca are the richest source of polypropionate metabolites with the pulmonate molluscs of the genus *Siphonaria* being the largest source.[14] These molluscs closely resemble limpets however it is only the siphonariids which contain polypropionate metabolites.[16-22] The Siphonariids are air-breathing and live on rock platforms in

intertidal zones where they feed on micro-organisms and encrusting algae. While exhibiting a physical defence system, (i.e. a shell) they are relatively sessile and it is thought that the polyketide metabolites may be employed in chemical defence.[23]

1.2.1 Cyclisation Modes

Polyketides are believed to exist as linear chains, or with stable aromatic groups such as those represented in Figure 1.6, within the organism but undergo further cyclisation and rearrangements upon isolation.[12] This theory is supported by the fact that the thermodynamic product is most commonly observed, suggesting enzyme involvement is not necessary. The most stable stereoisomer for the commonly observed six membered rings is that in which the alkyl substituents on the ring lie in the least sterically demanding, equatorial position and the oxygen on a carbon adjacent to the heteroatom lies in an axial position on the ring, gaining the benefit of the stabilising anomeric effect. Cyclisation reactions and rearrangements can occur *via* a number of mechanisms including Claisen condensation, retro-Claisen, nucleophilic addition and intramolecular [4 + 2] cycloaddition reactions. The most common cyclisation occurs by nucleophilic attack of a hydroxyl group on a carbonyl group situated five carbons away to give a hemiacetal, such as the denticulatins B and C represented in Figure 1.8. This commonly, but not exclusively, occurs if the two methyl groups positioned between the hydroxyl and the carbonyl will lie in an equatorial position in the cyclised product (i.e. the most thermodynamically favourable position). If a linear polyketide has more than one possible cyclisation mode, cyclisation will proceed to give the most thermodynamically stable product. For example the linear precursors (**10*S*)-1** and (**10*R*)-1** to the denticulatins B and C, which differ only in the orientation of the C10 methyl substituent, can undergo 3 potential cyclisation modes, depicted in Figure 1.8.[24]

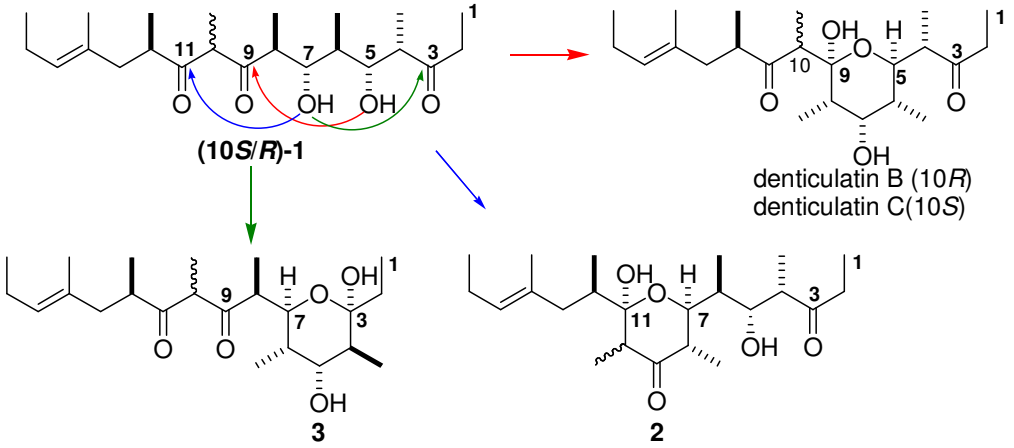


Figure 1.8 Possible cyclisation modes of (10*S*/*R*)-1, the linear precursors to denticulatins B and C.

The three possible cyclisation modes of linear precursors **(10*S*)-1** and **(10*R*)-1** produce cycloadducts of differing stabilities;

(1) Addition of the C5 hydroxyl group to the C9 carbonyl (represented in red) gives denticulatins B and C where all of the carbon substituents are equatorially oriented and both the C7 and C9 hydroxyl groups are axially oriented, with the C9 hydroxyl group satisfying the requirements of the anomeric effect. The axial hydroxyl groups are capable of hydrogen bonding with each other further stabilising these cycloadducts.

(2) Addition of the C7 hydroxyl group to the C11 carbonyl (represented in blue) can yield two different products **2α** and **2β** depending on the orientation of the C10 methyl group. In the α-orientation the C10 methyl group is axial while in the β-orientation the C10 methyl group is equatorial. In each case all of the other carbon substituents occupy the equatorial position.

(3) Addition of the C7 hydroxyl group to the C3 carbonyl (represented in green), produces hemiketal **3**. In accordance with the anomeric effect, the C5 hydroxyl group is axially oriented. The C4 methyl is also axially oriented while the remaining substituents occupy an equatorial orientation.

The products isolated from the natural source, denticulatins B and C, are the thermodynamically most stable cycloadducts resulting from cyclisation mode 1, represented in red. In these products the four alkyl substituents on the ring lie in the equatorial position, the hydroxyl groups occupy the axial position and enhanced stabilisation is provided by hydrogen bonding between the axial hydroxyl groups.[24-26]

Cascade cyclisations may occur where the nucleophile generated in the initial cyclisation is able to undergo nucleophilic attack on another carbonyl group located within the linear chain giving spiroacetal (eg. siphonarin B[21,27]) or 2,4,6-trioxaadamantane (eg. caloundrin B[18] and muamvatin[17,28]) ring structures, as represented in Figure 1.9. The linear precursors (**4** and **5**) to siphonarin B and caloundrin B are epimeric at the methyl bearing stereocentre, C8, situated between two carbonyls. The configuration of the C8 methyl appears to be responsible for controlling the direction of cyclisation accounting for the different polycyclic products observed. Cyclisation of linear precursor **4** (the epimer leading to siphonarin B) to produce the corresponding trioxadamantane ring structure is disfavoured due to steric interactions of the C8 methyl. Therefore thermodynamic cyclisation gives the spiroacetal, siphonarin B, in which all of the alkyl substituents lie in the equatorial position and both acetal oxygens lie in the anomerically-favoured axial position with respect to the other ring.[27] Conversely, cyclisation of the C8 epimer **5** (the epimer leading to caloundrin B) to the trioxaadamantane ring structure produces a thermodynamically more stable product, where the C8 methyl, in this orientation, does not experience unfavourable steric interactions.[18] The alternative cyclisation mode of linear precursor **5**, to give the spiroacetal, will produce a product higher in energy where the C8 methyl is axially orientated. Computational studies, carried out by Garson and co-workers,[29] on the relative stabilities of both the spiroacetal and trioxaadamantane moieties arising from cyclisation of each of the C8 epimers supported the theory that cyclisation is under thermodynamic control.

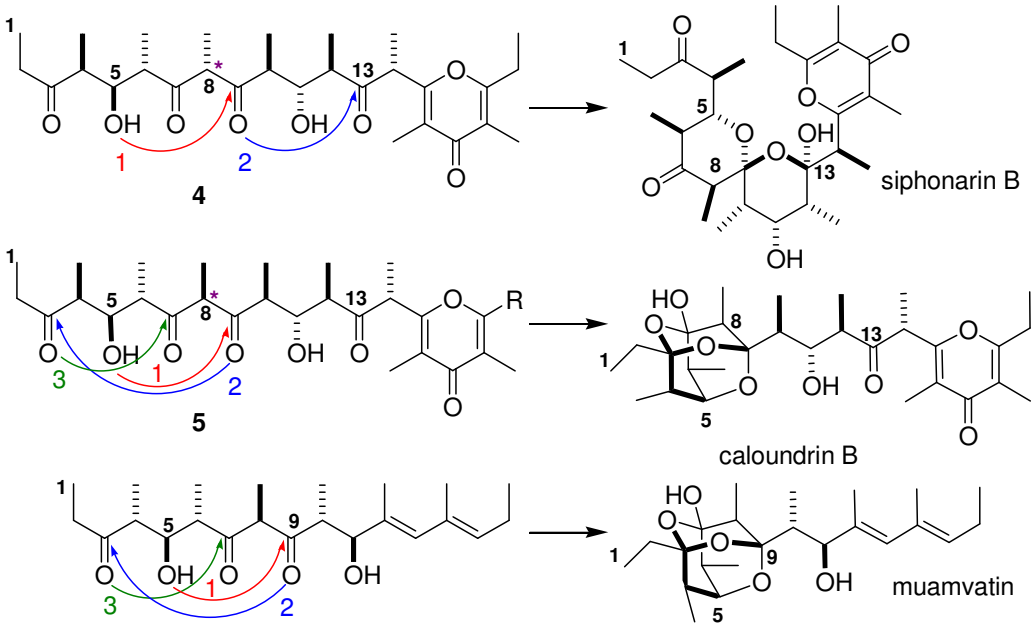


Figure 1.9 Linear polyketides may undergo cascade cyclisations forming polycyclic compounds.

In some cases second or third generation isolation artefacts are observed whereby the initial cyclisation product further rearranges or reacts, presumed to be driven by formation of a more stable product. In the bio-synthesis of maurenone, dehydration of the intermediate hemiacetal **6** is thought to give a more stable dihydropyrone ring **7**.[30] (Figure 1.10). Synthetic studies discussed in Chapter Two address the issue of the thermodynamic stability of the intermediate hemiacetal **6** and corresponding dihydropyrone **7** under mildly acid conditions.

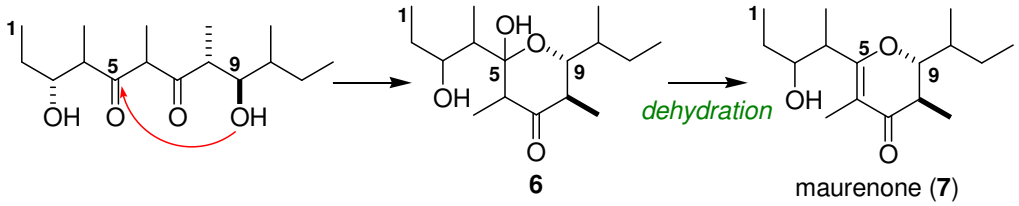


Figure 1.10 The proposed biosynthesis of maurenone involves formation of an intermediate hemiacetal 6 which dehydrates to the dihydropyrone 7.

Several natural products possess an ester linkage indicating that following formation of a hemiacetal intermediate, a base induced retro-Claisen reaction may occur to give the corresponding ring opened esters, such as those represented in Figure 1.11. Thermodynamically driven cyclisation and base-induced retro-Claisen reactions were confirmed in the total synthesis of the ester **8** isolated from *Siphonaria australis.*[16,31] Baconipyrone C also possesses an ester linkage suggesting a similar mechanism of formation. However, several total syntheses[32,33] have constructed the natural product through esterification reactions rather than base-induced retro-Claisen reactions, therefore the proposed biosynthetic mechanism has not been confirmed.

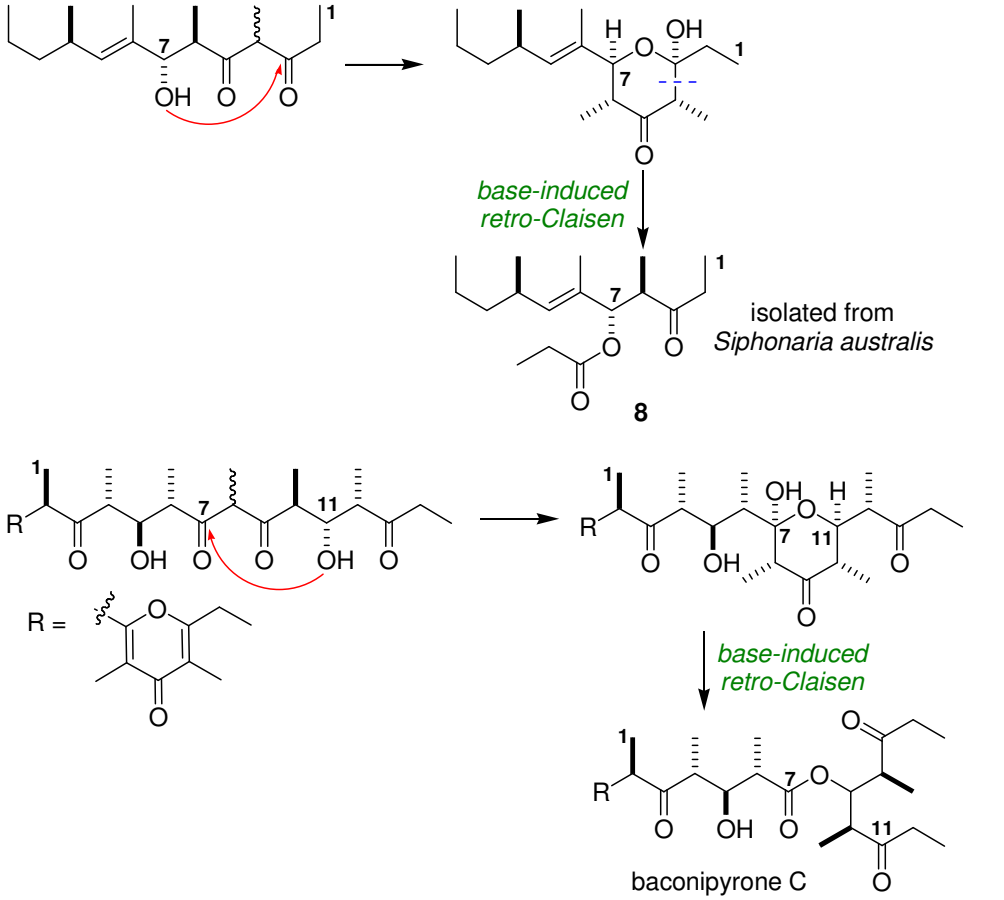


Figure 1.11 The biosyntheses of ester 8, isolated from *Siphonaria australis*, and baconipyrone C are suggested to involve a base-induced retro-Claisen reaction.

In the proposed biosynthesis of dolabriferol, described in Figure 1.12, following construction of the linear precursor **9**, a thermodynamically driven cyclisation to give hemiacetal **10** occurs. This then undergoes a base-induced retro-Claisen reaction to give ester **11** which subsequently cyclises to dolabriferol. Synthetic studies towards dolabriferol support the proposed base-induced retro-Claisen mechanism, however, the final cyclisation step could not be achieved due to difficulties in removal of the C13 protecting group.[34]

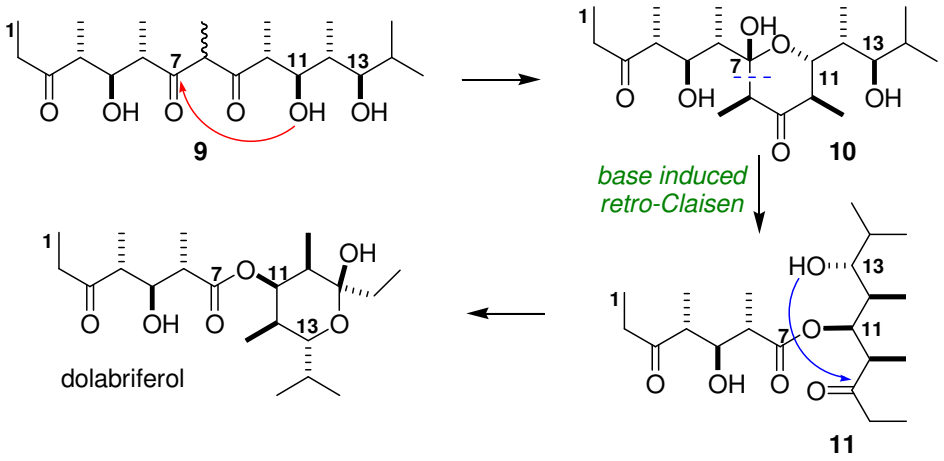
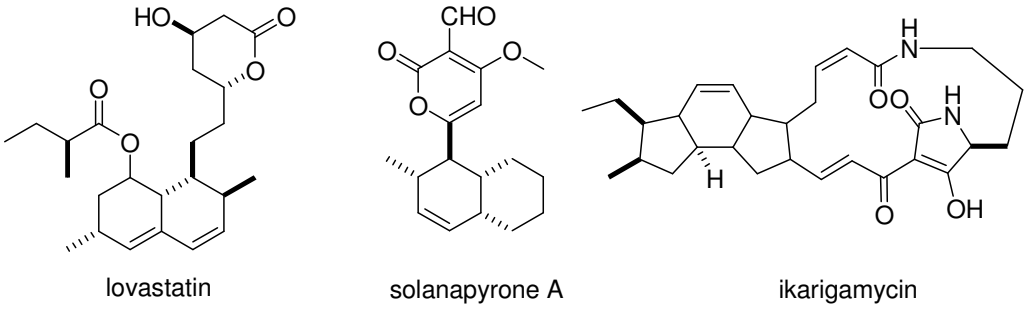


Figure 1.12 The biosynthesis of dolabriferol is proposed to involve a base-induced retro-Claisen reaction and subsequent cyclisation.

All of the unstable polyketide derived linear precursors are biosynthesised in the same way and undergo fundamentally similar cyclisation reactions. However these examples illustrate the broad range of molecular architectures ultimately achieved. It appears that the stereochemistry and functionality defined by the PKS system is the controlling factor determining the cyclisation directions and thus influencing the final molecular structure. Therefore, even if the cyclisation is driven by favourable thermodynamics, rather than enzymatic control, the PKS system ultimately governs the architecture in the isolated natural products.

In addition to cyclisations initiated by nucleophilic attack of oxygen to electron deficient carbon centres within the polyketide chain, intramolecular [4 + 2] cycloaddition reactions are also common. There are numerous examples of polyketide derived natural products (and others) which appear to be constructed *via* [4 + 2] cycloaddition reactions. Some examples are lovastatin, solanapyrone A and ikarugamycin, depicted in Figure 1.13, however more examples can be found in several review articles.[35,36]



lovastatin solanapyrone A ikarigamycin

Figure 1.13 Polyketide derived natural products which appear to be constructed *via* a [4 + 2] cycloaddition reaction.

The cyclisation reactions discussed so far, have all produced the thermodynamically most stable product indicating the reaction is driven by thermodynamic control. In contrast, it is unclear whether the intramolecular [4 + 2] cycloaddition reaction, which often occurs with high levels of stereoselectivity, occurs under enzymatic or thermodynamic control. Evidence suggests that in nature the [4 + 2] cycloaddition reaction can be facilitated by enzymes which control the stereo- or regio-chemical outcome in some instances, while in other cases the reaction is spontaneous and under thermodynamic control. Further discussion of enzymatic Vs thermodynamic control of [4 + 2] cycloaddition reactions is available in Section 1.2.2.

1.2.2 Total Synthesis of Polyketide Derived Marine Natural Products

While marine species provide a diverse array of polyketide derived natural products, typically only milligram quantities can be isolated from large numbers of marine organisms. Preliminary evaluation of the structure, biosynthesis, biological activity and mode of action can often be achieved however larger quantities are required for thorough evaluation. The sample collection, isolation and purification procedures are expensive, labour intensive and inefficient, therefore an easily achievable synthetic route is desired. Many of these metabolites have complex molecular architectures and multiple contiguous stereocentres so a highly efficient stereoselective synthesis is sought. As previously mentioned, the complex cyclic framework of the isolated natural products is thought to be generated *via* thermodynamically driven cyclisation events of linear polyketide precursors during isolation. As a result, a common approach to total synthesis is to exploit this thermodynamically driven cyclisation by constructing a linear polyketide which can be induced to cyclise. In nature the synthesis of these linear polyketides is achieved by successive condensation events

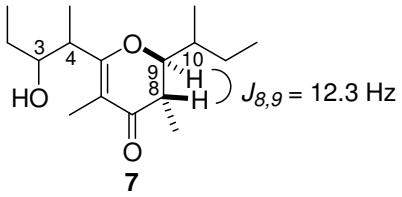
extending the chain small blocks at a time as described in Section 1.2. In contrast, synthetic chemists desire a more convergent approach whereby large fragments may be synthesised independently and then coupled.

An additional consideration in designing a strategy for total synthesis is that a biomimetic approach can be useful in providing information about the biogenesis of these bioactive compounds. Various natural products that are thought to be generated *via* intramolecular [4 + 2] cycloaddition reactions, are not necessarily formed by cyclisation to the thermodynamically most stable cycloadduct. This suggests that enzymes may be involved in facilitating formation of less stable cycloadducts by providing stability to the transition state. In these instances biomimetic total syntheses can be used to support or refute the suggestion of enzymatic involvement.[37] By inducing a linear polyketide precursor to cyclise under thermodynamic conditions and comparing the product(s) obtained to the natural product, conclusions can be drawn about the possible involvement of enzymes. If the thermodynamic product(s) obtained synthetically does not match the natural product or if the enantiomeric/diastereomeric ratios obtained synthetically are different to those observed in the natural product then enzymatic involvement is likely. However a biomimetic study can not rule out enzymatic involvement if the thermodynamic product obtained synthetically matches the natural product. Although biomimetic total syntheses cannot definitively prove or disprove the existence of an enzyme they are useful indicators of enzyme existence.[37]

Regardless of whether a natural product is thought to be formed *via* enzymatically facilitated cyclisation or by thermodynamically driven cyclisation, synthesis of the proposed linear precursor is a common approach used in total synthesis. The carbon to carbon bond forming reaction has become an integral part of construction of these complex structures in a highly stereoselective manner. These reactions range from construction of small molecules containing several stereocentres from small chiral starting materials or reagents, to coupling chiral fragments into larger more stereocomplex molecules. This thesis describes synthetic studies towards the total synthesis of two polyketide derived marine natural products, maurenone (**7**) and the spiculoic acid family of natural products. A brief introduction to maurenone (**7**) is detailed in Section 1.2.3 and the spiculoic acid family in Section 1.2.4.

1.2.3 Maurenone

Maurenone (**7**) is a polypropionate derived natural product isolated from a pulmonate mollusc from Jaco Beach, Costa Rica.[30] Structural investigation, using ^{1}H and ^{13}C NMR, UV and IR data, following isolation suggested a relatively uncommon, tetra-substituted dihydropyrone moiety, represented in Figure 1.14.



7

Figure 1.14 The proposed structure of maurenone containing a tetra-substituted dihydropyrone moiety.

The absolute and relative stereochemistry of the C3, C4 and C10 stereocentres was unable to be determined due to the conformational flexibility of the ring appendages. In addition the C3/C4 stereocentres are remote to the C10 stereocentre and stereochemical information is difficult to relay through the rigid ring. A *trans*-relative relationship between the C8 and C9 protons was revealed by the magnitude of the coupling constant, $J_{8,9}$ = 12.3 Hz, however the absolute stereochemistry was unknown. Thus from a synthetic perspective it has been concluded that there are 16 possible stereoisomers, or eight pairs of enantiomers (**12**-**19**) depicted in Figure 1.15, of which only one corresponds to the natural product.

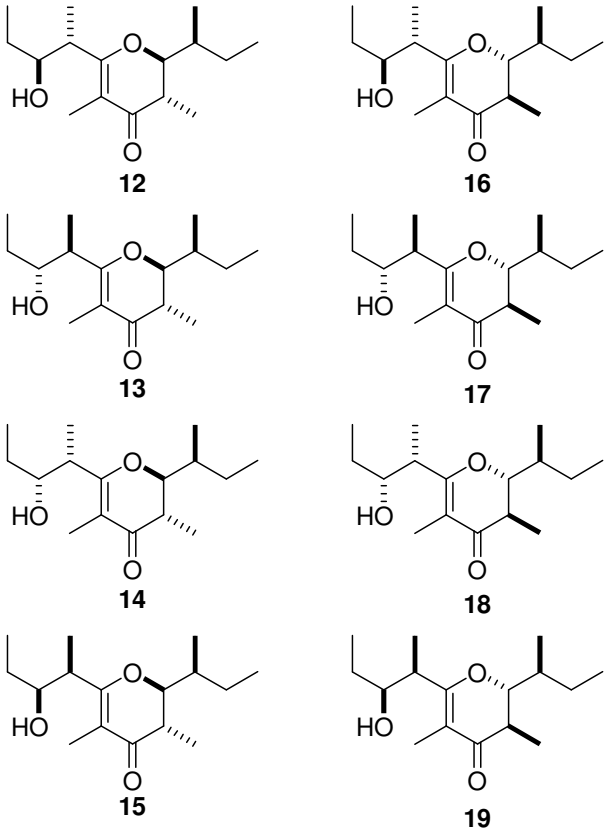


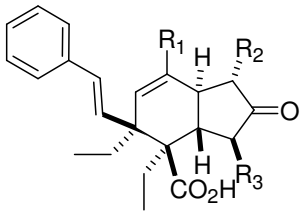
Figure 1.15 The eight isomers of one enantiomeric series, of the maurenone structure.

Due to the limited bioavailability of maurenone (**7**) and the value of polyketide-derived metabolites as potential drug targets or lead compounds, a synthetic approach was sought to provide material for biological evaluation. Total synthesis of the eight stereoisomers in one enantiomeric series (**12**-**19**) was anticipated to enable assignment of the relative stereochemistry by comparison of the spectroscopic data to the natural product. Therefore, the aim of this project, described in Chapter Two, was to synthesise the eight putative isomeric structures (**12**-**19**), shown in Figure 1.15, to elucidate the structure of maurenone (**7**).

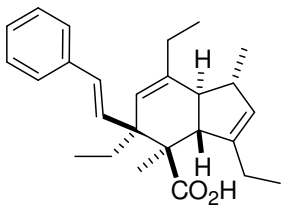
1.2.4 The Spiculoic Acids

The spiculoic acid family of marine natural products, represented in Figure 1.16, are polyketide in origin and were isolated from a Caribbean marine sponge.[38,39] Spiculoic acid A (**20**), iso-, *nor*- and *dinor*-spiculoic acid A (**22**-**24**) differ only in the methyl Vs ethyl substitution around the [4.3.0] bi-cyclic core, due to incorporation of either propionate or butyrate units during biosynthesis. Spiculoic acid B (**21**) is similar to spiculoic acid A (**20**) and derivatives **22**-**24** except that the carbonyl

functionality at C5 has been replaced by an olefin within the 5-membered ring, presumably during biosynthesis by the PKS system.



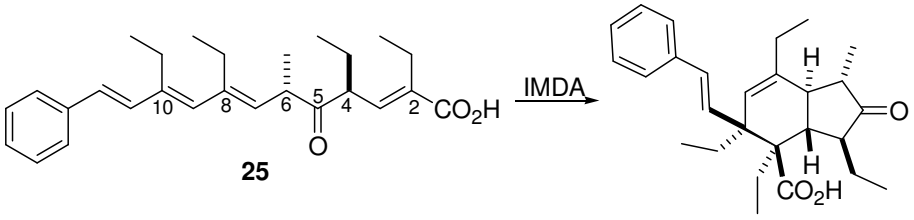
Spiculoic acid A (**20**); R_1 = Et, R_2 = Me, R_3 = Et
Isospiculoic acid A (**22**); R_1 = Et, R_2 = Et, R_3 = Me
Nor-spiculoic acid A (**23**); R_1 = Et, R_2 = Me, R_3 = Me
Dinor-spiculoic acid A (**24**); R_1 = Me, R_2 = Me, R_3 = Me



Spiculoic acid B (**21**)

Figure 1.16 The spiculoic acid family of natural products isolated from Caribbean marine sponges.

These natural products represent attractive synthetic targets demonstrating cytotoxicity against several cell lines as well as possessing a previously unreported spiculane skeleton. Of particular interest is the proposed biosynthesis which suggests the possible involvement of a Diels-Alderase in formation of the [4.3.0] bicyclic core. Figure 1.17 illustrates the proposed linear precursor (**25**) to spiculoic acid A (**20**) suggested to undergo an IMDA cycloaddition reaction, forming the [4.3.0] bicyclic core. Total synthesis of the spiculoic acids provides the potential of employing a biomimetic strategy in order to probe for evidence supporting the participation of a Diels Alderase. Synthesis of the linear precursors to the spiculoic acids followed by a thermally induced IMDA reaction is proposed. A thorough stereochemical analysis of the cycloadduct(s) may provide information supporting or contesting the involvement of an enzyme in the formation of the natural products.



25

spiculoic acid A (**20**)

Figure 1.17 The proposed linear precursor to spiculoic acid A (20) undergoes an IMDA reaction installing the spiculane skeleton.

Before embarking on the total synthesis of the putative isomeric structures of maurenone (**12**-**19**) and the spiculoic acid family of natural products (**20**-**24**), a synthetic approach to the construction of the linear precursors and the cycloadducts

through carbon to carbon bond formation was devised. Consideration was given to the stereochemistry required in the natural products and thus a stereoselective method for constructing the bonds sought. Strategies to suppress or eliminate potential side reactions or alternative cyclisation modes were also investigated, such as protection of reactive oxygen functionalities. The proposed approaches to the total synthesis of maurenone and the spiculoic acid family of natural products will be presented in Section 1.4, following a review of carbon to carbon bond forming reactions in Section 1.3.

1.3 Carbon to Carbon Bond Forming Reactions

One of the most important reactions in natural products synthesis is the carbon to carbon bond forming reaction. The first reported carbon to carbon bond forming reaction was in 1845 by Kolbe in the synthesis of acetic acid from inorganic precursors. Since this original report countless other carbon to carbon bond forming reactions have been discovered that have revolutionised synthetic organic chemistry. Reactions such as Aldol cross-coupling reactions, olefination reactions (such as Wittig,[40,41] Horner-Waddsworth-Emmons (H.W.E)[42-44] and Julia[45] and modifications), Diels-Alder[46] and other pericyclic reactions, organometallic reactions (such as Grignard,[47] Heck,[48,49] Stille[50,51] and Suzuki[52,53]) and many other carbon to carbon bond forming reactions have played a pivotal role in the development of natural product synthesis into the growing research area that it is today.

A brief summary of several key carbon to carbon bond forming reactions commonly employed in polyketide synthesis will be presented. The discussion will begin with the Aldol reaction which is undoubtedly the most commonly utilised of these reactions, providing access to poly-oxygenated compounds with high levels of stereocontrol. The installation of carbon to carbon double bonds through stereoselective olefination reactions such as Wittig, H.W.E. and Julia (and modifications) reactions will then be examined. An evaluation of the Diels-Alder or [4 + 2] cycloaddition reaction will follow as this is perhaps one of the most important of the pericyclic reactions, simultaneously forming two carbon to carbon σ bonds at the expense of two π bonds in a highly stereocontrolled manner. The last group of carbon to carbon bond forming reactions reviewed are the various palladium-catalysed cross-coupling reactions of organometallic reagents. Finally a brief

summary of the protecting groups commonly employed in natural products synthesis to inhibit competing side reactions or alternative modes of cyclisation is included.

1.3.1 The Aldol Reaction

The carbon backbones of polyketide derived natural products often contain many stereogenic centres which control the direction of thermodynamic cyclisations. Therefore a great deal of stereocontrol is required in the synthesis of these linear precursors. The aldol reaction is a highly effective and efficient method of forming carbon to carbon bonds, producing a β-hydroxy ketone product. The mechanism for the reaction, described in Figure 1.18, is such that the ketone **26** reacts with either a strong base or a Lewis acid and an amine base to generate an enolate **27** which undergoes nucleophilic attack on a carbonyl carbon simultaneously forming the carbon to carbon bond and generating a hydroxyl group (**28**). In most instances the Aldol reaction proceeds through a well defined, cyclic, six-membered Zimmerman-Traxler transition state (**TS-1**), whereby the metal bound to the enolate coordinates to the aldehyde oxygen. This rigid closed transition state dictates the stereochemistry in the product. Figure 1.18 represents a *Z*-(O)-enolate (**27**) reacting with an aldehyde *via* a cyclic transition state (**TS-1**) producing a *syn*-β-hydroxy ketone **28**.

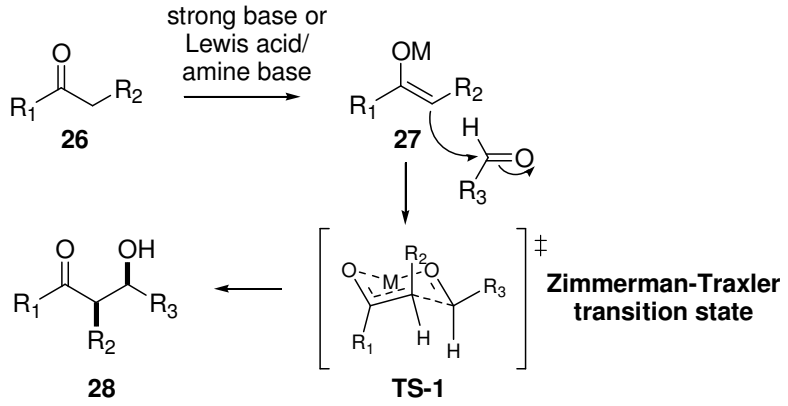


Figure 1.18 The mechanism of the aldol reaction.

α-Substituted enolates, derived from ethyl (or higher alkyl substituted) ketones, are particularly useful in the synthesis of polyketide natural products because they allow the generation of two new adjacent stereocentres. Considering the reaction of an aldehyde (**29**) and a *Z*-(O)-enolate (**27**), shown in Figure 1.19, reaction can occur through four alternative Zimmerman-Traxler transition states (**TS-2**-**TS-5**).[54] These transition states arise from reaction at each face (*Re* or *Si*) of both the aldehyde and

enolate coupling partners. If R_1-R_3 do not contain stereogenic elements two different pairs of enantiomeric products are obtained (**30/31** and **32/33**), while if either, R_1, R_2 or R_3 possess stereogenic elements the four products are diastereomeric.

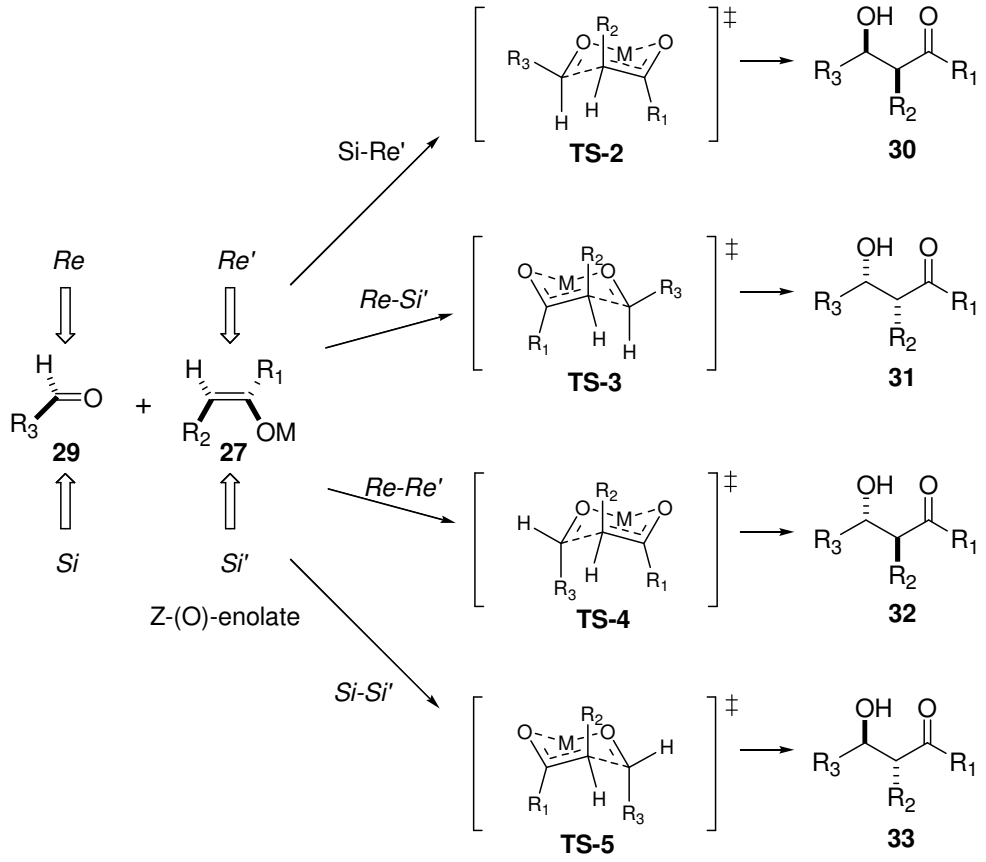


Figure 1.19 The alternative Zimmerman-Traxler transition states of a *Z*-(O)-enolate, leading to the four theoretically possible stereoisomeric products.

In addition to the four isomeric products from the *Z*-(O)-enolate (**30**-**33**), an *E*-(O)-enolate can also react through four possible transition states giving two *syn*- and two *anti*-aldol products. However, in actuality, only two of the four possible isomers are generally observed from each configuration of the enolate. *Anti*-aldol products are favoured from *E*-(O)-enolates, while *syn*-aldol products are favoured from *Z*-(O)-enolates. This stereocontrol can be rationalised by considering the cyclic, six-membered Zimmerman-Traxler transition states leading to both the *syn*- and *anti*-aldol adducts from both *Z*-(O)- and *E*-(O)-enolates (**27** and **34**) shown in Figure 1.20 (Note: the enantiomeric transition states and products are not shown).[54] Examination of the two transition states arising from the *Z*-(O)-enolate (**TS-6** and **TS-7**), reveals that **TS-7**, leading to the *anti*-adduct **32**, experiences disfavoured 1,3-diaxial interactions between R^3 and R^1, thus *syn*-adduct **30** is favoured. Conversely, examination of **TS-8** and **TS-9**, for the *E*-(O)-enolate (**34**), clearly indicates that **TS-**

9, leading to the *syn*-product **31**, experiences similar disfavourable, 1,3-diaxial interactions between R^3 and R^1, consequently favouring formation of the *anti*-adduct **33**. In essence the favoured product from each enolate arises from the transition state where the R group of the aldehyde (R_3) occupies the equatorial position. As a result control of the enolate geometry is of fundamental importance in imparting *syn*- Vs *anti*-stereocontrol.

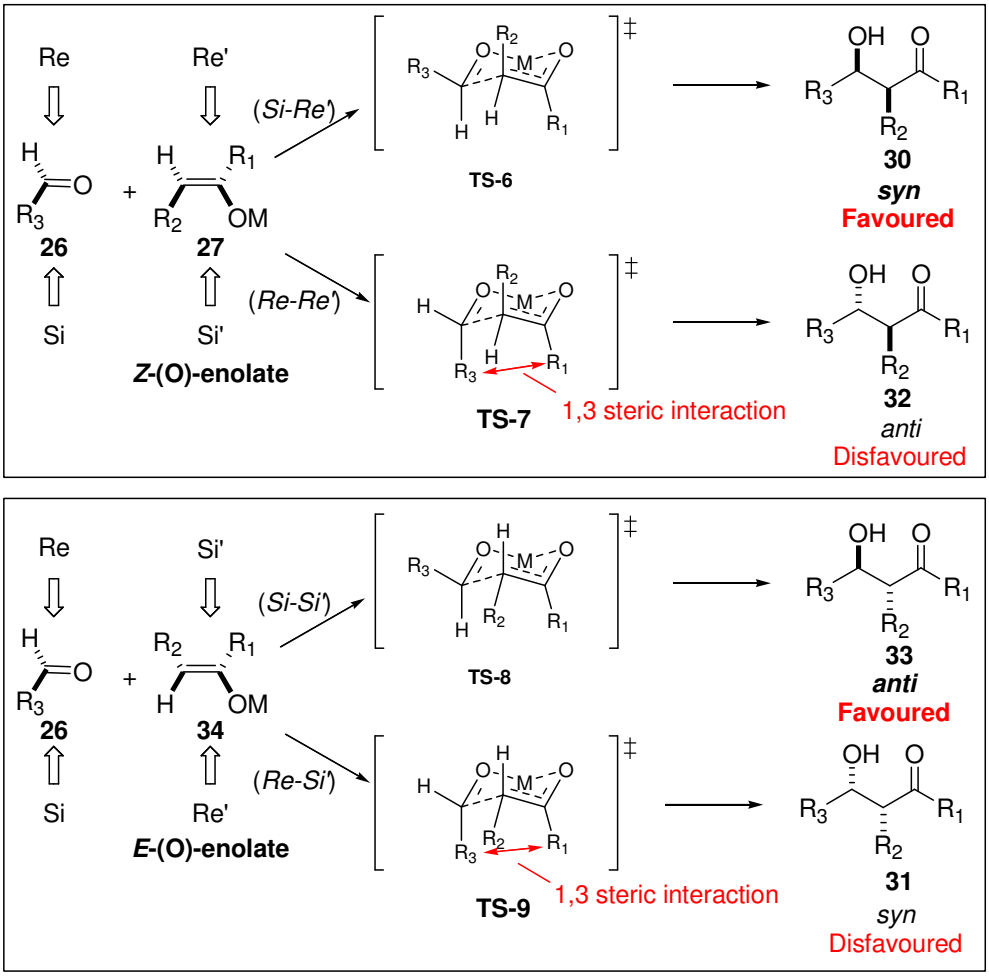


Figure 1.20 The favoured and disfavoured Zimmerman-Traxler transition states of the aldol reactions of *Z*-(O)- and *E*-(O)-enolates.

In natural product synthesis generally only one of the four possible aldol adducts (**30**-**33**) is desired with high selectivity, so control of the stereochemical outcome is required. Stereocontrol can be achieved in a number of ways; by controlling the geometry of the enolate during formation from the Lewis acid or by introducing chirality into the aldehyde and/or ketone coupling partners to differentiate the *Re* and *Si* faces enabling preferential attack at one face. Each of these approaches to imparting stereocontrol in the Aldol reaction will be discussed in turn.

1.3.1.1 π–Facial Selectivity of the Aldehyde

If the aldehyde is chiral at the α-carbon then approach of a nucleophile to the carbonyl occurs with π-facial selectivity. The Felkin model,[55] which was extended by Anh,[56] is generally accepted to explain the observed facial selectivity for addition of simple nucleophiles. This model suggests a reactant-like transition state where the torsional strain experienced between the partially formed bonds is a significant contributor to the energy barrier for reaction. This suggests a staggered conformation where the bulkiest ligand (L) on the α-carbon lies perpendicular to the carbonyl due to steric constraints. The incoming nucleophile approaches the carbonyl at an angle of ~109°, known as the Burgi-Dunitz trajectory. In Figure 1.21 the nucleophile approaches the carbonyl in the two possible rotamers where the largest ligand is perpendicular to the carbonyl. The Felkin/Anh model postulates that the mode of attack leading to the Felkin (*syn*) product is preferred as the approaching nucleophile experiences minimal torsional strain because the partially formed bond overlaps with the smallest α ligand (S). The *anti*-Felkin (*anti*) product is less favoured because the approaching nucleophile experiences more significant torsional strain with the partially formed bond overlapping with the larger α-ligand (M).

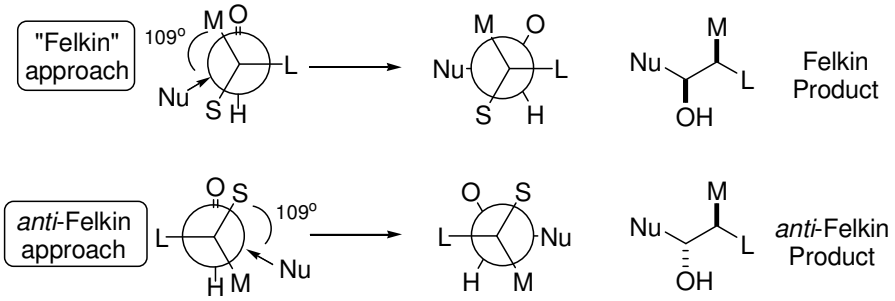


Figure 1.21 Rationalisation of the Felkin-Anh mode of nucleophilic approach.

While the Felkin-Anh model accurately predicts the reaction selectivity for reaction of *E*-(O)-boron enolates with chiral aldehydes there are numerous examples in the literature of *Z*-(O)-boron enolates favouring production of the *anti*-Felkin product in reactions with α-chiral aldehydes. Roush and co-workers rationalised this observed *anti*-Felkin selectivity by considering the competing transition states leading to the Felkin and *anti*-Felkin products for both the *E*-(O)- and *Z*-(O)-enolates.[57] Computational studies by Gennari and co-workers provided justification for the proposed steric effects controlling the reaction stereoselectivity.[58] Examination of the transition states for the *Z*-(O)-enolate, represented in Figure 1.22, reveals that the Felkin transition state (**TS-10**) experiences a *syn*-pentane interaction between the

medium group (Me) on the α-stereocentre of the aldehyde and the axial methyl group of the enolate. The corresponding transition state for the *anti*-Felkin approach of the nucelophile (**TS-11**), has the small group (H) of the α-stereocentre of the aldehyde in the axial orientation. The smaller group does not experience such significant unfavourable interactions with the axial methyl group of the enolate. Therefore aldol adduct **34**, predicted by the Felkin-Anh model, is not observed, instead aldol adduct **35** is the dominant product. Considering these alternative transition states it is quite apparent why the Felkin-Anh model fails to account for the observed stereoselectivity of *Z*-(O)-enolates.

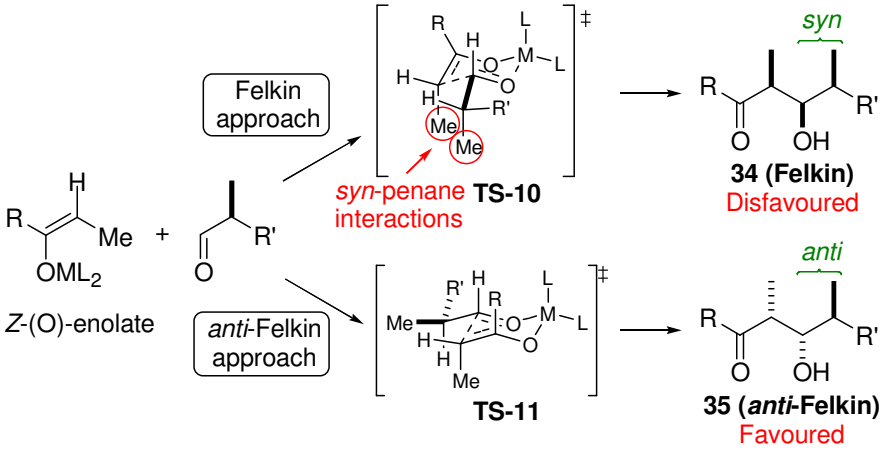


Figure 1.22 Rationalisation of the *anti*-Felkin control observed for reaction of *Z*-(O)-enolates with α-chiral aldehydes.

Similarly, by considering the two alternative transition states for reaction of an α-chiral aldehyde with an *E*-(O) enolate, represented in Figure 1.23, the high levels of Felkin control can be rationalised. In this instance the Felkin transition state (**TS-12**) has an equatorially oriented methyl group which does not experience any unfavourable *syn*-pentane interactions with the substituents on the α-stereocentre of the aldehyde because the largest R group is directed away from the enolate. In contrast, the *anti*-Felkin transition state (**TS-13**) has the medium group (the methyl group) of the α-chiral aldehyde directed away from the enolate. Thus unfavourable *syn*-pentane interactions occur between the equatorially oriented methyl group of the enolate and the bulky R group of the α-chiral aldehyde, raising the energy of **TS-13**, disfavouring formation of aldol adduct **37**. So in the case of the *E*-(O)-enolates the Felkin stereoselectivity predicted by the Felkin-Anh model is enhanced, with aldol adduct **36**, reported as the major product while adduct **37** the minor product.

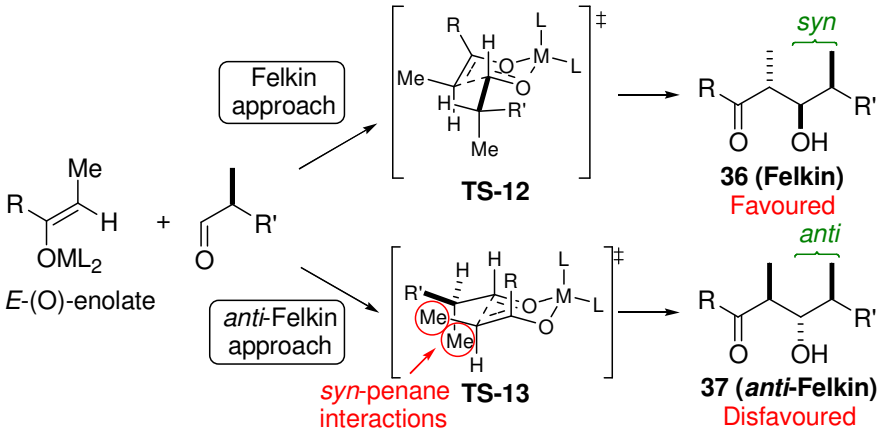


Figure 1.23 Rationalisation of the Felkin control observed for reaction of *E*-(O)-enolates with α-chiral aldehydes.

If the aldehyde has stereogenic centres more remote from the carbonyl, for example at the β or γ carbons, this may also influence the π–facial selectivity. Evans and co-workers[59] reported that heteroatoms on the β-carbon may impart stereocontrol in nucleophilic addition to aldehydes to either enhance or over-ride the stereocontrol imparted by the α-stereocentre. In this case stereocontrol is influenced by choice of solvent as well as the type of nucleophile employed.

1.3.1.2 Controlling the Enolate Geometry

There are a number of factors influencing the geometry of the enolate including the coordinating metal, ligands on the metal, ligands on the amide base and enolisation conditions, such as temperature, solvent and concentration. By controlling these variables it is possible to selectively generate both the *E*-(O)- and *Z*-(O)-enolates leading to *anti*- and *syn*-aldol adducts respectively. The metal-enolates most frequently employed in synthesis of natural products are lithium, boron, titanium and tin which will be discussed in turn.

1.3.1.2.1 Lithium Enolates

Lithium enolates have been in use since the 1950's when they were generated from $LiNH_2$ in liquid ammonia.[8] In recent times they have been generated from the more substituted lithium dialkyl and disilylamides (eg. lithium diisopropylamide or lithium bis(trimethylsilyl)amide) which are less nucleophilic and more soluble in organic solvents due to the presence of the bulky, hydrophobic alkyl groups. The stereochemistry of the lithium enolates is predominantly influenced by the R groups of the ketone, the size and nature of the ligands on the base and the solvent.[54] In

general, larger ligands on the amide base result in higher levels of *E*-(O)-enolate formation, while larger R groups on the ketone lead to enhanced formation of the *Z*-(O)-enolate.

1.3.1.2.2 Boron Enolates

Boron enolates are one of the most commonly employed enolates in stereoselective synthesis due to their versatility, effectiveness and higher selectivity than lithium enolates. This is due, in part, to a more compact transition state arising from the shorter boron to oxygen bond length (1.36-1.47 Å) compared with the lithium to oxygen bond length (1.92-2.00 Å).[54,60] Boron enolates are generated by addition of dialkylboron triflates or chlorides and a tertiary amine base to the ketone. A general rule is that small ligands on the boron (eg. ethyl or ^{n}-butyl), a good leaving group (eg. triflate) and a bulky amine base (eg. $^{i}Pr_2NEt$) favours formation of a *Z*-(O)-enolate, shown in Figure 1.24. In contrast, larger ligands on the boron (eg. ^{c}-hexyl), a poor leaving group (eg. chlorine) and a small amine base (eg. NEt_3) favours formation of an *E*-(O)-enolate. However this is just a guideline and there are examples of reversal of selectivity depending on the combination of the functionality within the ketone, the Lewis acid and the base.

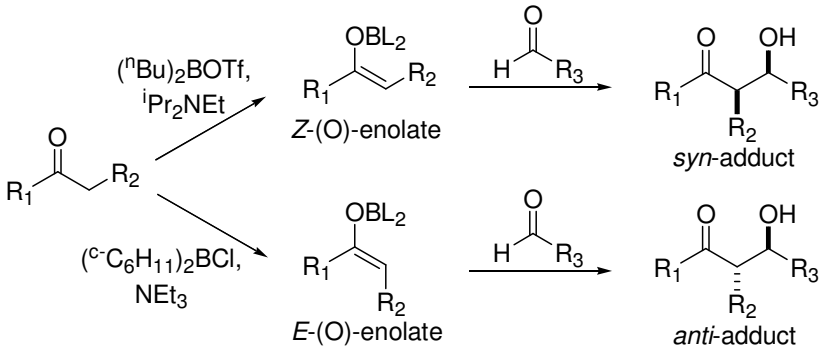


Figure 1.24 Selective formation of both *E*-(O)- and *Z*-(O)-boron enolates by control of the enolisation conditions.

1.3.1.2.3 Titanium and Tin Enolates

Both titanium and tin enolates have been found to favour formation of the *Z*-(O)-enolates producing adducts with high levels of *syn*-selectivity. Evans and co-workers developed a strategy for synthesis of *Z*-(O)-enolates employing $TiCl_4$ and related titanium (IV) halogen alkoxides and amines.[61] Mukaiyama and co-workers used $Sn(OTf)_2$ and tertiary amines to generate Z-(O)-enolates with excellent selectivity.[62-64] Both titanium and tin enolates generated in this manner have been extensively employed in total synthesis. It is also possible to preferentially generate the *E*-(O)-

enolate by employing chiral ligands on the titanium Lewis acid[65] or by providing additional sites for chelation of the metal atom, either by incorporating atoms at sites remote from the transition state[66,67] or by addition of external chelating agents such as TMEDA.[68,62]

1.3.1.3 π-Facial Selectivity of the Enolate

In addition to controlling the enolate geometry to give selectively *syn*- or *anti*-products, substrate based control can be used to govern the facial preference of the enolate. By introducing stereogenic elements into the enolate, the corresponding transition states (**TS-2** and **TS-3**, Figure 1.19) are no longer enantiomeric and energy differences between the transition states will dictate the reaction outcome. This method has proven to be much more effective at imparting stereocontrol than introducing chirality into the aldehyde coupling partner (refer to Section 1.3.1.1). This is partially due to the variety of approaches available to introduce chirality into the enolate, but is also due to the facial preference of some chiral ketones dominating the facial preference of chiral aldehydes in double stereodifferentiating mixed aldol reactions which are discussed in Section 1.3.1.5.[69-72] Strategies to introduce chirality into the enolate include implementing chirality in the ketone, either in the form of a chiral auxiliary or chirality at remote centres, or employing chiral ligands on the metal atom, each of which will be examined in turn.

1.3.1.3.1 Chiral Ketones

A number of ketones with stereocentres at the α- (and more remote) carbon atoms have been developed to influence the relative reactivities of the two π-faces of the corresponding enolate. The expanse of available literature on this topic demonstrates its success and general applicability. Several chiral ketones that have been employed extensively in natural product synthesis will be discussed. Paterson and co-workers[71,73-77] have developed several α-chiral ketones **(*R*)-38**, **(*S*)-39** and **(*S*)-40** and their enantiomers (Figure 1.25) which demonstrate high levels of π-facial selectivity.

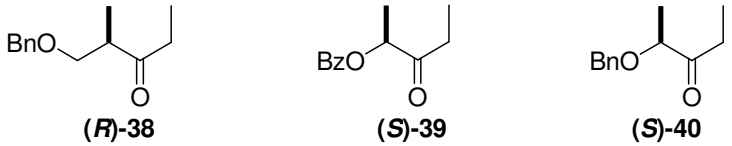


Figure 1.25 The α-chiral ketones developed by Paterson and co-workers impart π-facial control.

With choice of a suitable boron enolate derivative 1,2-*syn*-2,4-*anti*-, 1,2-*syn*-2,4-*syn*- and 1,2-*anti*-2,4-*anti*-aldol adducts can be achieved from ketone **(*R*)-38** with high diastereoselectivity, outlined in Figure 1.26. The *Z*-(O)-enolate of ketone **(*R*)-38**, which can be generated stereoselectively from $(Ipc)_2BOTf$ and Et_3N or $^iPr_2NEt$, allows nucleophilic attack at both faces of the enolate depending on the stereochemistry of the isopinocamphyl ligands on the boron. This means that both *syn*- or *anti*-relationships are attainable between the pre-existing α-stereocentre on the ketone and the developing methyl-bearing stereocentre with up to 93 % ds.[73,74] In addition, the *E*-(O)-enolate which can be generated from $(^{c-}C_6H_{11})_2BCl$ and Et_3N gives the corresponding 1,2-*anti*-2,4-*anti*-product with ≥ 95 % ds.[74] Computational studies using transition state modelling have been used to identify the favoured transition states leading the products observed.[78,79] In some cases the preferred geometry of the transition states can be attributed to a number of competing effects.

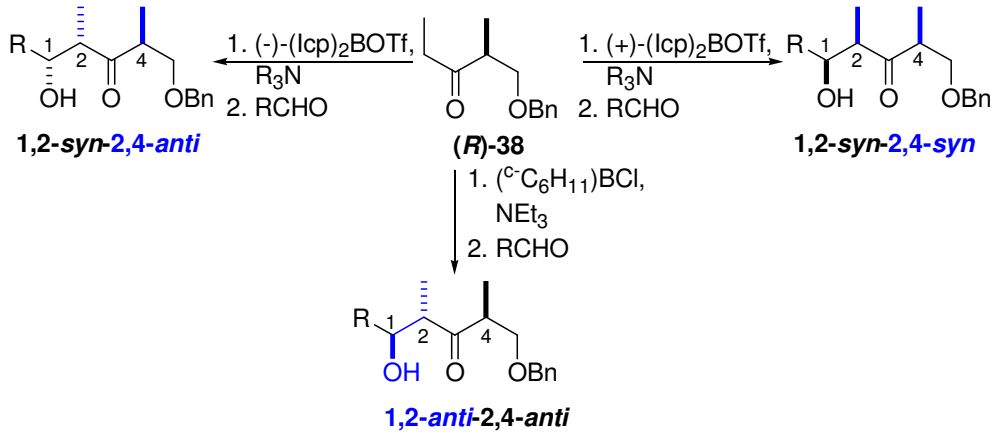


Figure 1.26 By employing different ligands on the boron enolates of ketone (*R*)-38 a range of aldol adducts with various stereochemistries can be achieved.

Lactate derived ketones **(*S*)-39** and **(*S*)-40** (Figure 1.25) are identical except for the hydroxyl protecting group, benzoyloxy ester Vs. benzyl ether, however this protecting group governs the enolate geometry generated from $(^{c-}C_6H_{11})_2BCl$. Figure 1.27 outlines the formation of the *Z*-(O) and *E*-(O)-enolates of ketones **(*S*)-39** and **(*S*)-40** respectively, resulting in the stereoselective formation of the aldol adducts shown. Addition of ketone **(*S*)-39** and Me_2NEt to a solution of $(^{c-}C_6H_{11})_2BCl$ in Et_2O at -78 ^oC and subsequently warming to 0 ^oC and stirring for 2 hours gives the *E*-(O)-enolate selectively leading to 1,3-*anti*-3,4-*anti*-aldol adducts with 97-99.5 % ds.[71] Alternatively, addition of ketone **(*S*)-40** and NEt_3 to a solution of $(^{c-}C_6H_{11})_2BCl$ in Et_2O at -78 ^oC and stirring at this temperature for 2 hours gives the *Z*-(O)-enolate selectively, leading to 1,3-*anti*-3,4-*syn*-aldol adducts with 90-92 % ds.[71]

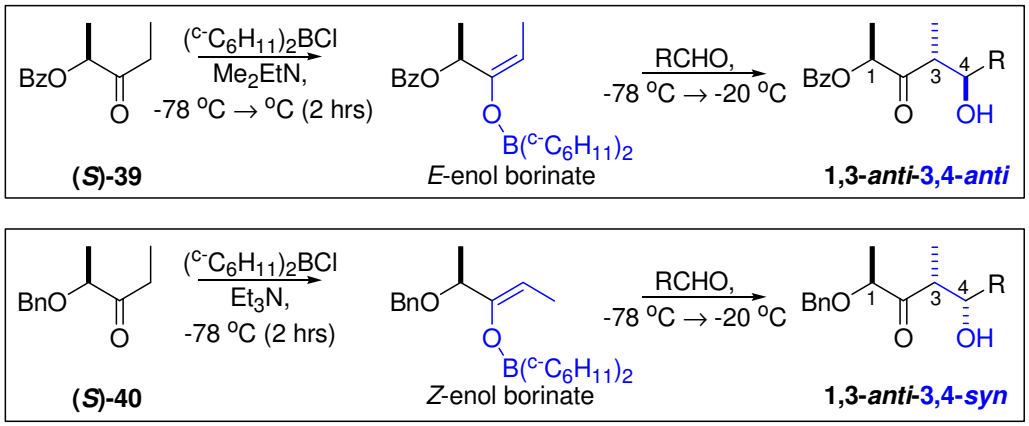


Figure 1.27 Ketones (*S*)-39 and (*S*)-40 produce *E*-(O)- and *Z*-(O)- boron enolates respectively.

The α-stereocentre from both ketones **39** and **40** controls the facial selectivity of the enolate inducing an *anti*-relationship between the developing methyl-bearing stereocentre and the pre-existing α-stereocentre with both *Z*-(O)- and *E*-(O)-enolates. This can be rationalised by considering the alternate Zimmerman-Traxler transition states for reaction of an achiral aldehyde with each face of the chiral enolates. The most stable transition states arising from reaction of ketone **39**, are shown in Figure 1.28.[71] The rotamer around C2 exists such that A(1,3)-allylic strain with the *E*-enol methyl group is minimised (i.e. the smallest group, the hydrogen, eclipses the methyl group) which is represented in green in Figure 1.28. In transition state **TS-14** the axial proton of the aldehyde and the carbonyl of the benzoate ester experience stabilising hydrogen bonding interactions facilitating reaction at this face of the enolate. The product arising from **TS-14** is such that the relationship between the developing methyl bearing centre and the pre-existing α-stereocentre is *anti*. In the alternative transition state (**TS-15**), which represents reaction at the alternative face of the enolate, destabilising lone pair interactions are experienced between the carbonyl of the benzoate ester and lone pair of the enolate oxygen. Thus **TS-15**, leading to the 1,3-*syn*-adduct is disfavoured, accounting for the high levels of selectivity of the 1,3-*anti*-adduct.

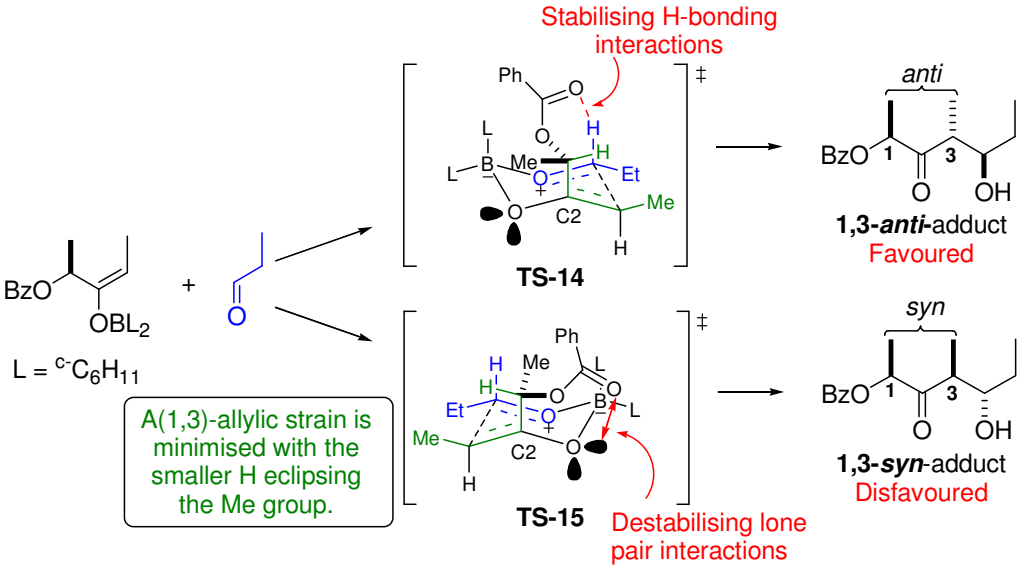


Figure 1.28 The most stable, alternative Zimmerman-Traxler transition states for reaction of an achiral aldehyde with each face of the *E*-(O)- enolate of ketone 39.

A similar rationale for the π-facial selectivity of ketone **40** can be derived.[80] The most stable Zimmerman-Traxler transition states arising from reaction of an achiral aldehyde with both faces of the *Z*-(O)-enolate of ketone **40** are represented in Figure 1.29. Lone pair repulsions between the benzyl ether oxygen and the enolate oxygen dictates the rotamer around C2, which is represented in green in Figure 1.29. In transition state **TS-16** the smaller hydrogen atom lies in the more sterically demanding position over the chair while in transition state **TS-17** the bulkier methyl group occupies this position. As a result the 1,3-*anti*-adduct arising from **TS-16**, which is clearly more stable than **TS-17**, is the dominant product achieved, with high levels of diastereoselectivity.

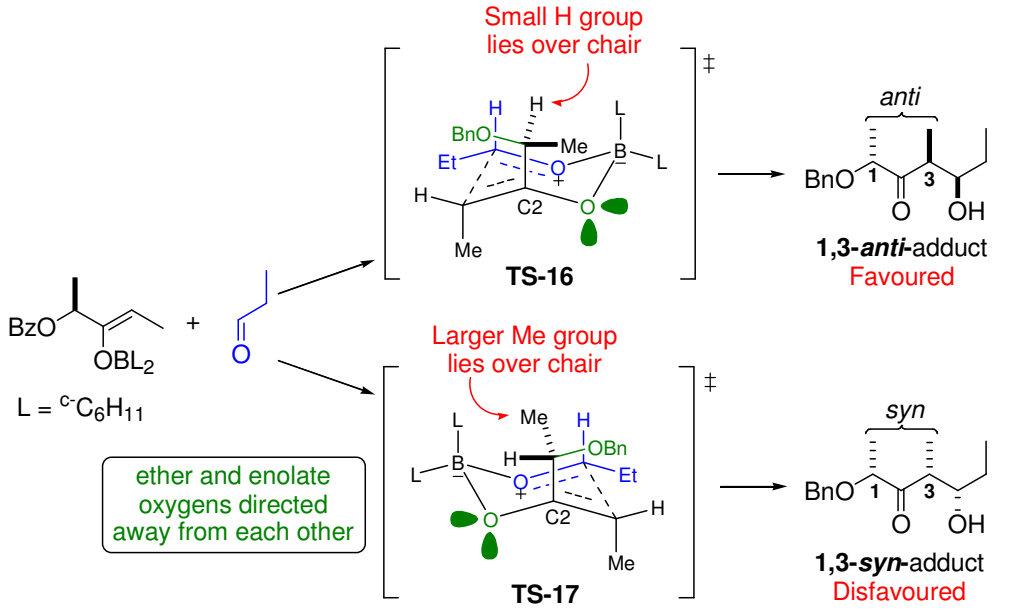


Figure 1.29 The most stable alternative Zimmerman-Traxler, transition states for reaction of an achiral aldehyde with each face of the *E*-(O)- enolate of ketone 40.

An added advantage of lactate derived chiral ketones **39** and **40** is that the α-stereocentre controlling the π-facial selectivity of the ketone in the aldol coupling can either be retained in the target molecule or cleaved at a later stage depending on the requirements, as outlined in Figure 1.30.[75] Reductive removal of either the benzoate (Bz) ester or benzyl (Bn) ether with SmI_2 to generate the corresponding ethylketone has been reported. Alternatively, if the adduct is a benzoate ester, simultaneous reduction of the ketone and ester functionalities, with $LiBH_4$, to give the 1,2-diol and subsequent periodate oxidation gives the corresponding aldehyde. If the adduct is a benzyl ether, reduction of the carbonyl group with $NaBH_4$, followed by hydrogenolysis of the benzyl ether gives the 1,2-diol which can be oxidised with sodium periodate to the corresponding aldehyde.

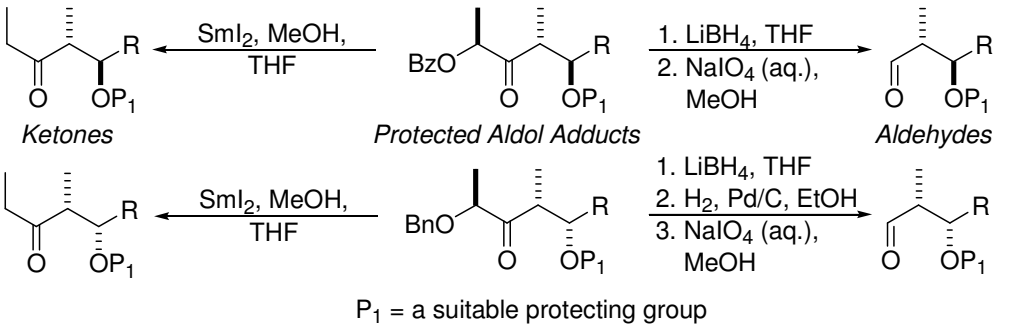
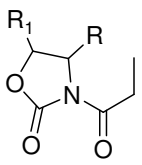


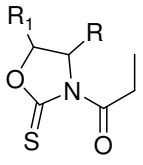
Figure 1.30 Removal of the α-stereocentre from the aldol adducts from ketones 39 and 40.

1.3.1.3.2 Chiral Auxiliaries

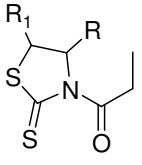
Chiral auxiliaries have been exploited in organic synthesis to impart π-facial selectivity to enolates. A chiral auxiliary is a chiral group which can be added to the enolate providing stereocontrol to a diastereoselective step and readily removed after the reaction. Evans and co-workers have developed several chiral N-acyloxazolidinone auxiliaries with the general structure **41a-c** (Figure 1.31) with various R groups in particular orientations.[81-83] More recently, the related N-acyloxazolidinethiones (**42a-e**) and N-acylthiazolidinethiones (**43a-d**), have also been developed.



41
a; R = Bn, R_1 = H
b; R = Me, R_1 = Ph
c; R = ^{i}Pr, R_1 = H



42
a; R = Et, R_1 = H
b; R = iPr, R_1 = H
c; R = Me, R_1 = Ph
d; R = Bn, R_1 = H
e; R = Bn, R_1 = Me(2)



43
a; R = Bn, R_1 = H
b; R = Ph, R_1 = H
c; R = ^{i}Pr, R_1 = Ph
d; R = Me, R_1 = Ph

Figure 1.31 Various chiral auxiliaries developed to impart π-facial selectivity.

Enolates derived from N-acyloxazolidinones (**41**) react with high levels of facial selectivity in alkylation reactions[84] and aldol condensation reactions.[83] The orientation of the R groups on the oxazolidinone controls the facial preference of the enolate, directing addition to the least hindered face. By considering the Zimmerman-Traxler transition states this stereocontrol can be rationalised.[60] Figure 1.32 depicts a *Z*-(O)-enolate reacting with an achiral aldehyde at both faces of the chiral enolate, represented by the two transition states, **TS-18** and **TS-19**. The preferred rotamer of the axial N to C bond is such that the dipoles of the carbonyl group of the auxiliary and the enolate oxygen are opposed, represented in green. In **TS-18** the smaller H group lies in the more sterically demanding position above the chair while in **TS-19** the bulky R group occupies this position. As a result the dominant product is the so called "Evans" 1,2-*syn*-aldol adduct, where reaction occurs at the face of the enolate opposite to the R group, reacting through the favoured transition state **TS-18**. The *Z*-(O)-enolate can be generated with high stereoselectivity (>99 % ds) from Bu_2BOTf.[82] Cleavage of the auxiliary can yield a variety of products (eg. amides, Weinreb amides, carboxylic acids, alcohols, esters or

thioesters) depending on the conditions used and as true chiral auxiliaries the chiral heterocycles can be recovered and reused.[85]

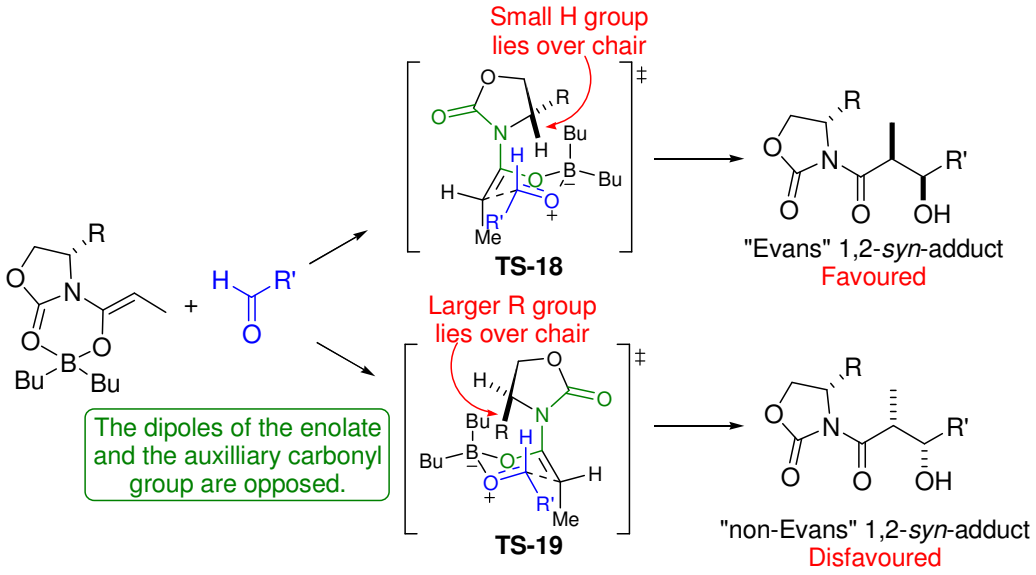


Figure 1.32 The alternative Zimmerman-Traxler transition states for the (*Z*)-(O)-boron enolate of oxazolidinone 41.

1.3.1.3.3 Lewis Acid Initiated π-Facial Selectivity.

The choice of Lewis acid can also play a significant role in controlling the π-facial selectivity. In some instances simultaneous coordination of the metal atom to remote atoms within the enolate (such as chiral auxiliaries) affects the stabilities of the transition states, influencing reactivity at each π-face.

The first example of internal chelation involves the chiral N-acyloxazolidinethiones **42** and N-acylthiazolidinethiones **43**, (Figure 1.31) which are related to the Evans auxiliary discussed above. These compounds offer several advantages over the oxazolidinones being synthetically simpler to prepare, cleaved under milder conditions and providing access to adducts with a larger variety of stereochemistries depending on the Lewis acid employed.[86] The dialkyl boron *Z*-(O)-enolates of these derivatives can be formed with high stereoselectivity producing the "Evans" *syn*-adduct, *via* the analogous transition state to **TS-18** in Figure 1.32. However by employing titanium (IV) *Z*-(O)-enolates, it is possible to achieve the "non-Evans" *syn*-adducts. In this instance the *Z*-(O)-enolate, represented in Figure 1.33, reacts through an alternative low energy transition state, **TS-20**, in which the imide or thioamide carbonyl coordinates to the titanium atom. The diastereoselectivity of this reaction can be controlled by the nature and amount of base used to generate the

enolate. If two equivalents of an amine base are employed the "Evans" *syn*-adduct is formed as the second equivalent of the amine base coordinates preferentially to the titanium atom and the reaction proceeds through the non-chelated transition state, **TS-18**, in Figure 1.32. However when only one equivalent of amine base is used the thioamide carbonyl can coordinate to the titanium and the reaction proceeds *via* the chelated transition state **TS-20**, producing the "non-Evans" *syn*-adduct.

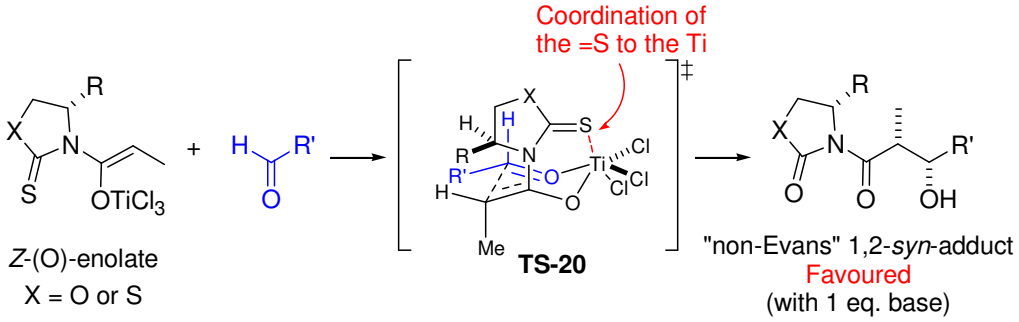


Figure 1.33 The chelated transition state of the titanium enolates of oxazolidinethione 42 and thiazolidinethione 43.

A further example of the differing π-facial selectivities imparted by careful selection of the Lewis acid was reported by Oppolzer and co-workers.[66,67] The choice of metal atom employed in generating the enolate of sultam **44**, Figure 1.34, controls the transition state geometry. Internal chelation to the sultam oxygen can occur with metal atoms which have high coordination potentials, such as lithium and tin, resulting in formation of adduct **45** as the major product. However the reaction selectivity is reversed if a boron enolate is generated. The lower coordination potential of boron prevents further coordination to the sultam oxygen and thus the reaction proceeds through an alternative transition state leading to adduct **46**.

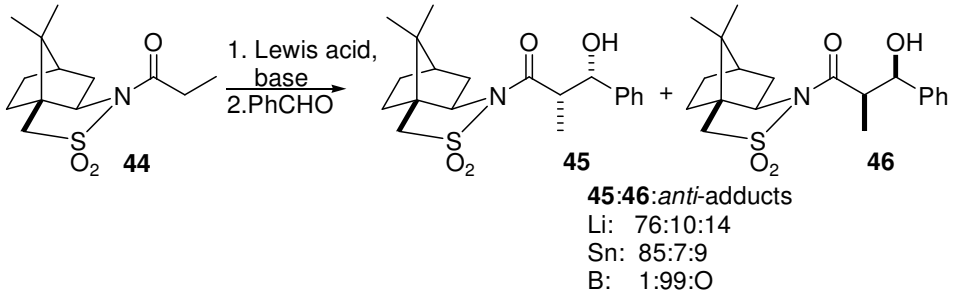


Figure 1.34 Oppolzer and co-workers report that stereocontrol can be imparted by internal coordination of the metal atom of the enolate. [66,67]

1.3.1.4 Reagent Control in Stereoselective Aldol Reactions

In addition to substrate based control, where the aldehyde and ketone coupling partners impart stereocontrol through remote chiral centres and enolate geometry, another strategy that has been successfully implemented is reagent based control.[54] The philosophy behind this approach is to influence the relative energies of the chair transition states by introducing chirality making the alternative transition states diastereomeric. This is generally achieved by using chiral reagents, routinely chiral ligands attached to the metal atom of the Lewis acid.

1.3.1.4.1 π-Facial Selectivity Imparted by Chiral Ligands

A number of chiral ligands attached to boron have been developed to impart stereocontrol in aldol reactions, some popular examples are shown in Figure 1.35. Boron reagent **47**, derived from α-pinene and developed by Paterson and co-workers, has been used extensively in the synthesis of *syn*-aldol adducts with high diastereoselectivity and good enantioselectivity (>90 % ds, 66 - 90 % ee).[87] The related boron reagent **48**, also developed by Paterson and co-workers and derived from the natural product menthone, gives *anti*-aldol adducts with high diastereoselectivity and good enantioselectivity (86 - 100 % ds, 56 - 88 % ee).[88] A variety of chiral boron enolates having C2-symmetric ligands, such as **49** and **50**, have also been used in additions to aldehydes with high enantioselectivity. Enolates of compound **49**, developed by Reetz and co-workers, routinely react with moderate to good yields to give *anti*-aldol adducts with exceptional enantioselectivity(> 90 %).[89-91] Finally, outstanding *Z*-(O)-enolate selectivity (> 95 %) is achieved with enolates of borane **50** reacting in good-excellent yields (70 - 95 %).[92,93] In addition borane **50**, gives highly selective formation of *E*-(O)-enolates of *tert*-butyl esters and *Z*-(O)-enolates of thioesters.[92,93]

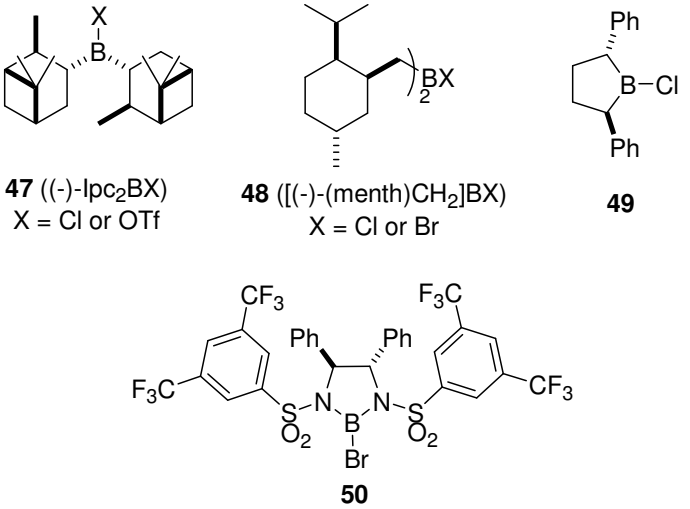


Figure 1.35. Chiral ligands on boron provide another approach to imparting π-facial selectivity into the enolate.

1.3.1.5 Double Stereodifferentiating Reactions

In the examples discussed thus far, π-facial selectivity has been imparted by only one of the two aldol coupling partners, either the chiral aldehyde or chiral enolate. The enolate geometry dictates the relative relationship between the developing methyl and hydroxyl bearing stereocentres, due to the restraints imposed by the cyclic six-membered transition state. However, in a reaction between a chiral aldehyde and a chiral enolate the situation is more complicated. Both coupling partners have π-facial preferences for reaction and thus the requirement of satisfying the π-facial preferences of each of the coupling partners becomes an important issue affecting the stereochemical outcome of the reaction. Stereogenic elements within the enolate may impart control over the orientation of the developing methyl bearing stereocentre, while stereocentres within the aldehyde may impart control over the orientation of the developing hydroxyl bearing stereocentre. As the enolate geometry dictates the relative relationship, the facial preferences of the enolate and aldehyde components cannot always be satisfied. The case of reaction of a chiral aldehyde with a chiral ketone is known as a double stereodifferentiating aldol reaction.

In basic terms, double stereodifferentiating reactions can be matched, where both the enolate and the aldehyde facial preferences are satisfied or mis-matched where neither the facial preference of the enolate nor the aldehyde is satisfied. Heathcock and co-workers reported a simple example of a double stereodifferentiating aldol reaction between chiral ketone **51** and both the *R* and *S* enantiomers of α-chiral

aldehyde **52**, illustrated in Figure 1.36.[94] In the reaction of the *Z*-(O)-enolate of ketone **51** with the *S*-enantiomer **(*S*)-52**, the *anti*-Felkin product **53** is achieved in high diastereoselectivity. This result is as predicted for the reaction of a *Z*-(O)-enolates with an α-chiral aldehyde which proceeds through the *anti*-Felkin transition state preferentially. In addition the facial preference of the chiral ketone, determined by reaction of the ketone with achiral benzaldehyde, is also satisfied, thus the double stereodifferentiating aldol reaction is matched.

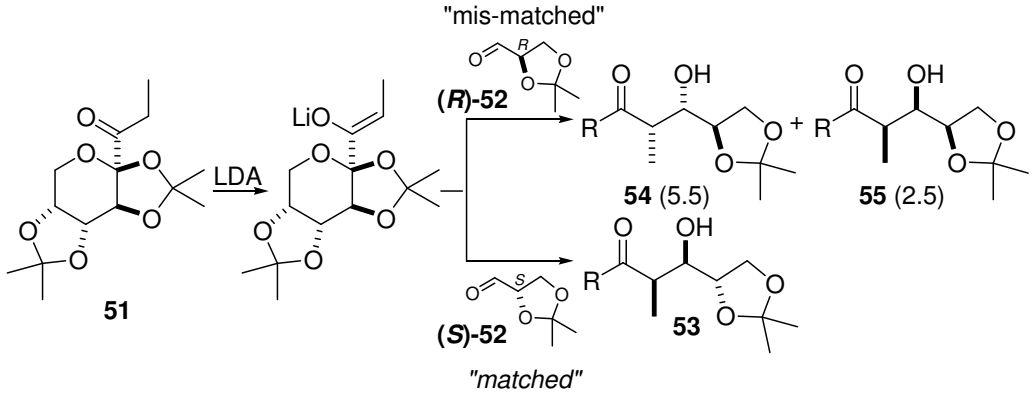


Figure 1.36 An example of a double stereodifferentiating aldol reaction reported by Heathcock and co-workers.[94]

In the case of the reaction between the *Z*-(O)-enolate of ketone **51** and the *R*-enantiomer **(*R*)-52**, the diastereoselectivity is significantly less, producing adducts **54** and **55** as well as a minor component which was unable to be assigned (ratio 5.5:2.5:1). The major product **54**, the *anti*-Felkin product is formed much less selectively because the inherent diastereofacial preference of the enolate is opposed to the *anti*-Felkin preference of aldehyde **(*R*)-52**. The other dominant product, adduct **55**, satisfies the inherent diastereofacial preference of the enolate however with respect to aldehyde **(*R*)-52** the nucleophile approaches in a Felkin fashion. Thus the transition state leading to this product experiences unfavourable *syn*-pentane interactions in the transition state. This reaction is an example of a mis-matched double stereodifferentiating aldol reaction.

Double stereodifferentiation can be further complicated when there are two or more stereogenic centres in either of the reactants which may each impart different facial preferences. This often occurs in the synthesis of complex natural products where the coupling partners can be quite large with multiple stereogenic centres. As a result several elements of stereocontrol may be acting simultaneously but towards different

goals. This can lead to instances where the reaction may be partially matched because either the α-, β- or more remote stereocentres may be matched while the other centres are mis-matched. In the case of partially matched, double stereodifferentiating aldol reactions, the facial preference of one of the reactants or stereogenic centres generally predominates. Evans and co-workers investigated the affect that orientation of both the α- and β- stereocentres of chiral aldehyde **56**, has on the stereochemical outcome of an aldol coupling with chiral *E*-enolate **57**.[95] Some of the results of their study are displayed in Figure 1.37. In the case of both the matched reaction, between enolate **57** and aldehyde **(*S*,*S*)-56**, and the partially matched reaction, between enolate **57** and aldehyde **(*S*,*R*)-56**, where the α-stereocentre of the aldehyde is matched with the facial preference of enolate **57**, the stereoselectivity is excellent. When enolate **57** and the β-stereocentre of aldehyde **(*R*,*S*)-56** are matched the selectivity decreases with the Felkin control of the α-stereocentre being partially overridden by facial preference of the β-stereocentre. In the final case where neither of the stereocentres of aldehyde **(*R*,*R*)-56** nor enolate **57** are matched the stereoselectivity is poor as predicted.

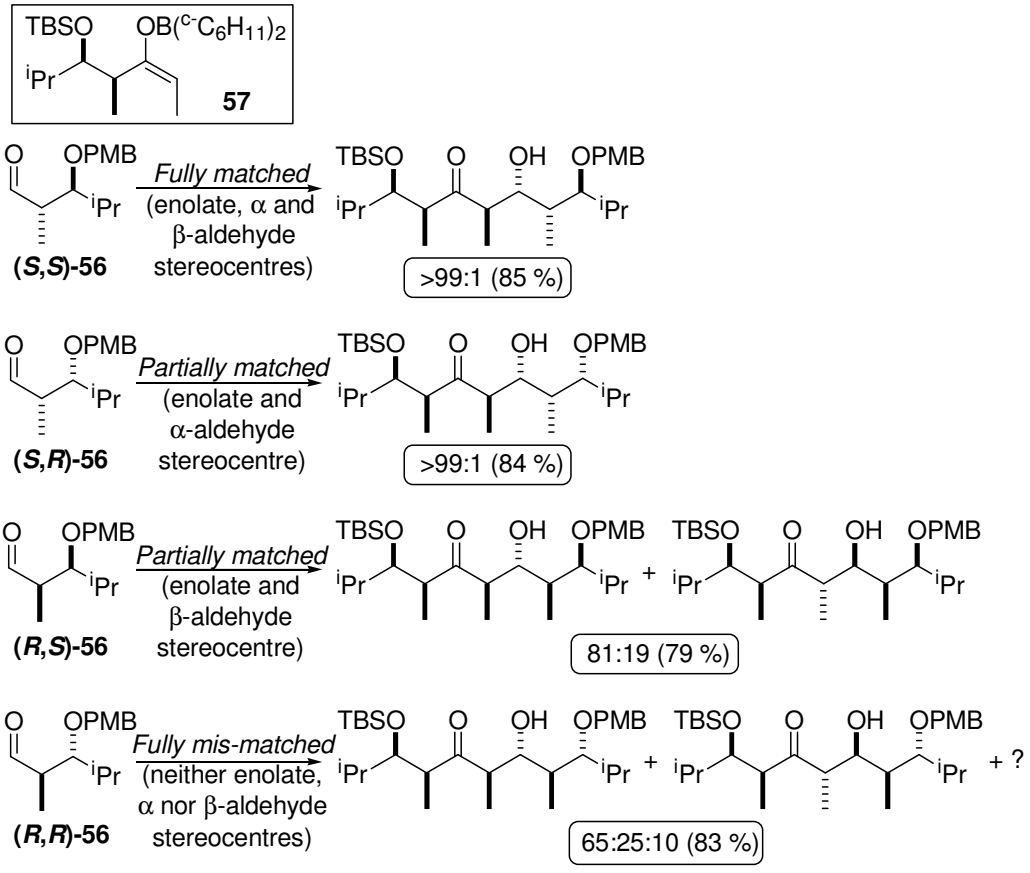


Figure 1.37 An investigation of the affects the α- and β-stereocentres of chiral aldehydes 56 on double stereodifferentiating aldol reactions.[95]

1.3.1.6 Summary of the Aldol Reaction

The aldol coupling reaction has proven to be of fundamental importance in the total synthesis of polyketide derived natural products generating a β-hydroxyketone and two new stereogenic centres with high stereocontrol. This brief review of methods of imparting stereocontrol in aldol condensation reactions has provided a snapshot of the expanse of literature on this topic. A plethora of options are available to impart stereocontrol such as employing chiral coupling partners, chiral ligands or by careful selection of the Lewis acid and reaction conditions. It is therefore possible to stereoselectively achieve aldol adducts with a range of different stereochemical combinations, making this one of the most widely employed carbon to carbon bond forming reactions utilised in natural products synthesis.

1.3.2 The Wittig Olefination Reaction

Olefination of aldehydes was once considered an arduous task for synthetic organic chemists due to the potential variability of the double bond geometry and the double bond position. In the 1950's Wittig and co-workers revolutionised alkene synthesis, publishing a generally applicable method of preparing a variety of alkenes with control over the location of the double bond.[40,41] The procedure, outlined in Figure 1.38, involves the reversible aldol condensation of a phosphonium ylide **58** with an aldehyde or ketone (**59**) to form diastereomeric, four membered cyclic intermediate oxaphosphetanes **60**, which undergo an irreversible *syn*-elimination to give an alkene (**61**) and trialkylphosphine oxide (**62**).

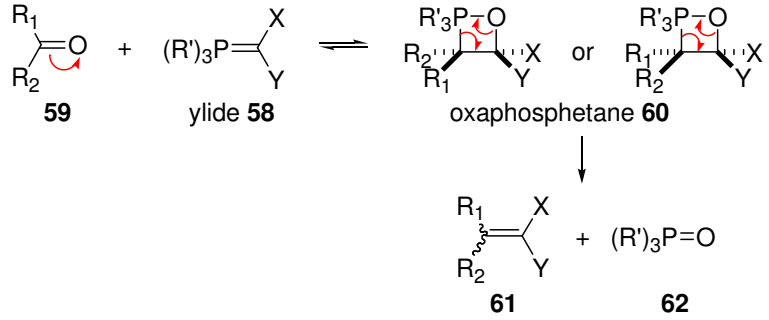


Figure 1.38 General mechanism for the Wittig olefination reaction.

In general the reaction stereoselectivity is affected by the type of ylide, the type of carbonyl compound or the reaction conditions (for example temperature, solvent or addition of salts).[96] Predicting the likely stereochemical outcome of the Wittig reaction is possible by applying a few simple rules which are widely accepted in the

chemistry community.[96,97] Instances where the X or Y groups on the ylidic carbon are electron withdrawing (eg. CO_2CH_3, CN or SO_2Ph), known as "stabilised" ylides, generally favour formation of alkenes with an *E*-geometry. If the substituents, X and Y, are mildly conjugating (eg. Ph or allyl) the ylide is termed "semi-stabilised" and gives little olefin stereoselectivity. The last group of ylides are the "non-stabilised" ylides possessing groups, X and Y, not capable of conjugation, favouring formation of alkenes with a *Z*-geometry.

The above trends in stereoselectivity can be rationalised by considering the generally accepted mechanism outlined in Figure 1.38. The oxaphosphetanes (**60**) produced from stabilised ylides are relatively stable compared with those from non-stabilised ylides due to their ability to delocalise the charge. This enhanced stability means that *syn*-elimination to the alkene does not occur as readily.[98] Thus the two possible isomers of oxaphosphetane **60** are able to equilibrate through the starting materials to the thermodynamically favoured isomer with the larger groups on each carbon in opposite orientations. Upon elimination the *E*-alkene is predominantly formed. In contrast, when non-stabilised ylides are available the reaction is under kinetic control. Under salt free conditions the rapidly formed oxaphosphetanes readily collapse to the alkenes and thus thermodynamic equilibration cannot occur.[98]

This stereocontrol has been further rationalised by Schneider who proposed a model accounting for the preferential formation of the *Z*-isomer from non-stabilised ylides and the *E*-isomer from stabilised ylides.[99] Preferential coordination of the oxygen to the phosphorous, giving complex **63**, occurs prior to carbon to carbon bond formation as depicted in Figure 1.39. This complex is oriented such that the ylide carbon is equatorial and the oxygen of the aldehyde is axial to enable carbon to carbon bond formation between the two groups to occur. For non-stabilised ylides the R_2 group of the ylide is distorted away from the phosphorus to decrease steric interactions with the Ph groups on the phosphorous. In order for formation of the carbon to carbon bond to occur, the carbon to oxygen bond of the aldehyde (in blue) must rotate bringing the planar components into a co-facial arrangement. Rotation to the left, shown in purple, gives the *erythro* oxaphosphetane leading to the *Z*-alkene in which the R_1 and R_2 groups eclipse, however only one phenyl group is sterically compressed. Alternatively, rotation to the right, shown in green, produces the *threo* oxaphosphetane leading the *E*-alkene where the R_1 and R_2 groups are opposed which

is more favourable, however steric compression of an additional phenyl group occurs. Thus the *erythro* arrangement is preferentially formed and rapidly collapses to the *Z*-alkene.

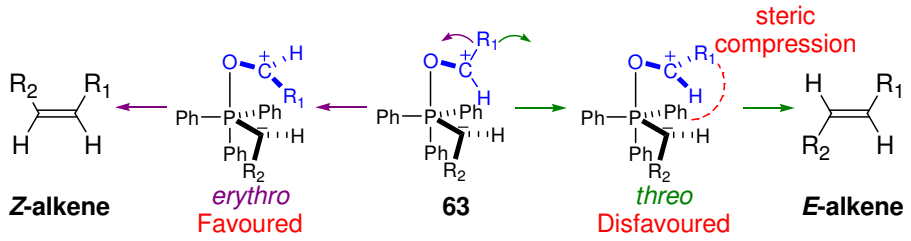


Figure 1.39 Schneider's rationalisation of the *Z*-selectivity of the Wittig olefination with non-stabilised ylides.[99]

In the case of stabilised ylides, outlined in Figure 1.40, the positive end of the aldehyde orients itself towards the negative charge stabilised by the electron withdrawing group. Thus, rotation occurs to give the *threo* oxaphosphetane leading to the *E*-olefin with high selectivity.

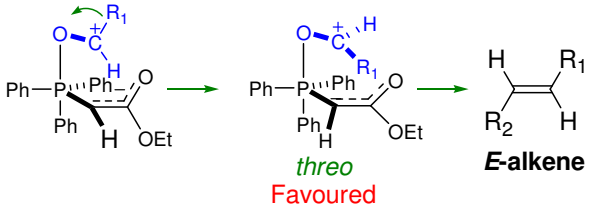


Figure 1.40 Schneider's rationalisation of the *E*-selectivity of the Wittig olefination with stabilised ylides. [99]

Modifications to the reaction conditions, such as temperature, solvent, ligands on the phosphorus or the addition of salts, allows these generally observed trends in selectivity to be manipulated. For non-stabilised ylides reaction at room temperature gives generally good *Z*-selectivity, however lowering the temperature increases the levels of *Z*-selectivity.[100] In general, as the bulk of the phosphorus ligand increases the *E*-selectivity decreases. In addition, by employing hindered aldehydes the *Z*-selectivity can be enhanced significantly compared with unbranched aldehydes. Therefore by utilising a hindered aldehyde and bulky phosphorous ligands, high levels of *Z*-selectivity are attainable.[100] Schlosser and co-workers reported that addition of lithium salts to the reaction mixture can enhance formation of the *E*-alkenes from non-stabilised ylides.[101,102] Their proposed mechanism, shown in Figure 1.41, suggests that the intermediate species **64**, which is stable to inversion, reacts with another equivalent of ^{n}BuLi forming anion **65** which can rapidly equilibrate to the thermodynamic form. Upon protonation with *tert*-butanol the intermediate **66** can

undergo *syn*-elimination to the *E*-alkene selectively. Choice of solvent and concentration is important when employing lithium salts because polar solvents will competitively bind to the lithium and concentration will affect the stereoselectivity of the reaction.[103] Addition of relatively insoluble non-electrophillic salts such as sodium and potassium halides have little affect on the reaction selectivity.[100]

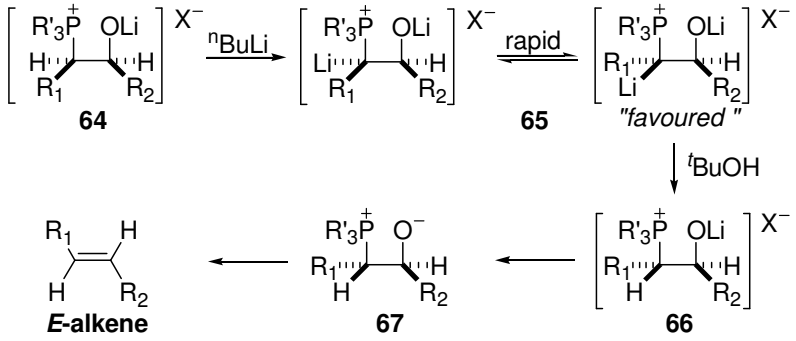


Figure 1.41 Proposed mechanism for the Wittig olefination using lithium salts.

Wittig olefination reactions with ketones are appreciably more difficult due to the decreased reactivity of the carbonyl and the competitive enolisation of the ketone in the presence of the base. As the steric bulk of the reactants increases the reaction is further inhibited. There are a number of strategies commonly employed to combat the low reactivity and competitive enolisation.[100] The use of potassium bases, such as KHMDS, rather than lithium bases to generate the ylide enhances the product formation because enolisation is either avoided or the reaction is reversible allowing eventual conversion of the ketone into the alkene. The rate of reaction with the less reactive ketones can be improved by increasing the concentration of the reactants.

There are a variety of commercially available stabilised ylides which can be employed directly in olefin synthesis. Alternatively, as outlined in Figure 1.42, synthesis can be achieved by reaction of a trialkylphosphine with an appropriate halide, generating the phosphonate salt and subsequent reaction with a base produces the ylide. While several trialkylphosphines are commercially available, such as triphenylphosphine, some require synthesis from the Grignard reagents and phosphorous trichloride which can be cumbersome requiring strictly anhydrous conditions.[104]

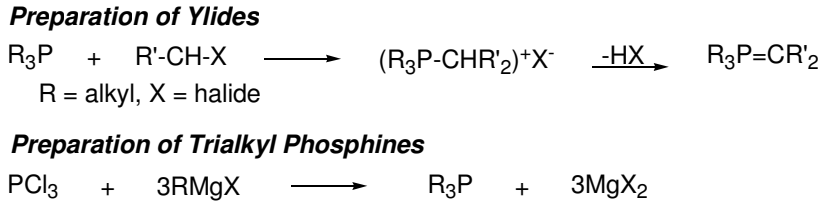


Figure 1.42 Synthesis of ylides from trialkyl phosphines and synthesis of the trialkyl phosphines.

1.3.3 The Horner-Waddsworth-Emmons Olefination Reaction

A modification of the Wittig reaction, initially utilised by Horner and co-workers[43,42] but further extended by Wadsworth and Emmons,[44] involves reaction of a phosphoryl-stabilised carbanion (**69**) with aldehydes and ketones to generate the alkene. The carbanion is typically stabilised by groups such as COR, CO_2R, CN, aryl, vinyl, SO_2R, $P(O)(OR)_2$, SR, OR and NR_2.[104] The absence of an α-substituent capable of stabilising the carbanion results in poor yields of the alkene products. The mechanism is thought to be analogous to that described for the Wittig reaction and is represented in Figure 1.43. After generation of the phosphonate carbanion **69**, a reversible aldol condensation generates two diastereomeric oxyanions (**70**), which fragment *via* an irreversible *syn*-elimination to give the alkene product.[104]

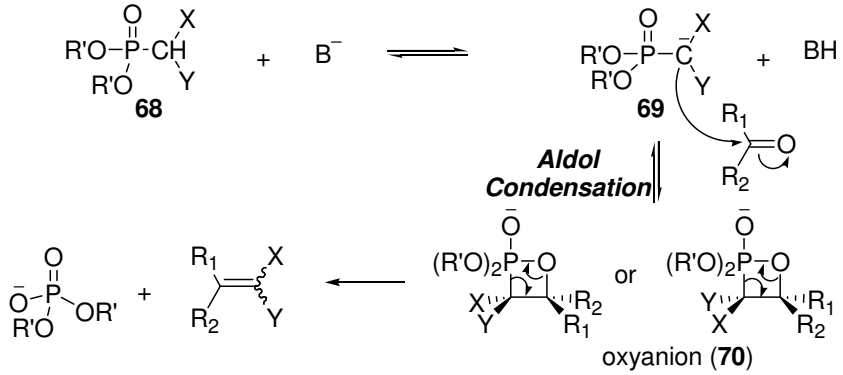


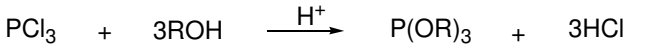
Figure 1.43 General mechanism for the H.W.E. olefination reaction.

This approach to alkene synthesis, commonly referred to as the Horner-Wadsworth-Emmons (H.W.E.) reaction, offers several advantages over the Wittig olefination reaction.[44,104] The by-products, highly water soluble alkali metal dialkylphosphate salts, are readily removed by aqueous washing or precipitating out of low polarity solvents. In contrast, the phosphine oxides, which are the by-products of the Wittig reaction, can be cumbersome to remove from the reaction product as they have similar solubilities. Phosphoryl stabilised carbanions are more reactive than their

ylide counterparts due to the overall neutral structure of the latter, enabling condensation with less reactive carbonyl compounds or reaction under milder conditions. In addition, stabilised phosphonate carbanions are much more reactive towards ketones than the phosphorane counterparts providing access to more highly substituted olefins.[104] The Wittig reaction generally produces more undesirable side products possibly as a consequence of the lower reactivity of Wittig reagents in olefin formation. Phosphonate anions are often cheaper than their phosphorane counterparts and synthetically simpler to prepare.

Just as some stabilised ylides are commercially available for the Wittig reaction, some phosphonate salts are commercially available for the H.W.E. olefination. The Michaelis-Arbuzov rearrangement has been employed extensively as the method of choice for phosphonate synthesis. Reaction of a phosphorus trihalide with an alcohol in the presence of an acid gives the trialkylphosphite which can then react with an appropriate alkyl halide to give the desired phosphonate, as indicated in Figure 1.44. Several trialkylphosphites are commercially available at reasonable cost so in many instances the first step can be eliminated. Most commonly triethyl and trimethyl phosphites are employed in this Michaelis-Arbuzov reaction, where the valence shell of the phosphorus is expanded. The energy of the P=O bond is high enough that generation of this bond is thermodynamically desirable dominating the detrimental influence of expanding the valence shell. Other methods of synthesis of phosphoryl-stabilised anions are also available but won't be discussed here.[104,97]

Preparation of Trialkylphosphites



Preparation of Phosphonates (Michaelis-Arbuzov Reaction)

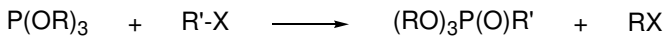


Figure 1.44 Synthesis of trialkylphospites and subsequent synthesis of phosphonates *via* a Michaelis-Arbuzov Reaction.

As a general rule phosphonates produce the *E*-olefin more selectively than the corresponding Wittig reagents however isomer ratios from both olefinations can be manipulated. By controlling the reaction conditions it is possible to influence the ratio of *E* to *Z* stereoisomers. Selective formation of both *E* or *Z* isomers can be achieved by isolation and purification of the diastereomeric intermediate β-hydroxy phosphine oxides which can then undergo stereoselective decomposition to the alkene.[105,106] This is an advantage over the Wittig reaction where isolation of the

intermediate species is not readily achieved, however this technique is not commonly employed.

The H.W.E. olefination has become a popular tool in natural products synthesis for stereoselectively introducing unsaturation while concurrently lengthening the carbon chain. In particular the high levels of *E*-selectivity have lead to the reaction being employed in the synthesis of isoprenoid compounds such as terpenes, sesquiterpenes, diterpenes and their oxygenated analogues as well as in carotenoid synthesis.[104]

1.3.4 The Julia Olefination Reaction

In 1973 Marc Julia and Jean-Marc Paris reported a novel connective olefination procedure in which a β-alkoxysulfone undergoes reductive elimination forming an *E*-alkene with high stereoselectivity.[45] Lythgoe and Kocienski[107-110] have also made significant contributions to the development of the "Classical Julia Olefination" as it has become known. This olefination process involves four distinct synthetic transformations represented in Figure 1.45;[111] metallation of a phenyl sulfone (**71**), addition of the metallated sulfone **72** to the aldehyde or ketone, acylation of the resulting β-alkoxysulfone **73** and reductive elimination of the β-acyloxysulfone **74** with a single electron donor (sodium mercury amalgam) generating the desired alkene **75**. Experimentally yields are improved if the β-hydroxysulfone is isolated however it is possible to perform this four step sequence in one pot. The high degree of *E*-selectivity observed is independent of the configuration of the β-acyloxysulfone **74** as the intermediate radical species, formed during sodium mercury amalgam reduction, undergoes stereochemical equilibration to the thermodynamically favoured *E*-alkene.

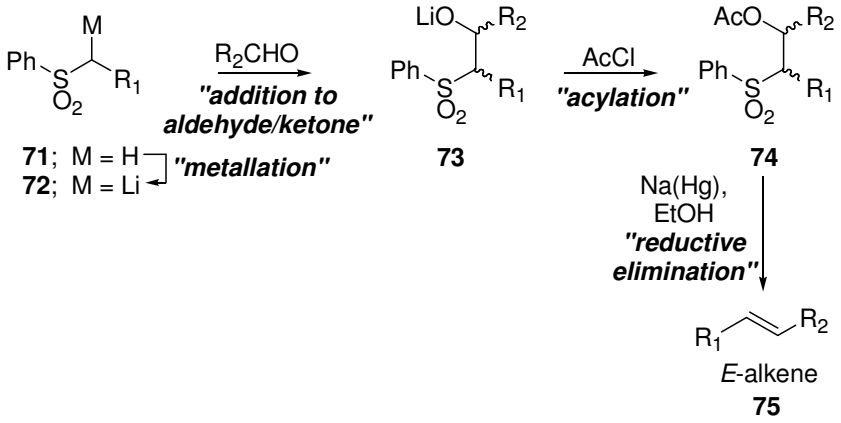


Figure 1.45 Mechanism of the "Classical Julia Olefination".

Sylvestre Julia and co-workers[112] investigated the use of heteroarylsulfones (eg. benzothiazole-2-ylsulfone **76** represented in Figure 1.46) rather than the established phenyl sulfones. They discovered that while the metallated sulfone adds to the aldehyde or ketone *via* a similar mechanism to the "Classical Julia Olefination" the β-alkoxysulfone **77** is highly unstable. Figure 1.46 describes the mechanism where the sulfone **77** is thought to form a spiro-cyclic intermediate **78** which then rearranges to the sulfinate salt **79** in which the heterocycle has migrated from the sulphur to the oxygen. A facile Smiles rearrangement[113] follows, in which the sulfur dioxide and lithium benzothiazolone are eliminated, producing the alkene product.

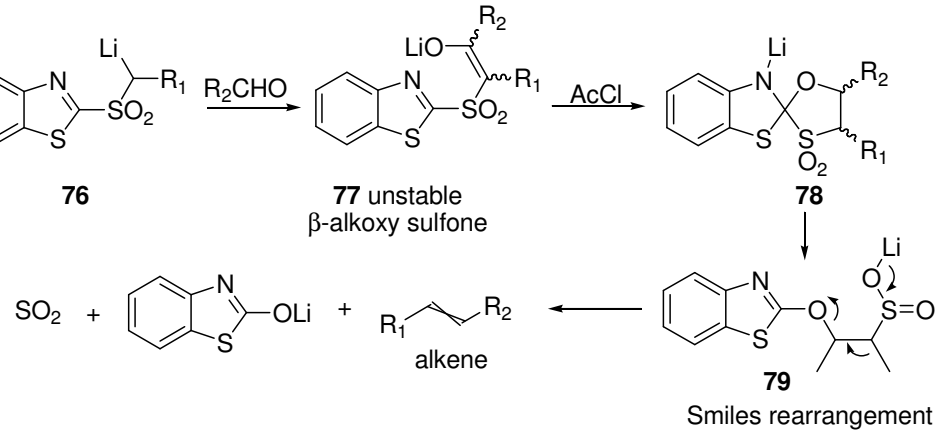


Figure 1.46 The proposed mechanism of the "modified" Julia olefination of benzothiazole-2-ylsulfones.

This reaction is commonly referred to as the "modified" or "one-pot" Julia olefination reaction because isolation of the intermediate β-hydroxysulfone is not required. Since the discovery of the BT-sulfones several different heterocyclic activators have been developed and employed extensively. The four most commonly used heterocyclic activators, benzothiazole-2-yl (BT), pyridine-2-yl (PYR), 1-phenyl-1H-tetrazole-5-yl (PT) and *tert*-butyl-1H-tetrazole-5-yl (TBT), are represented in Figure 1.47. The "modified" Julia olefination is operationally simpler than the "Classical Julia Olefination" due to the "one-pot" procedure, is higher yielding and is extremely versatile with high functional group tolerance. Modifications to the specific reactions conditions, such as solvent, base and heterocyclic activator can impart stereocontrol to the olefination reaction.

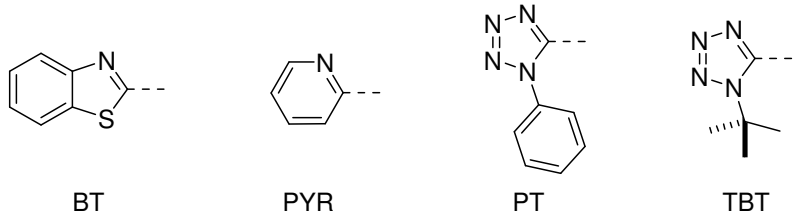


Figure 1.47 The commonly used heterocyclic activators of the "modified" Julia olefination.

An investigation, by Sylvestre Julia and co-workers,[114] of the base-mediated elimination of the stereo-defined β-hydroxy-BT-sulfones (**77**) indicated that simple β-alkoxy-BT-sulfones retain their stereochemistry in the alkene product; ***anti*-77** produces the *E*-alkene, while the ***syn*-77** produces the *Z*-alkene. (Figure 1.48) As a result diastereomeric control in generation of simple olefins requires selectivity in the nucleophilic addition of the sulfone to the carbonyl compound.

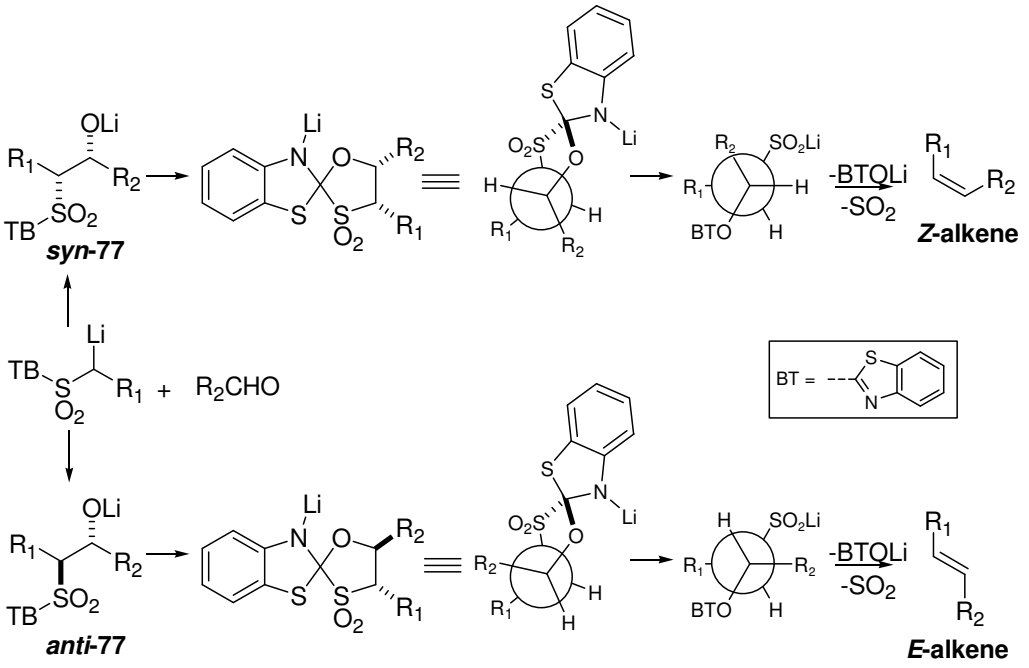


Figure 1.48 Rationalisation of the selectivity of the "modified" Julia olefination.

In some cases β-alkoxy sulfones **77** can fragment into α-metallated sulfones and carbonyl compounds and subsequently reassemble as described in Figure 1.49.[115] Stereocontrol of the nucleophilic addition is not important because equilibration occurs upon fragmentation. Equilibration results in high levels of stereoselectivity in some instances and is thus desirable, while in others mixtures of *E*- and *Z*-alkenes result.

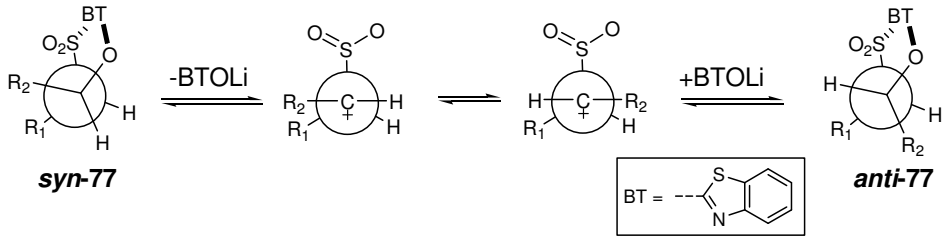


Figure 1.49 Proposed fragmentation of the β-alkoxy sulfones.

The selection of the heterocyclic activator is particularly important in controlling the reaction outcome as each exhibits different features making them suitable under particular reaction conditions, with particular aldehydes or in imparting stereochemical control. As a result the individual features of each of the heterocyclic activators in Figure 1.47, which have been compared in several reviews,[111] will be discussed in turn.

1.3.4.1 Benzothiazole-2-yl (BT) Sulfones

Benzothiazole-2-yl (BT) sulfones (Figure 1.50) can be susceptible to nucleophilic attack at C2 and *ipso* substitution, resulting in loss of the sulfinate nucleofuge, however, use of a non-nucleophilic base such as LDA can prevent this occurrence. Self condensation of the BT sulfones can also be a problem due to the donor-acceptor nature of the metallated sulfones although low temperature conditions can suppress this reaction. Barbier developed conditions to reduce the extent of self condensation. This involves addition of the base to a mixture of the sulfone and the aldehyde enabling the metallated sulfone to be captured by the aldehyde immediately after its formation. While this method greatly improves yields it is not suitable for sensitive or complex aldehydes which can be affected by the base. The stereochemical outcome of Julia olefination reactions with BT sulfones can be controlled with the careful selection of reaction conditions. In particular, high stereospecificity can be achieved with α, β-unsaturated aldehydes and as a result the BT sulfones are generally most useful for the synthesis of conjugated, 1,2-disubstituted *E*-olefins. However, the alternative approach to conjugated, 1,2-disubstituted *E*-olefins, employing β, γ-unsaturated sulfones demonstrates poor stereoselectivity. This is due to the propensity of the metallated sulfones to fragment into resonance stabilised α-metallated sulfones and carbonyl compounds which subsequently equilibrate and reassemble producing mixtures of *E*- and *Z*-olefins as

described in Figure 1.49.

BT PYR

Figure 1.50 BT and PYR sulfones, heterocyclic activators of the Julia olefination reaction.

1.3.4.2 Pyridin-2-yl (PYR) sulfones

Pyridin-2-yl (PYR) sulfones (Figure 1.50) are less susceptible to nucleophilic attack than the BT sulfones. The PYR sulfone is highly stable due to reduced electrophilicity of the pyridyl nucleus and therefore self condensation is not a problem. As a result the PYR-sulfones are more suitable for coupling to sensitive or complex aldehydes. In general yields are lower than the corresponding BT sulfones however, in contrast to the poor stereospecificity of the BT sulfones, high levels of *Z*-selectivity are achievable with β, γ-unsaturated PYR sulfones. Similarly, *Z*-selective olefinations can be achieved with α, β-unsaturated aldehydes providing access to dienes with the opposite stereochemistry at the "new" olefinic bond, than can be achieved with the corresponding BT sulfones.

1.3.4.3 1-Phenyl-1H-tetrazole-5-yl (PT) sulfones

Kocienski and co-workers developed the 1-phenyl-1H-tetrazole-5-yl (PT) sulfones (Figure 1.51) as a highly *E*-selective alternative to the BT sulfones.[116] The *E*-selectivity producing non-conjugated, 1,2-disubstituted olefins is enhanced with solvent polarity and the electropositivity of the counter ion of the base, thus DME and KHMDS are commonly employed. The *E*-selectivity has been attributed to the diastereoselective addition of simple alkyl PT sulfones to non-conjugated aldehydes yielding *anti*-β-alkoxysulfones selectively under kinetic control. In addition the remarkably high levels of *E*-selectivity are not affected significantly by chain branching. The PT-sulfones offer advantages over the BT-sulfones in that they have a reduced tendency to self condense and are more stable due to the 1-phenyl appendage shielding the electrophilic sulfone-bearing carbon from nucleophilic attack. However, they do not offer significant advantages over their BT-sulfone counterparts for the synthesis of conjugated *E*-olefins although there are exceptions.

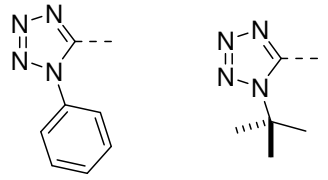


Figure 1.51 PT and TBT sulfones, heterocyclic activators of the Julia olefination reaction.

1.3.4.4 *tert*-Butyl-1H-tetrazole-5-yl (TBT) sulfones

Finally, the structurally related *tert*-butyl-1H-tetrazole-5-yl (TBT) sulfones demonstrate increased stability due to the bulkier *tert*-butyl group protecting the sulfone bearing carbon from nucleophilic attack. The TBT-sulfones are much less *E*-selective than the PT-sulfones in the synthesis of non-conjugated 1,2-disubstituted olefins, however 1,2-disubstituted *Z*-olefins can be achieved in high stereoselectivity utilising allylic or benzylic TBT-sulfones. This is due to the ability of these sulfones to fragment, equilibrate and reassemble as outlined in Figure 1.49. The bulky *tert*-butyl group facilitates equilibration between the *syn*- and *anti*-β-alkoxysulfone intermediates by raising the energy barrier to the Smiles rearrangement allowing time for fragmentation and equilibration to occur.

As the above examples have suggested the extensive arsenal of heterocyclic activators enables considerable stereocontrol to be achieved in olefination reactions between a wide variety of sulfones and carbonyl compounds. This has lead to extensive employment of the "modified" Julia olefination reaction towards natural products synthesis since the first application to the synthesis of potent immunosuppressant, rapamycin.[117] Several reviews of the application of the "modified" Julia olefination in natural product synthesis have since been published.[118,111]

1.3.5 The Diels-Alder Reaction

The Diels-Alder (D.-A.) reaction or [4 + 2] cycloaddition reaction was discovered by Otto Diels and his student Kurt Alder in 1928.[46] They were recognised for their contribution to chemistry in 1950 when they were awarded the Nobel Prize for this discovery. The D.-A. reaction involves the cycloaddition of a 1,3-diene and an alkene or alkyne (a dienophile) to give a 6-membered ring. The famous example of this reaction, as discovered by Diels and Alder, is the reaction of two equivalents of

cyclopentadiene with quinone and is shown in Figure 1.52. The reaction is extremely efficient forming two carbon to carbon σ bonds at the expense of two carbon to carbon π bonds, in the process generating up to four stereogenic centres in a single step. The reaction conditions are tolerant to a wide variety of functional groups on the diene and dienophile enabling synthesis of a vast array of cyclic products.

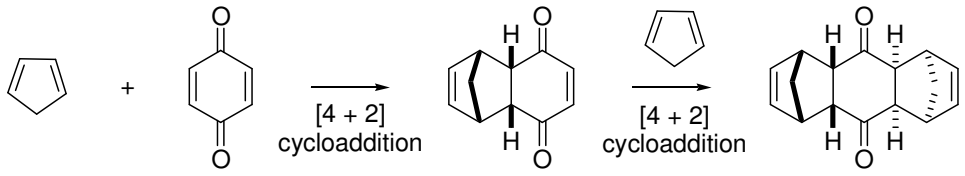
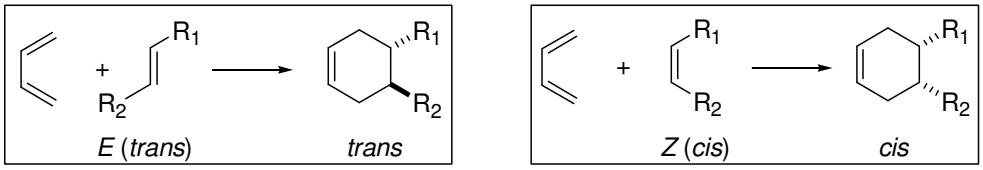


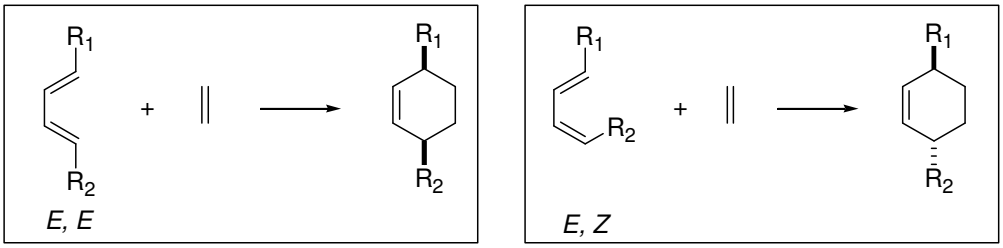
Figure 1.52 The [4 + 2] cycloaddition reaction discovered by Otto Diels and Kurt Alder.

Despite the fact that four stereogenic carbon centres are generated in a single reaction step, and thus eight racemic cycloadducts could be formed, the D.-A. reaction demonstrates remarkable stereospecificity. The high levels of stereospecificity can be attributed to the retention of the configuration of the starting materials in the cycloadduct, commonly referred to as the *Cis* Principle.[119] Surprisingly, the integrity of this rule is unwavering with no known exceptions, suggesting that mechanistically the bond forming and bond breaking events occur simultaneously (a discussion of the mechanism will be addressed in Section 1.3.5.1). There are three factors influencing the stereochemistry of the Diels-Alder adducts;

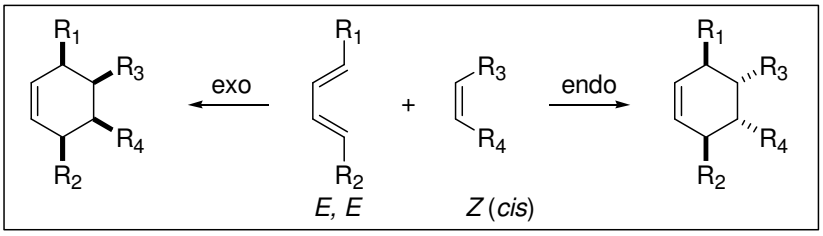
The stereochemistry of the dienophile. This is conserved in the product, thus an *E* (*trans*) alkene will give a *trans*-relationship on the ring while a *Z* (*cis*) alkene will give a *cis*-relationship on the ring.



The stereochemistry of the diene. An *E*,*E*- or a *Z*,*Z*-diene will give a cycloadduct with R groups on the same face of the ring and an *E*,*Z*-diene will give a cycloadduct with the R groups on the opposite face of the ring.



The relative relationship between the addends (i.e. the diene and dienophile). The relative relationship between the stereocentres arising from the diene and dienophile is determined by endo or exo docking of the dienophile onto the diene.



The first two factors are governed by the geometry of the starting materials which are strictly observed in the product. In contrast, the relative relationship between the addends is potentially influenced by a number of forces including steric control imparted by both the diene and dienophile and the Endo Effect,[119] each of which will be discussed.

Steric approach control plays an important role in governing the configuration of the D.-A. adducts with asymmetric dienes and dienophiles. This principle simply suggests that the faces of the appended planes which offer the least non-bonded repulsions will be juxtaposed in the developing preliminary complexes and transition states.[120] Steric affects of the diene appear to have little effect, as even in the presence of bulky substituents reaction occurs quite readily. However the steric affects of the substituents on the dienophile are more significant. In some instances highly substituted dienophiles fail to react or given a choice of alkenes the least substituted alkene with react preferentially.

The Endo effect, first described by Alder and Stein, suggests that the most stable transition state for the [4 + 2] cycloaddition reaction is such that following pre-orientation of the reactants into a "sandwich-like" transition state, the dienophile will add in an orientation such that there exists a maximum overlap of π-orbitals. This

rule encompasses the π system directly participating in the cycloaddition reaction as well as those of "activating ligands" on the dienophile. They suggested that this stability is due to spatial orbital overlap or steric accommodation. A pertinent example of the control described by the Endo rule is the addition of maleic anhydride to cyclopentadiene represented in Figure 1.53. In the endo orientation the π systems of the anhydride carbonyls overlap with the π-systems of the diene providing enhanced stability to the transition state. In the exo orientation, the anhydride carbonyls are oriented outside of the developing transition state, thus this transition state doesn't gain the benefit of enhanced stability due to the π-bond overlap. As a result of the π-orbital overlap the endo adduct is formed almost exclusively, despite the fact that the exo adduct is more thermodynamically stable with equatorial orientation of the five membered heterocycle in the product. While the Endo rule is sufficient to describe the selectivity observed in a variety of D.-A. reactions there are numerous exceptions revealing that other factors may also affect the stereochemical outcome.

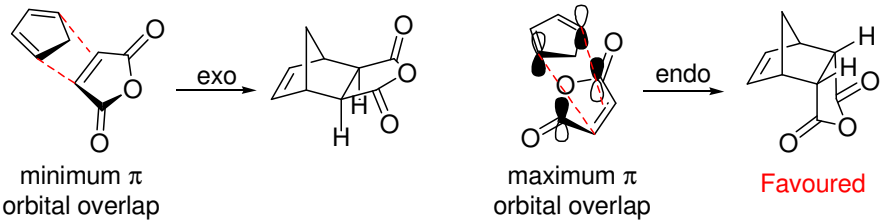


Figure 1.53 The Endo rule predicts maximum overlap of π-orbitals in the developing transition state.

The D.-A. reaction is driven by the formation of new σ bonds which are energetically more stable than π bonds. Figure 1.54 shows the molecular orbitals of both the diene and dienophile components and the overlap between these orbitals in the D.-A. cycloaddition reaction. Overlap between the Highest Occupied Molecular Orbital (HOMO) of the diene and the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile is thermally allowed, providing the orbitals are of similar energy. This is commonly referred to as a "normal electron demand" D.-A. reaction and is facilitated by the presence of an electron withdrawing group on the dienophile and electron donating groups on the diene. The decreased electron density in the dienophile lowers the energy of the LUMO of the dienophile. Similarly the increased electron density in the diene raises the energy of the HOMO of the diene. Thus the energy of activation is lowered facilitating the reaction. High levels of endo selectivity are generally achieved for a "normal electron demand" D.-A. reaction due

to π orbital overlap of the electron withdrawing group , the "activating ligand", and the π system of the diene.

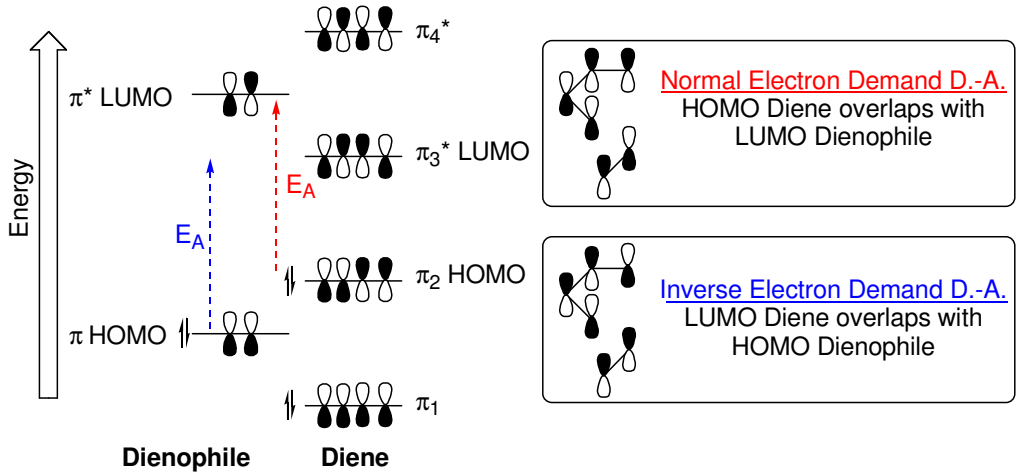


Figure 1.54 Molecular Orbital overlap in the Diels-Alder reaction.

Alternatively, if the electron withdrawing group is on the diene and an electron donating group is on the dienophile an "inverse electron demand" D.-A. reaction can occur. In this instance the LUMO of the diene and the HOMO of the dienophile overlap. The increased electron density of the dienophile raises the HOMO and the decreased electron density of the diene lowers the LUMO resulting in a lower energy of activation for the reaction.

1.3.5.1 The Mechanism of the Diels-Alder Reaction

The exact mechanism of the D.-A. reaction has been the subject of controversy within the literature since its discovery in 1928. Several suggestions of possible mechanisms for the formation of the two σ bonds at the expense of the two π bonds in the [4 + 2] cycloaddition reaction have been proposed, and are outlined in Figure 1.55. A concerted reaction mechanism is one in which the two σ bonds are formed simultaneously in a multicentre mechanism. This is suggested to occur in either a synchronous manner, where the various changes in bonding have progressed to similar extents in the transition state, or an asynchronous manner, where one developing bond is much shorter and stronger in the transition state. The energy profiles for these reaction pathways require only one activation barrier. An alternative proposal is that a two step reaction occurs with a biradical or zwitterionic intermediate species being formed. The energy profile of this reaction pathway requires two activation barriers.[121,122] Literature support for each of the proposed

mechanisms will be presented although the exact mechanism remains undefined at this time.

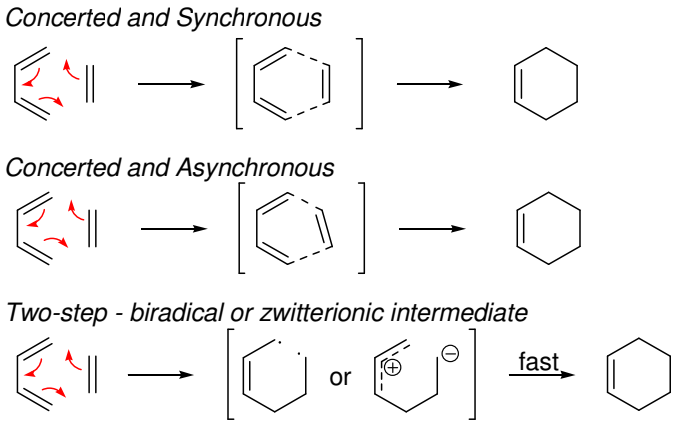


Figure 1.55 The proposed mechanisms of the Diels-Alder reaction.

Concerted formation of the two σ bonds was initially suggested based on the retention of stereochemistry of the starting materials in the cycloadduct. However, a two step mechanism can produce products with retention of stereochemistry if the second bond forming event occurs faster than rotation about a carbon to carbon single bond. Bartlett and co-workers suggested, in 1964, that a biradical intermediate accounted for the lack of stereoselectivity in the reaction of *cis*, *trans*-1,4-dimethylbutadienes with 2,2-fluoroethylene, suggesting the rate of the second bond forming event and bond rotation were similar.[123,124]

The mechanism of the D.-A. cycloaddition reaction was still under investigation, with many people unconvinced by Bartlett and co-workers proposal. Studies by Woodward and Hoffman in their theory of pericyclic reactions (1969) suggested that "allowed" pericyclic reactions occur in a concerted and synchronous manner.[125] In 1984, Dewar and Pierini[121] performed detailed kinetic studies on reverse D.-A. reactions, reporting that there was no solid evidence for a concerted and synchronous mechanism in symmetrical dienes. In the case of unsymmetrical dienes the results indicated the reaction proceeded *via* an unsymmetrical transition state. Studies by Leach and Houk,[126] in 2001, compared the reaction activation energies and stereo- and regio-selectivities predicted using Density Functional Theory calculations with the experiment results. In agreement with Dewar and Pierini, they concluded that the reaction mechanism is concerted and asynchronous.

Despite the variety of mechanistic studies reported in numerous publications, several of which have been discussed, the mechanism of the D.-A. cycloaddition reaction remains unclear. Both theoretical and practical approaches to solving the problem have been applied however whether the reaction is concerted (synchronous or asynchronous) or non-concerted remains a question to be answered.

1.3.5.2 Imparting Stereocontrol to the Diels-Alder Reaction

There are a number of strategies commonly employed to manipulate the stereoselectivity of the D.-A. reaction which will be examined. By performing the reaction under high pressure or by employing catalysts to facilitate the Diels-Alder reaction the energy barrier for reaction is lowered and thus the reaction can occur at lower temperatures. As a result of the lower temperatures, endo/exo stereocontrol can be imparted with higher levels of the kinetic (endo) product achievable compared to the thermodynamic (exo) product. This is due to the greater stabilisation of the endo transition state due to the secondary orbital overlap dominating the thermodynamic effects at lower temperature. Addition of Lewis acid catalysts, such as $AlCl_3$, Et_2AlCl, BF_3, $B(OAc)_3$, $ZnCl_2$, $SnCl_2$ and $TiCl_4$, to the dienophile will facilitate a "normal electron demand" D.-A. reaction. The Lewis acid coordinates to the electron withdrawing group, further withdrawing electron density from the alkene. This lowers the energy of the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile thus lowering the activation energy required for reaction. In some instances the use of Lewis acids can even produce products not achievable by thermally induced D.-A. reactions by reversing the regiochemical course of the cycloaddition reaction. Control of the stereochemical outcome of the D.-A. reaction can also be achieved by using chiral Lewis acid catalysts to impart high levels of stereocontrol. Several reviews examine enantioselective synthesis employing chiral catalysts in the D.-A. cycloaddition reaction.[127,128]

1.3.5.3 The Diels-Alder Cycloaddition Reaction in Natural Product Synthesis/Biosynthesis

Countless natural products have been isolated that appear to be products of a [4 + 2] cycloaddition reaction. Diels and Alder realised the potential applications of their reaction to natural product synthesis making the bold statement in 1928, "we explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems (the synthesis of natural products)". [46] In subsequent years

their research focus shifted to new areas and as a result very little work was done in applying the Diels-Alder reaction to natural product synthesis for the next 20 years. Finally, in the 1950's and 1960's, the Diels-Alder reaction began to be utilised to its full potential when it was employed in several total syntheses of complex natural products. In 1951, Stork and co-workers reported the first natural product synthesis featuring a [4 + 2] cycloaddition in the stereocontrolled synthesis of cantharidin.[129,130] This was followed immediately by Gates and Tschudi who employed the reaction to the first total synthesis of morphine.[131] Since that time the Diels-Alder reaction has become an important tool in the synthesis of natural products.[132,36,127] This can be largely attributed to its versatility which has been extended with the development of intramolecular Diels-Alder reactions, hetero Diels-Alder reactions and pressure and Lewis acid-catalysed Diels-Alder reactions (including chiral catalysis to impart stereocontrol).

Intramolecular D.-A. (IMDA) reactions have played a major role in natural product synthesis due to their ability to efficiently construct complex polycyclic systems from linear precursors in a stereocontrolled fashion. The IMDA reaction has been applied to the total synthesis of natural products from a range of distinct classes of compounds such as the terpenoids, alkaloids and polyketides. Cascade cyclisations have also been employed to construct larger polycyclic structures by sequential D.-A. cycloaddition reactions. Numerous examples of both cascade and IMDA reactions are available in several reviews. [36,128,132]

1.3.5.4 Enzyme Catalysis of the Diels-Alder Reaction

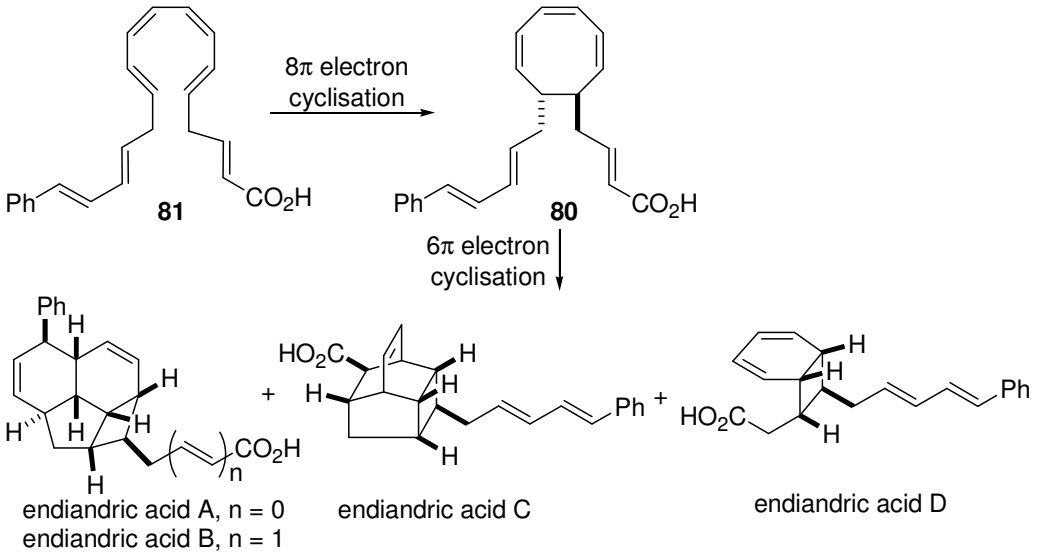
Due to the large number of natural products which appear to be products of a [4 + 2] cycloaddition reaction, attention has focused in recent years on the search for an enzyme in nature which may catalyse the [4 + 2] cycloaddition reaction. While some evidence suggests that enzyme catalysis may be responsible for the stereoselectivity of the Diels-Alder reactions in nature, it is largely circumstantial and remains to be proven. In order to establish whether enzyme catalysis is involved biophysical and kinetic studies must be undertaken.

The general mechanism of enzyme catalysis needs to be considered in order to discuss the potential existence of a Diels-Alderase enzyme. The mode of action of most enzyme catalysts is such that the starting substrate and product bind weakly to

the enzyme while the transition state structure is more tightly bound.[35] This stabilises the developing transition state facilitating the reaction. Following reaction, the product is less tightly bound to the enzyme and is subsequently released. In the case of the [4 + 2] cycloaddition reaction the highly ordered transition state is structurally analogous to the cyclic product. This suggests that the product will competitively bind to the enzyme inhibiting catalysis. An alternative proposal for the mechanism of action of such an enzyme to the [4 + 2] cycloaddition reaction suggests that the free energy of activation of the reaction is lowered.[35] While there is no solid evidence to support this theory it is thought that increasing the ground state energy of the reactants (possibly through the introduction of torsional strain) could achieve this. Thus, discovery of enzymes which catalyse the Diels-Alder reaction and studies on the mechanism of the reaction could lead to a more comprehensive understanding of enzyme catalysis through investigations of a possible novel catalysis mechanism.

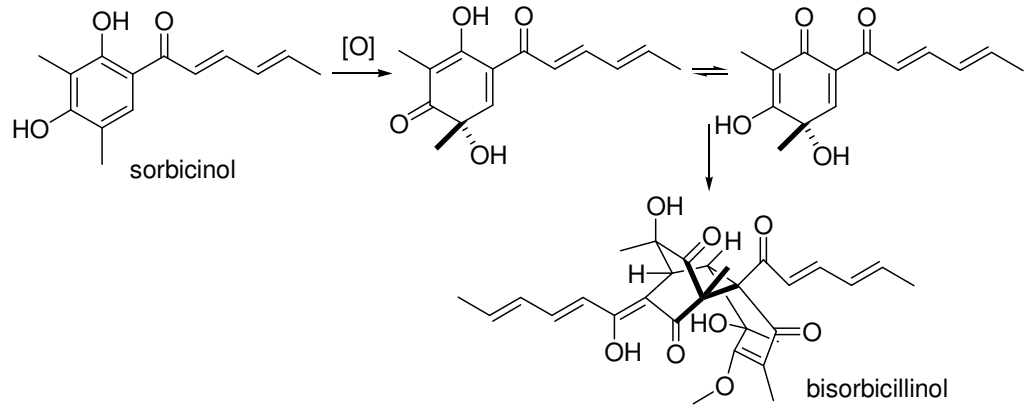
As discussed in Section 1.2.2, biomimetic syntheses of natural products employing a thermally induced D.-A. cycloaddition reaction can be used to support or refute enzymatic involvement in formation of the cycloadduct. However isolation and characterisation of the responsible enzyme is required for proof of its existence. As enzyme isolation and characterisation is an arduous task a common approach is to simply employ a biomimetic synthetic strategy to provide useful information as to the likelihood of enzymatic involvement. An overview of studies in this area, citing several examples of biomimetic studies, enzymatic catalysis of the D.-A. reaction and isolation and characterisation of Diels Alderases, will be presented.

Several biomimetic syntheses of [4 +2] cycloadducts found in nature have been found to proceed without the need for an enzyme. An example is the endiandric acids which were isolated as a racemic mixture. Nicolaou and co-workers were able to synthesise the endiandric acids *via* the synthetic approach outlined in Scheme 1.1.[133-136] Following synthesis of linear precursor **81**, Nicolaou and co-workers confirmed that two spontaneous cycloaddition reactions occurred producing the endiandric acids A-D, *via* compound **80**. They concluded that following biosynthesis of the linear precursor **81**, enzymatic involvement is not necessary to achieve the endiandric acids A-D in the natural system.



Scheme 1.1 Nicolaou and co-workers biomimetic synthesis of the endiandric acids.[133-136]

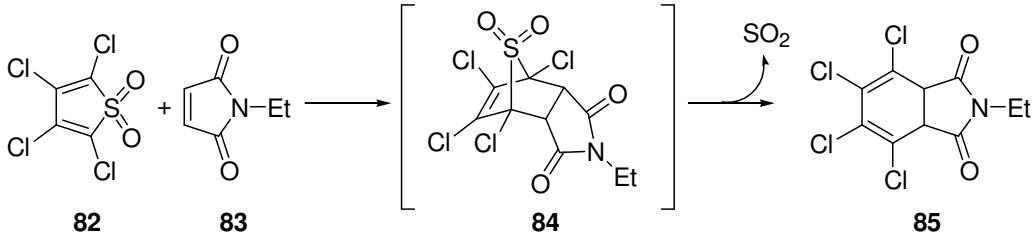
The stereochemical purity of many natural products suggests that enzymatic catalysis may be involved in biosynthesis, however a stereoselective reaction doesn't prove the involvement of an enzyme. During a biosynthetic study of the bisorbicillinoids, outlined in Scheme 1.2, Abe and co-workers discovered that upon concentration, a solution of sorbicillinol spontaneously underwent a regio- and stereo-selective [4 + 2] cycloaddition reaction to form bisorbicillinol.[137,138] This confirmed that the stereoselective reaction occurs readily under mild conditions without the involvement of an enzyme.



Scheme 1.2 Abe and co-workers biomimetic synthesis of the bisorbicinillinoids.[137,138]

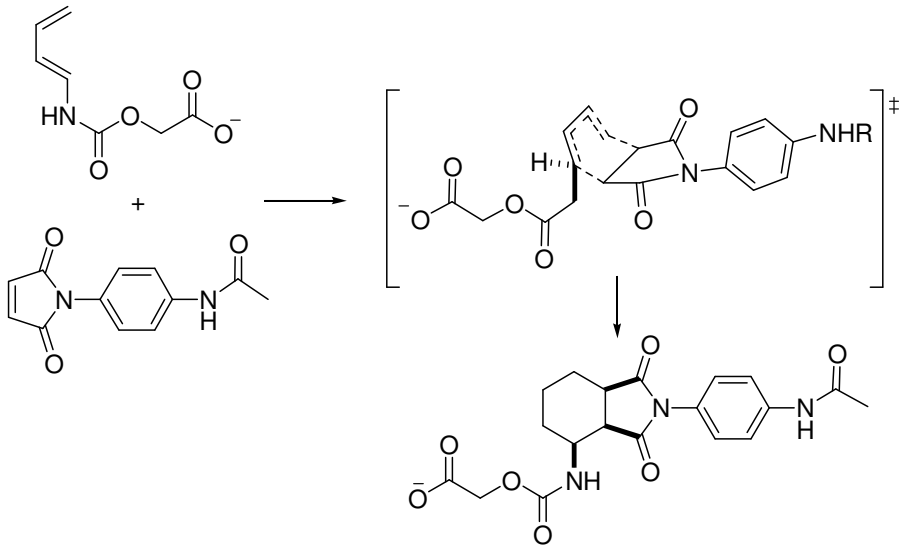
The first reported enzyme catalysis of a D.-A. cycloaddition reaction, represented in Scheme 1.3, was in 1989 by Hilvert and co-workers.[139] They prepared an antibody which catalysed the Diels-Alder reaction between tetrachlorothiophene dioxide (**82**) and N-ethylmeleimide (**83**) by binding the substituents in a reactive conformation,

thus lowering the entropy of activation. The problem of competitive binding of the cycloadduct to the enzyme was overcome by elimination of SO_2 from the labile adduct **84**. The resulting product **85** was weakly bound to the enzyme and expelled from the active site.



Scheme 1.3 The first enzyme catalysis of a D.-A. cycloaddition reaction, reported by Hilvert and co-workers.[139]

In 1990, Braisted and Schultz[140] reported use of an ethano bridge to lock the enzyme into a conformation resembling the transition state for the Diels-Alder reaction, depicted in Scheme 1.4. This allowed binding of the reactants to the enzyme to occur thus facilitating the reaction. Release of the product from the active site of the enzyme was proposed to be driven by the energy requirements of the product preferring a twisted chair rather than a rigid boat conformation dictated by the enzyme.

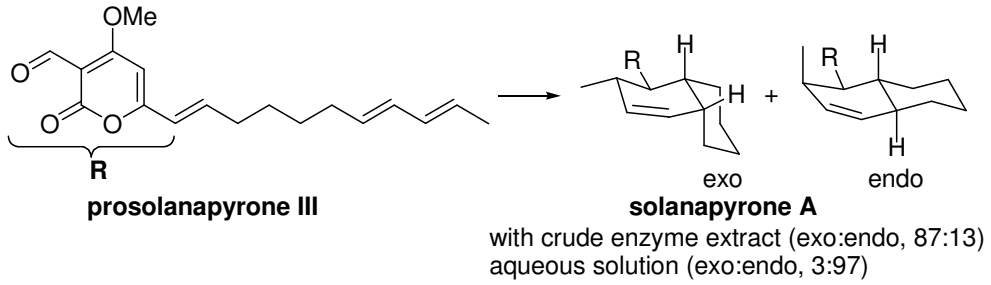


Scheme 1.4 Evidence of enzymatic involvement in the D.-A. cycloaddition reaction reported by Braisted and Schultz.[140]

In 1995, pioneering work on the discovery of the first Diels Alderase, solanapyrone synthase, was reported by Oikawa and co-workers.[141,142] Since that time two additional Diels Alderases have been purified and characterised; lovastatin

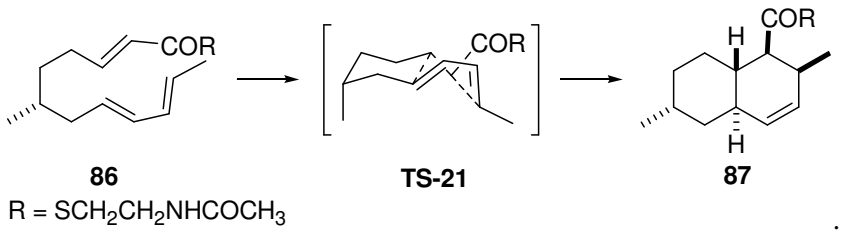
nonaketide synthase and macrophomate synthase. Each of these enzymes will be discussed in turn.

Oikawa and co-workers reported catalysis of the [4 + 2] cycloaddition reaction of prosolanapyrone III to solanapyrone A using a crude enzyme extract from *Alternaria Solani,* illustrated in Scheme 1.5.[141,142] The product was obtained with high exo selectivity (exo:endo 87:18) in the presence of the crude enzyme extract while in the absence of the enzyme or using denatured enzymes the selectivity is reversed (exo:endo 3:97).



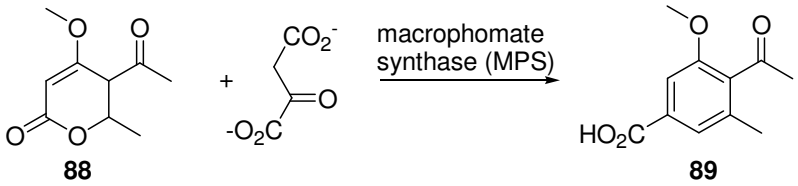
Scheme 1.5 Enzyme catalysed conversion of prosolanapyrone III to solanopyrone A, investigated by Oikawa and co-workers.[141,142]

More recently in 2000, Vederas and co-workers reported that LNKS (lovastatin nonaketide synthase) catalyses the IMDA reaction of a hexaketide triene **86**, outlined in Scheme 1.6.[143] Formation of the endo product **87** requires a transition state (**TS-21**) in which the methyl group is in the more sterically demanding *pseudo*-axial position. When LNKS was present the endo adduct **87** was detected however in the absence if LNKS no endo adduct **87** was formed. This lead to the conclusion that the enzyme binds the substrate in a conformation resembling the *endo* transition state, providing stability to the developing transition state. It was also proposed that the protein catalyses the cycloaddition reaction by forming a hydrogen bond to the carbonyl oxygen withdrawing electron density from the dienophile thus lowering the activation energy.



Scheme 1.6 The LNKS catalysed D.-A. reaction, discovered by Vederas and co-workers.[143]

The final enzyme reported to facilitate the D.-A. reaction is macrophomate synthase, an enzyme that catalyses an unusual five step transformation of 2-pyrone **88** to the benzoate analogue **89**, outlined in Scheme 1.7. Detailed mechanistic studies by Oikawa and co-workers suggest that decarboxylation, two carbon to carbon bond formation reactions (i.e. a Diels-Alder cycloaddition reaction), decarboxylation and concomitant dehydration reactions are facilitated by the enzyme.[144-146] Isolation of the enzyme and characterisation has provided information on the structure of the active site and the reaction mechanisms.



88 **89**

Scheme 1.7 The five step transformation proposed by Oikawa and co-workers to be catalysed by macrophomate synthase.[144-146]

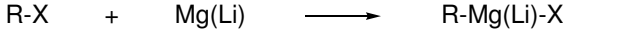
Since these initial reports of enzyme catalysed [4 + 2] cycloaddition reactions and subsequent isolation and characterisation of the enzymes involved, there have been numerous reports of further enzyme catalysed D.-A. reactions occurring in nature. Similarly, there have been reports of D.-A. adducts found in nature which have not required the assistance of an enzyme to facilitate the reaction. Thus it is clear that D.-A. reactions are common in the formation of natural products, both enzymatically facilitated and non-enzymatically facilitated. Due to the vast body of literature available there have been several comprehensive reviews addressing the issue of enzymatic involvement in the D.-A. reaction in nature.[35,37,147]

1.3.6 Organometallic Cross-Coupling Reactions

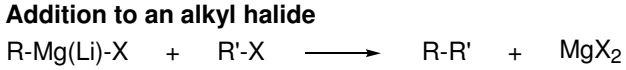
Perhaps some of the most common and simplest reactions for the formation of carbon to carbon bonds are the cross-coupling reactions of organic halides and organometallic reagents. Until the mid-1960's cross-coupling reactions of this type were relatively uncommon in synthesis with Grignard and organo-lithium couplings of alkyl halides being most prevalent. This can be attributed to problems associated with the organometallic reagents which are difficult to prepare, exhibit poor chemoselectivity and are limited to reaction with sp^3 carbon halides.[148] The general schematic of synthesis of Grignard and organolithium reagents and the subsequent couplings to organic halides is represented in Figure 1.56. Grignard and

organolithium reagents are generated by the reaction of magnesium or lithium with alkyl halides and are then reacted in situ with another alkyl halide to form a carbon to carbon σ bond.

Generation of Grignard or Organo-lithium Reagents



Addition to an alkyl halide



X = halide, R' = sp^3 carbon centre

Figure 1.56 The Grignard and organo-lithium reactions.

In 1972, Kumada[149-153] and Corriu[154] independently reported the catalysis of Grignard reactions of alkenyl or aryl halides with Ni-phosphine complexes. Previous reports of transition metal catalysis without phosphines up until this time had numerous synthetic complications so this discovery paved the way for the development of transition metal catalysis. The use of palladium-phosphine complexes in catalysis of cross-coupling reactions was reported by several research groups in 1975-1976.[155-163] These reactions had distinct synthetic advantages over the nickel counterparts including enhanced stereoselectivity and yields as well a being true catalytic organometals.[148]

Throughout the later part of the 20th Century the use of transition metals to catalyse a variety of different organometallic cross-coupling reactions flourished, enabling synthetic chemists to elegantly construct complex chemical frameworks. An abundance of organometallic reagents have been successfully developed for these reactions including tin, copper(I), boron, zinc and silicon. These reactions constitute a significant extension to the Grignard and organo-lithium reactions in that they are able to construct carbon to carbon σ bonds between two unsaturated carbon groups. This has revolutionised synthesis in areas as diverse as natural product synthesis, medicinal and process chemistry, chemical biology and nanotechnology. As a result a large number of reviews are available on the synthesis of organometallic reagents and their corresponding palladium-catalysed cross-coupling reactions.[164-169]

1.3.6.1 The Catalytic Cycle

In general there are three reaction steps common to a variety of cross-coupling reactions of organometallic species with organic halides or triflates; oxidative

addition, transmetallation and reductive elimination. These steps are represented for palladium in the catalytic cycle shown in Figure 1.57.

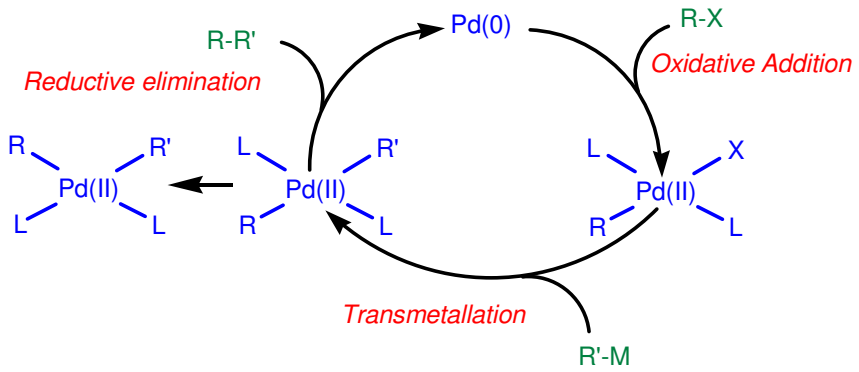


Figure 1.57 **The catalytic cycle of palladium-catalysed cross-coupling reactions.**

The catalytic cycle begins with oxidative addition, which involves the insertion of the metal into the organic halide resulting in a loss of electrons converting Pd(0) (an 18 electron system) to Pd(II) (a 16 electron system). The intermediate complex formed is a stable *trans*-σ-palladium(II) species. The stereochemical outcome is well defined with alkenyl halides complexing with retention of configuration while allylic and benzylic halides complex with inversion of configuration. Transmetallation, the rate determining step of the cycle, is the dissociation of the halide ligand from the metal centre by an organometallic species producing a diorgano-palladium complex. The final step, reductive elimination, results in regeneration of the catalyst by reduction of the metal centre, back to Pd(0), an 18 electron system, when the two carbon-metal bonds break and a new σ bond forms between the carbon ligands. This can only occur from the *cis* configuration so the *trans* complex must first undergo a *trans* to *cis* isomerisation.

1.3.6.2 Palladium-Catalysed Cross-coupling Reactions in Natural Product Synthesis

The most common palladium-catalysed cross-coupling reactions utilised in natural product synthesis are the Heck,[49,48] Stille,[50,51] Suzuki,[52,53] Sonogashira,[161,170] Tsuji-Trost[171,172] and Negishi[173,174] reactions. A range of different palladium catalysts are available and a variety of reaction conditions have been employed in these coupling reactions. As a result of the expanse of literature on this topic a brief summary of the types of coupling partners, the features of the organometallic reagents and reaction conditions and an example of the reaction in total synthesis has been included for

each of the named cross-coupling reactions listed above.

1.3.6.2.1 The Heck Reaction

The Heck reaction reported independently by Mizoroki[48] and Heck[49] is a palladium-catalysed coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes (generally mono or 1,2-disubstituted alkenes) as represented in Figure 1.58. The alkene product has the alkenyl or aryl group replacing the hydrogen on the original alkene coupling partner. Both intermolecular and intramolecular Heck reactions have been applied extensively in natural products synthesis.[175,164] An advantage of the intramolecular variant is the ability to employ tri- and tetra-substituted alkenes to efficiently install quaternary carbon centres.[175] In addition this reaction displays high functional group tolerance and gives products with predictable regio- and stereo-chemistry.

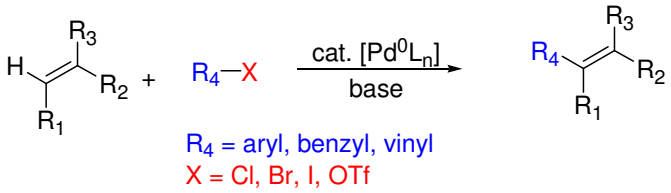
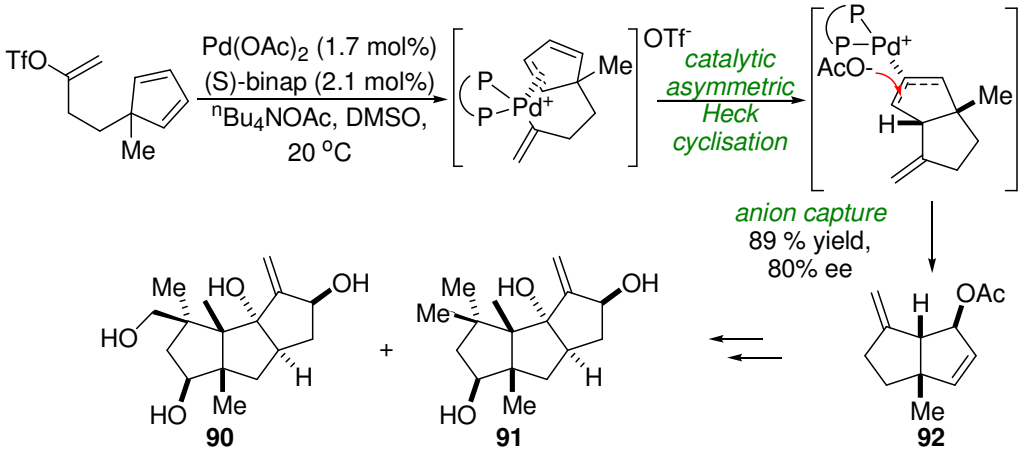


Figure 1.58 The Heck reaction.

In 1989 the first examples of asymmetric Heck reactions were reported in the total synthesis of complex triquinane sequiterpernes **90** and **91**.[176-178] This example outlined in Scheme 1.8, involves an intramolecular Heck reaction, using a Pd^0-(*S*)-binap complex catalyst, followed by an anion capture. The palladium preferentially complexes to the double bond depicted in Scheme 1.8, due to the chirality within the Pd^0-(*S*)-binap complex. The capture of the AcO^- occurs regioselectively to the least hindered terminus of the π-allyl system and stereoselectively to the face opposite to the palladium. Thus diquinane **92** was achieved in 89 % yield with high stereoselectivity (80 % ee), ultimately leading to natural products **90** and **91**.



Scheme 1.8 An intramolecular Heck reaction/anion capture reported by Shibasaki and co-workers in the total synthesis of the triquinane sesquiterpenes 90 and 91.[176-178]

1.3.6.2.2 The Stille Reaction

The Stille reaction reported by Stille, in 1978, is the palladium-catalysed cross-coupling reaction of vinyl organotin reagents with organic electrophiles as outlined in Figure 1.59.[51,50] Due to the mild reaction conditions, functional group tolerance, ease of preparation and handling of coupling partners, regio-, stereo- and chemo-selectivity and high reaction yields, this reaction has become one of the most widely applied carbon to carbon bond forming reactions in synthetic chemistry. A significant disadvantage of this approach however, is the high toxicity of the reagents and by-products containing tin.

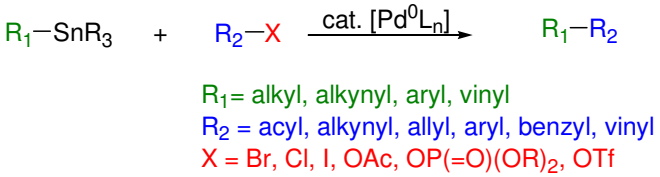
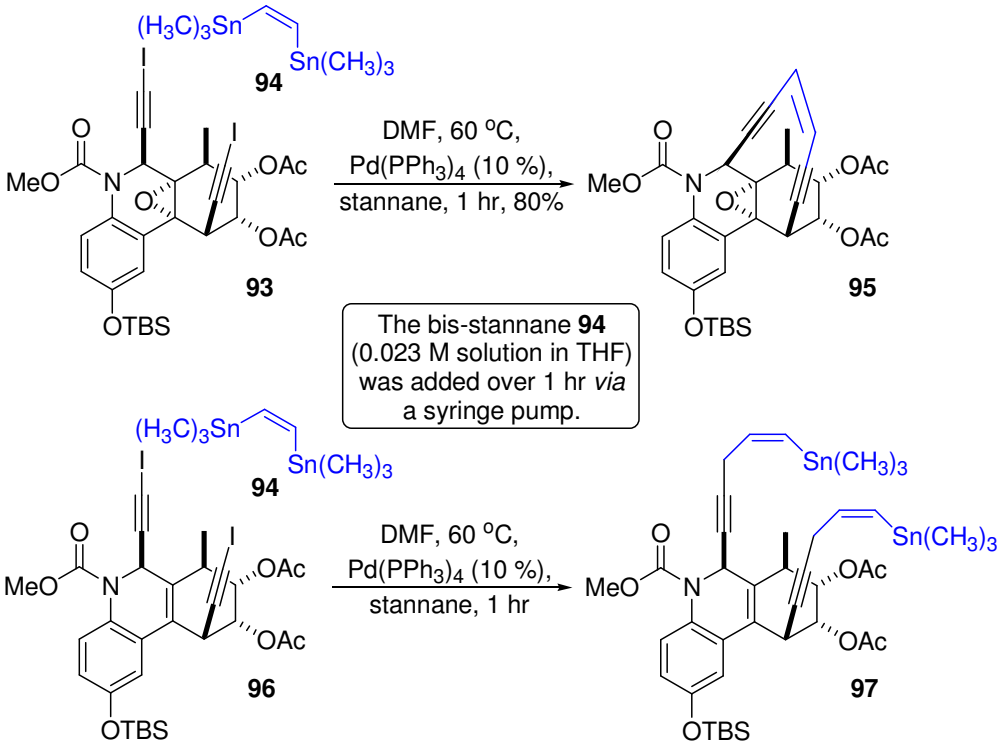


Figure 1.59 The Stille Reaction.

The Stille reaction has been utilised extensively in natural products synthesis constructing macrocyclic systems through the intramolecular Stille reaction with relative ease.[164,179] An extension of this is the double Stille coupling "stitching-cyclisation", whereby a linear molecule is stitched together to give a macrocycle with the palladium acting as template bringing the remote reactive sites together. This elegant reaction provides access to large macrocycles or complex polycyclic structures and has been exploited in the total syntheses of rapamycin[180,181] and dynemicin.[182-184] The "stitching cyclisation" employed in the total synthesis of dynemicin A is represented in Scheme 1.9. The double Stille cross-coupling reaction

to form the enediyne **95** occurs in 80 % yield when a dilute solution of the bis-stannane **94** is slowly added to diiodide **93** over one hour. Interestingly, the related compound **96** reacts only to give the bis-stannylenyne **97** despite slow addition of a dilute solution of the bis-stannane **94**. This difference in reaction outcome is proposed to be due to either increased distance between the acetylenic termini in **96** or because compound **93** is predisposed to cyclisation due to hybridisation differences.[182-184]



Scheme 1.9 Double palladium-mediated Stille cross-coupling reaction employed in the synthesis of dynemicin A. [182-184]

1.3.6.2.3 The Suzuki Reaction

Another reaction widely applied in total synthesis is the Suzuki coupling reaction. This reaction, discovered by Akira Suzuki in 1979,[52,53] involves the palladium-mediated coupling of organic electrophiles (eg. aryl or alkenyl halides or triflates) with organo-boron compounds, as described in Figure 1.60. Due to the covalent nature of the boron to carbon bond, coordination of a negatively charged base to the boron atom is required to enhance the nucleophilicity. This facilitates transfer of the organic group on the boron to the adjacent positive carbon centre.

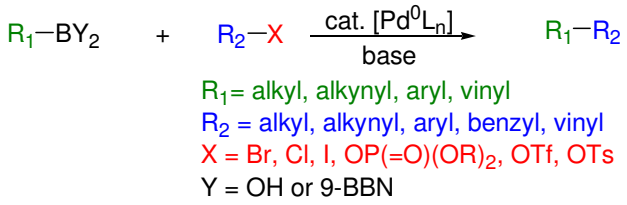
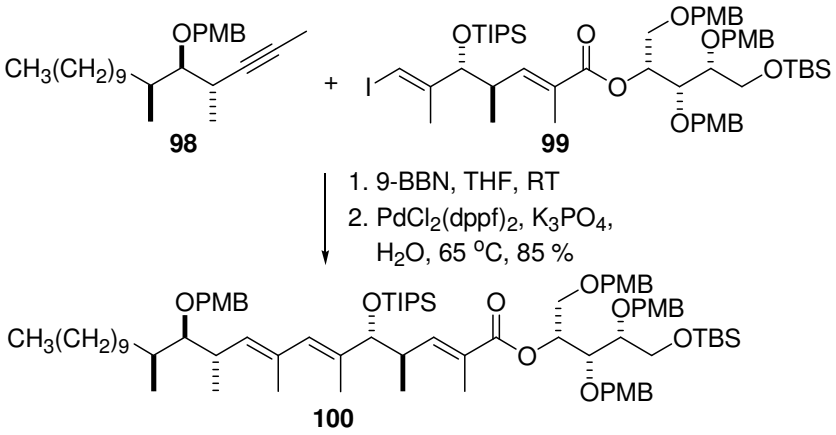


Figure 1.60 The Suzuki Reaction.

The Suzuki reaction is particularly effective in the stereoselective synthesis of conjugated dienes and higher polyenes and biaryl systems. Organoboranes are relatively easily synthesised, stable to heat, air and water, require moderate coupling conditions and a variety of boronic acids are commercially available making this a synthetically attractive coupling option.[164-166,185] In addition, boronic acids are environmentally safer than other organometallic reagents and produce benign by-products. The Suzuki coupling reaction was instrumental in Kishi and co-workers[186-188] total synthesis of palytoxin, the largest (in molecular weight and the number of stereogenic centres) secondary metabolite synthesised to date. During the coupling of two smaller fragments in this total synthesis, it was discovered that the use of thallium hydroxide as the base when sensitive substrates are present is effective. Since that time the use of TlOH, TlOEt and Tl_2CO_3 have become commonplace in Suzuki couplings of sensitive substrates.[165,164] A modification of the Suzuki coupling is the β-alkyl Suzuki-Miyaura coupling of alkyl (i.e. sp^3, not just sp^2 and sp^1) organoboranes and vinyl or aryl halides or triflates.[167,165] This is synthetically superior to other similar couplings due to the ease of synthesis of the alkyl boranes, mild reaction conditions and ease of removing boron containing by-products.

An example of the Suzuki coupling reaction was reported by Kobayashi and co-workers, in their total synthesis of khafrefungin and is outlined in Scheme 1.10.[189] This synthesis is particularly noteworthy because it proceeds without the need for toxic thallium reagents, making it amenable to large scale, commercial synthesis. In a one-pot procedure, acetylene **98** was converted to the corresponding organoborane with 9-BBN and was subsequently coupled to vinyl iodide **99**, producing **100** with high stereochemical purity in 85 % yield on large scale.



Scheme 1.10 Suzuki cross-coupling reaction employed in the total synthesis of khafrefungin.[189]

1.3.6.2.4 The Sonogashira Reaction

Sonogashira, in 1975, reported the use of co-catalytic Cu(I) salts to accelerate the palladium-catalysed cross-coupling of terminal alkynes with vinyl and aryl halides as represented in Figure 1.61.[170,161] This reaction has found synthetic utility in the synthesis of conjugated acetylenic compounds in a variety of areas including natural product synthesis, pharmaceuticals, biotechnology and nanotechnology due to its reliability, broad application and convenience.[164]

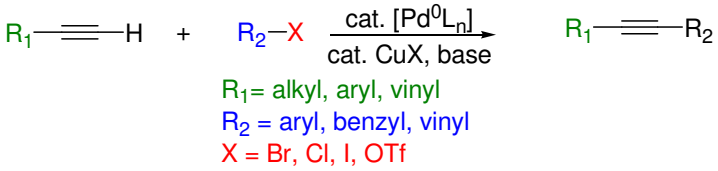
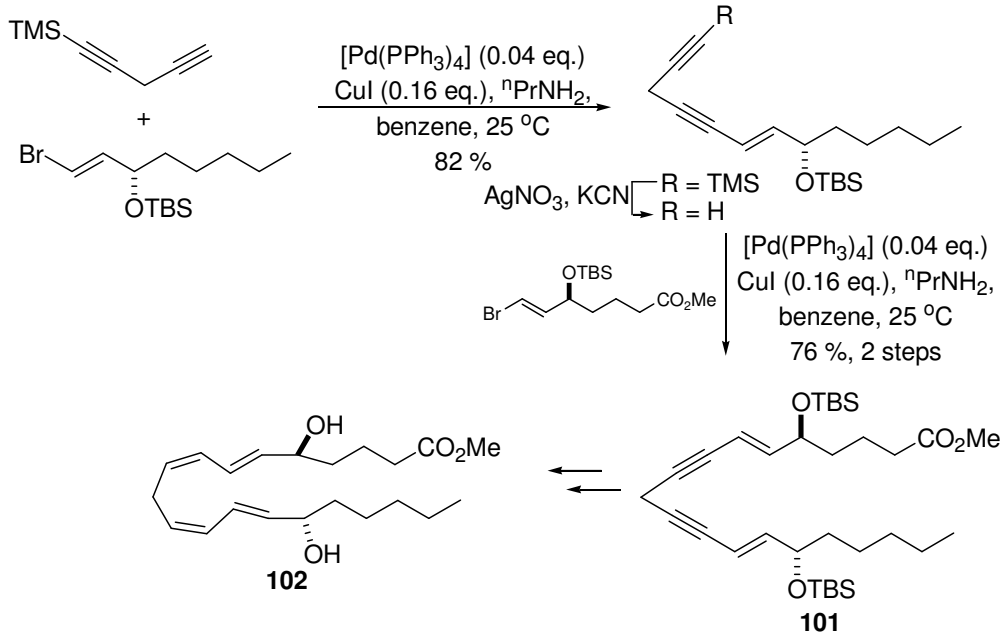


Figure 1.61 The Sonogashira Reaction.

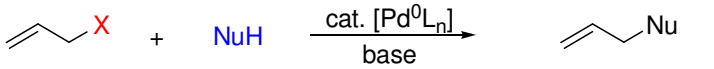
Nicolaou and co-workers developed a general synthetic route to the lipoxins and eicosanoids, employing the Sonogashira cross-coupling reaction.[190] Synthesis of these polycyclic compounds, an example of which is represented in Scheme 1.11, was challenging due to the different double bond geometries of the conjugated systems. Two Sonogashira cross-coupling reactions were employed to generate the bis-acetylenic compound **101**. These acetylenic functionalities were installed to act as masked *Z*-alkenes during construction of the conjugated system and then revealed as *Z*-alkenes in compound **102** by selective hydrogenation.[190]



Scheme 1.11 Nicolaou and co-workers approach to the lipoxins and eicosanoids using acetylenic masked *Z*-alkenes.[190]

1.3.6.2.5 The Tsuji-Trost Reaction

One of the most synthetically versatile palladium-catalysed carbon to carbon bond forming reactions is the Tsuji-Trost reaction.[171,172] This reaction, outlined in Figure 1.62, involves nucleophilic substitution onto a variety of allylic compounds, most commonly allyl acetates. The versatility can be attributed to the mild reaction conditions, the high and predictable levels of chemo-, regio- and stereo-selectivity observed and the variety of different coupling partners available. In addition, a range of leaving groups on the allylic partner are effective and nucleophiles containing heteroatoms may also be employed.[164]

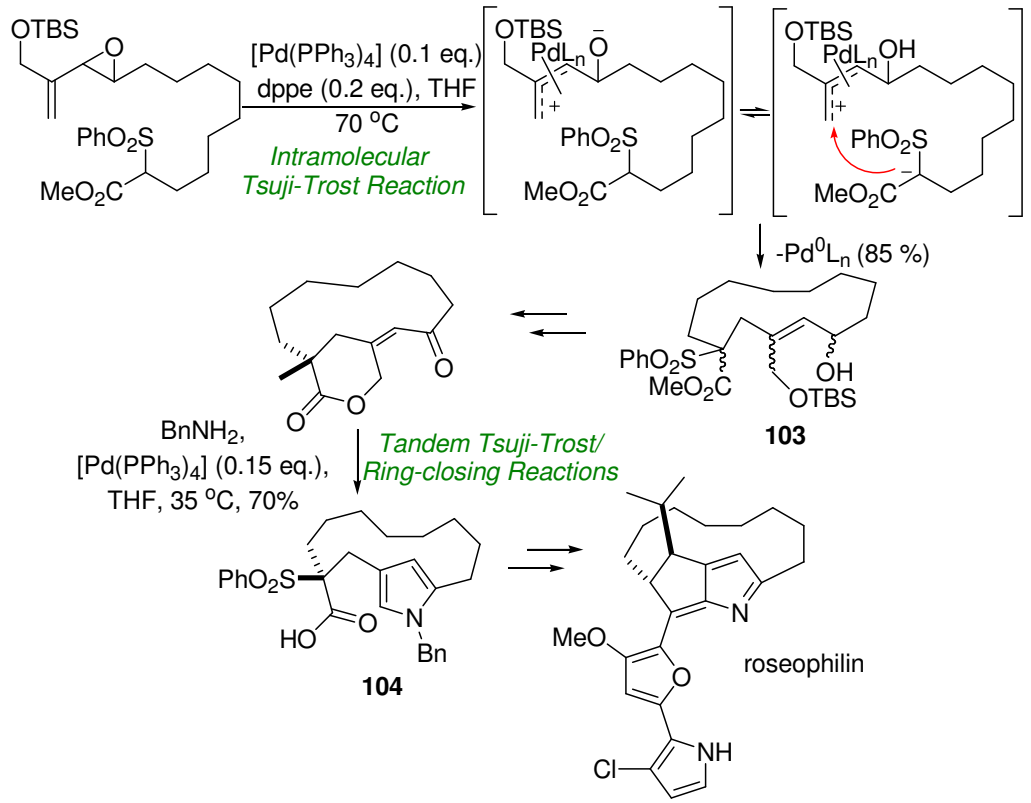


X = Br, Cl, OCOR, OCO_2R, SO_2R, $P(=O)(OR)_2$
NuH = β-dicarbonyls, β-ketosulfones, enamines, enolates

Figure 1.62 The Tsuji-Trost Reaction.

The Tsuji-Trost reaction has proven to be a successful method for the installation of a variety of ring systems. Sequential Tsuji-Trost cross-couplings were utilised in the total synthesis of the architecturally unique alkaloid, roseophilin, by Furstner and Weintritt, outlined in Scheme 1.12.[191,192] These cross-coupling reactions involved construction of a strained 12 membered-ring system (**103**) as well as an azafulvene-

type chromophore (**104**).



Scheme 1.12 The sequential Tsuji-Trost reactions in the total synthesis of roseophilin.[191,192]

1.3.6.2.6 The Negishi Reaction

Finally, the Negishi coupling reaction, which until recently has experienced limited use in total synthesis due to the overwhelming popularity of the Stille and Suzuki couplings, was first reported in 1977.[173,174] This reaction involves the coupling of nucleophilic organozinc reagents with electrophiles as represented in Figure 1.63. Advantages of the organozinc reagents in palladium-catalysed cross-coupling reactions include their very high intrinsic reactivity, the variety of synthetic methods available for their synthesis and their low toxicity. However in competing with the Stille and Suzuki methods they fall short due to poor functional group tolerance and sensitivity towards oxygen and water.[164]

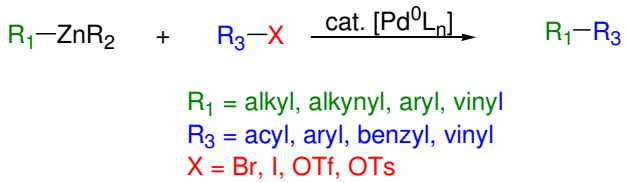
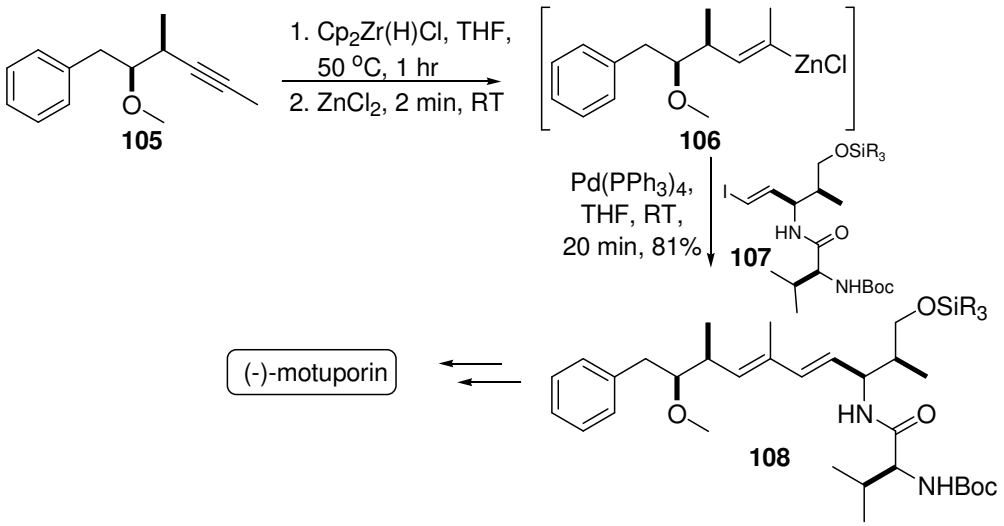


Figure 1.63 The Negishi Reaction.

The Negishi cross-coupling reaction has been exploited by Hu and Panek in their total synthesis of (-)-motuporin (Scheme 1.13).[193] Alkyne **105** was converted to the zinc chloride **106**, which was coupled in situ to vinyl iodide **107**, yielding the *E*,*E*-diene **108** selectively in 81 % yield. A feature of this approach is the stereoselective formation of the tri-substituted olefin which can often be a difficult task for synthetic chemists.



Scheme 1.13 Negishi cross-coupling exploited in the total synthesis of (-)-motuporin.[193]

1.3.7 Protecting Groups

Important considerations when planning a total synthesis of natural products, particularly those of polyketide origin which exhibit polyoxygenation, are the potential side reactions of the highly reactive oxygen functionalities. In many instances masking reactive hydroxyl functionalities, which are potential nucleophiles, is required to eliminate alternative reaction pathways. Hydroxyl functionalities are commonly masked as ethers, such as silyl or benzyl, or esters, such as benzoate, to reduce the nucleophilicity. The method of removal of the protecting groups and whether they can withstand the conditions proposed in the planned reaction pathway are factors that must be deliberated when designing a synthetic strategy. Due to the importance of the role of protecting groups in total synthesis a brief discussion of commonly employed hydroxyl protecting groups follows.

One of the most widely used protecting groups for alcohols in organic synthesis are the silyl ethers which are highly versatile, due to the range of substituents available on the silicon. A small selection of the most commonly employed silyl protecting groups highlighting the variety of substituents, are represented in Figure 1.64.

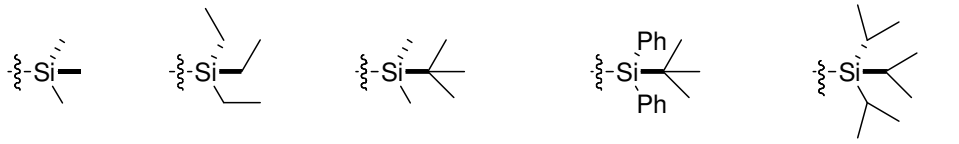


Figure 1.64 A selection of commonly employed silyl protecting groups used in natural product synthesis.

Modification of the substituent chain length, degree of branching or electron withdrawing abilities can drastically affect the ease of cleavage due to differences in the steric and electronic environments.[194] Silyl ethers with electron withdrawing substituents on the silicon atom are much more susceptible to base hydrolysis but more stable to acid hydrolysis.[194] In general as the steric bulk of the protecting group increases the stability also increases. The generally observed relative stabilities of trialkylsilyl ethers in acidic media is:
TMS (1) < TES (64) < TBS (20 000) < TIPS (700 000) TBDPS (5000 000).[195]
Under basic conditions a slight difference in relative stabilities has been observed;
TMS (1) < TES (10 000) < TBS~TBDPS (20 000) < TIPS (100 000).[195]

The environment of the alcohol within the molecule also influences how easily the silyl ether is cleaved, for example primary silyl ethers are generally cleaved more readily than secondary silyl ethers. In addition, alkyl silyl ethers are more easily cleaved by acid while phenolic silyl ethers are more readily cleaved by base.[194] Cleavage of silyl ethers is most commonly achieved using a fluoride ion, due to the high affinity of the fluoride ion for silicon. The driving force behind the reaction is the formation of the Si-F bond which is 30 kcalmol^{-1} stronger than the Si-O bond.[194] The two most frequently used fluoride sources are tetrabutylammonium fluoride[196] and hydrofluoric acid (in aqueous acetonitrile[147,197] or pyridine). HF/pyridine buffered with excess pyridine is a mild method used to prevent acid-catalysed side reactions for example dehydration of the alcohol.[198]

Another popular method for protecting alcohols is as the benzyl ethers. However

these can be unsuitable in the presence of acid sensitive systems because generation of the benzyl ethers requires acidic conditions.[199] Cleavage of benzyl ethers is readily achieved by hydrogenation although this method of cleavage is not suitable for unsaturated systems. An alternative to the benzyl ether, useful in unsaturated systems, are substituted benzyl ethers, such as *para*-methoxybenzyl ethers, which can be oxidatively cleaved using dichlorodicyannobenzoquinone (DDQ).[200]

Benzoate esters are among the most common esters used in protecting alcohols. Their popularity stems from the fact that they are more resistant to hydrolysis than acetates and are less likely to migrate to adjacent hydroxyls.[194]

Hydroxyl groups may be protected as a range of less reactive functionalities which can be generated and cleaved under a variety of reaction conditions. While only the most commonly employed examples have been presented, vast arrays of alternative protecting groups are available to suit the majority of situations. A comprehensive review of protecting groups used in organic synthesis has been prepared by Greene and Wuts.[194]

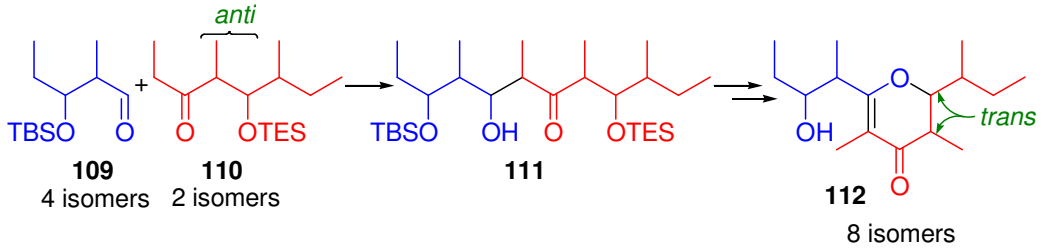
1.4 Proposed Synthetic Approaches to Maurenone and the Spiculoic Acids

A wide variety of stereoselective carbon to carbon bond forming reactions which have been discussed in Section 1.3 are available for consideration in the development of synthetic strategies towards natural products. In addition, by employing carefully selected protecting groups, control of the potential side reactions of highly oxygenated compounds can be achieved. A brief outline of the proposed syntheses towards the eight putative stereoisomeric structures of maurenone (**12-19**) and the spiculoic acids (**20**-**24**) will be described.

1.4.1 Maurenone

As introduced in Section 1.2.3, the synthesis of eight putative stereoisomeric structures of maurenone (**12**-**19**) was proposed in order to identify the stereochemistry of the natural product. A convergent approach was developed to achieve each of the structures in a time efficient and cost effective manner. Only six

key fragments containing the five desired stereocentres could be synthesised and coupled in various combinations to achieve the eight required stereoisomers of linear precursor **111**, as outlined in the general synthetic strategy in Scheme 1.14. Synthesis of two stereoisomers of ketone **110** and four stereoisomers of aldehyde **109** was proposed *via* stereoselective substrate-controlled aldol cross-coupling reactions. Coupling each of these isomers *via* eight separate double stereodifferentiating aldol couplings, will produce all of the desired stereochemical orientations of linear precursor **111**. Following the proposed oxidation, deprotection, thermodynamic cyclisation/dehydration and a final deprotection step, each of the eight putative isomeric structures, represented by cycloadduct **112**, should be achieved as shown in Scheme 1.14. Employing this approach it is proposed that the formation of the eight dihydropyrones (**12**-**19**), introduced in Section 1.2.3, by thermodynamic cyclisation/dehydration of a linear polypropionate precursor can be exploited, thus confirming the proposed biosynthesis of maurenone (**7**). Spectroscopic comparison of the data of each of the isomers (**12**-**19**) with that reported for the natural product[30] will enable the relative stereochemistry of maurenone (**7**) to be defined.



Scheme 1.14 Proposed synthetic approach to the eight putative stereoisomeric structures of maurenone (7).

1.4.2 Spiculoic Acids

In Section 1.2.4 the spiculoic acid family of natural products (**20**-**24**) were introduced and the proposed biogenesis, involving an enzyme-catalysed IMDA cycloaddition reaction, was presented as outlined in Figure 1.65. The IMDA reaction simultaneously installs four stereogenic centres and the [4.3.0] spiculane skeleton in a single reaction step. Due to the structural complexity of the spiculane skeleton, containing two quaternary and 2 tertiary stereocentres to be generated *via* the D.-A. cycloaddition reaction, a structurally less complex model system was proposed. The model system was designed with the goal of exploring a synthetic approach to the linear precursors which could be applied to the natural products and with the aim of

investigating the factors affecting the stereochemical outcome of the subsequent IMDA reaction. Figure 1.65 shows the proposed model system (**113**), developed containing many of the structural features of the spiculoic acids (**20**-**24**) with a significantly simplified structure. By synthesising the linear precursor **114,** with different stereochemical orientation of the C5 stereocentre and different dienophile geometries at C2, it was hoped that an understanding of the factors affecting the stereochemical outcome of the thermally induced IMDA reaction could be developed. Synthesis of each of the linear polyene precursors (**114**) was anticipated *via* a stereoselective substrate-controlled aldol cross-coupling reaction to install the C4-C6 stereotriad and subsequent olefination reactions to assemble the polyene precursors. Thermally induced IMDA reactions of the linear precursors are proposed to achieve the [4.3.0] spiculane skeleton. A thorough analysis of the stereochemistry of the cycloadducts (**113**) employing 2D NMR techniques will then be performed. This information may be used to devise a convergent approach to the stereoselective synthesis of the spiculane skeleton identified in the spiculoic acid family of natural products (**20**-**24**).

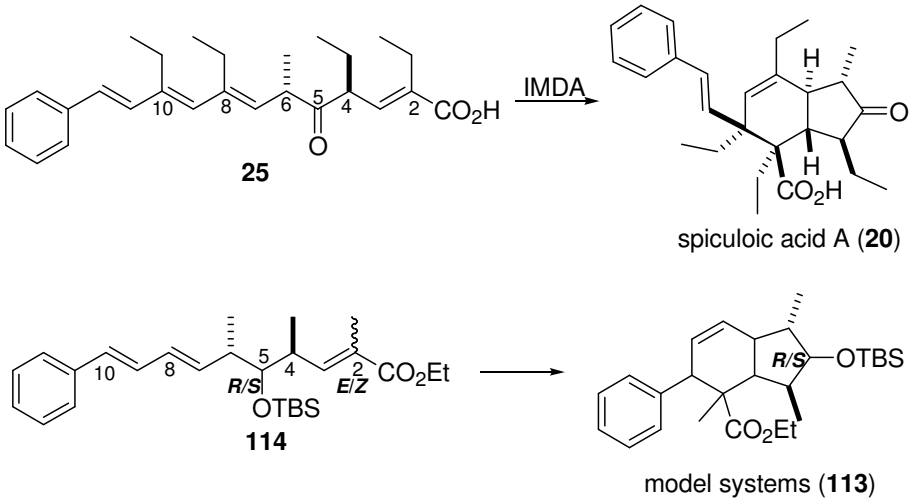


Figure 1.65 The linear precursors to spiculoic acid A and the proposed model system (113), developed to study the stereoselectivity of the IMDA cycloaddition reactions.

1.5 Summary

The plethora of bioactive compounds isolated from marine organisms has made the marine environment a popular source of potential drug targets. Of particular interest have been the polyketide derived metabolites of which a significantly higher proportion demonstrate drug activity. The complex chemical structures containing multiple contiguous stereocentres pose a challenging synthetic target for organic chemists. Armed with the comprehensive arsenal of carbon to carbon bond forming reactions, many of which occur with stereo- or regio-selectivity, the synthetic chemist can hope to achieve these complex structures in an efficient manner.

There are several reasons, often acting simultaneously, that compel a synthetic organic chemist to target the total synthesis of a particular natural product. Due to the very small amounts of the bioactive natural products isolated from the marine organisms a synthetic route is often desired to obtain sufficient quantities for thorough bio-evaluation. In many instances biomimetic syntheses can provide information about the biogenesis of these compounds in natural systems. This can contribute to the understanding of the role of these metabolites within the organism and the role of enzymes in biosynthesis. The final factor attracting synthetic chemists to natural products synthesis is the pursuit of a challenge. Targeting complex chemical structures offers the opportunity to investigate and develop new methodologies and extend known synthetic approaches. A combination of these factors has led to the selection of the natural products targeted in this thesis, maurenone (**7**) and the spiculoic acid family of natural products (**20**-**24**). A detailed account of the total synthesis and structural elucidation of (-)-maurenone is discussed in Chapter Two. Chapter Three provides a literature review of previous and parallel synthetic efforts towards the spiculoic acids and the development of the model systems investigated within this study. The synthesis and detailed stereochemical analysis of the cycloadducts achieved by thermally induced IMDA reaction of the model linear precursors is reported in Chapter Four. Finally, Chapter Five describes the development of a synthetic strategy towards the synthesis of the spiculoic acid family of natural products, the synthetic efforts to date and future directions proposed to achieve the total synthesis.

CHAPTER 2 TOTAL SYNTHESIS AND STRUCTURAL ELUCIDATION OF (-)-MAURENONE

The total synthesis of (2*S*, 3*S*)-2,3-dihydro-6-[(1'*S*, 2'*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (**14**), the (-)-enantiomer of the marine polypropionate, maurenone, was achieved in nine linear steps (13 % overall yield), from (*R*)-2-benzylpentan-3-one ((***R*)-40**)) and (*R*)-2-benzoyloxypentan-3-one ((***R*)-39**). Key fragments were synthesised using highly diastereoselective *syn*- and *anti*-boron aldol reactions and were coupled *via* a lithium-mediated aldol reaction. Trifluoroacetic acid-promoted cyclisation/dehydration was then used to install the γ-dihydropyrone ring. Eight isomers of one enantiomeric series were synthesised by coupling two ketones with each of four aldehydes. Comparison of the ^{1}H and ^{13}C NMR data for the eight isomers with that reported for maurenone established the relative stereochemistry of the natural product.

2.1 Siphonariids, a Source of Unusual Polyketide Secondary Metabolites

Pulmonate molluscs of the genus *Siphonaria* are air-breathing molluscs generally found in intertidal zones of regions of warm temperate to tropical, rocky shores in the southern hemisphere, some examples of which are shown in Figure 2.1.[201] There is some conjecture as to whether they evolved from marine or terrestrial ancestry and it is suggested that they may represent an evolutionary link between marine and terrestrial gastropods.[201] Siphonariids are herbivores, feeding on micro-organisms and encrusting algae at low tide, while at high tide they are often submerged making them vulnerable to predation by both marine and terrestrial predators.[201] As a result they exhibit a physical defence system (i.e. a shell) as well as a chemical defence system. When disturbed Siphonariids excrete a white mucus from the lateral pedal glands which contains an abundance of secondary metabolites.[201] These compounds, containing highly methylated and oxygenated skeletons, are thought to be biosynthesised through successive condensations of propionate units and commonly undergo intramolecular cyclisations to produce pyrone and hemi-acetal ring systems.[14] Relatively little is known about the ecological role of these metabolites or their acyclic precursors although many of them display potent biological activity, for example toxicity in fish, suppression of bacterial growth and inhibition of the development of fertilised sea urchin eggs.[201]

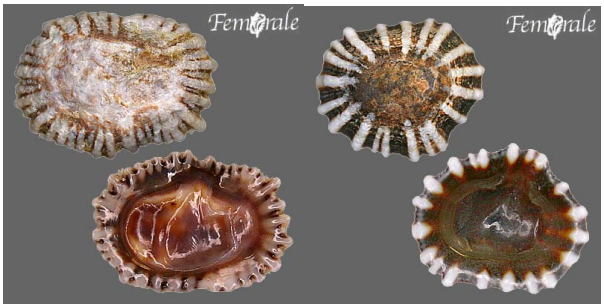


Figure 2.1 Pulmonate molluscs of the genus *Siphonaria*.

2.2 Isolation and Structural Assignment of Maurenone

Maurenone (**7**), a polyketide derived marine natural product, was isolated by Faulkner and co-workers from *Siphonaria maura*, a pulmonate mollusc found on the shores of Jaco Beach, Costa Rica.[30] A meagre 5.3 mg of maurenone (**7**) was isolated from 230 specimens of the mollusc, indicating that the biological source is not a viable option to secure material for thorough biological testing. The structure of maurenone was assigned on the basis of ^{1}H and ^{13}C NMR, IR and UV data. A polyketide origin was indicated by the presence of six methyl group resonances in the ^{1}H NMR spectrum. Absorptions at 1655 cm^{-1} and 1610 cm^{-1} in the IR spectrum and at 276 nm in the UV spectrum suggested the presence of a β-alkoxy-α,β-dialkyl-α,β-unsaturated ketone. An absorption at 3490 cm^{-1} in the IR spectrum also revealed the presence of a hydroxyl group. The relatively uncommon, tetra-substituted dihydropyrone moiety represented in Figure 2.2, was thus suggested as the planar structure of maurenone (**7**). Stereochemical information was limited and the configurations at C3, C4 or C10 were not assigned. This is due to both conformational flexibility within the ring appendages and these chiral appendages being located at remote sites on the ring system preventing relative stereochemical information from being relayed. Only the *trans*-relationship between the C8 and C9 substituents, on the rigid ring, was indicated by the relatively large coupling constant, $J_{8,9}$ = 12.3 Hz, however the absolute stereochemistry at these centres could not be deduced. Unfortunately the optical rotation was not reported in the isolation paper and correspondence with the authors revealed that this information had not been recorded. Five stereocentres were identified in the proposed dihydropyrone structure (**7**), however, considering the *trans*-relationship between the C8 and C9 protons, there are effectively four stereocentres. This translates to 16 possible stereoisomers, or 8 pairs of enantiomers, one of which corresponds to maurenone. Enantiomeric

pairs have identical physical properties, excluding the sign of the optical rotation so there is no advantage to be gained in considering all 16 possible stereoisomers. Thus, examination of only 8 possible stereoisomers in one arbitrarily selected enantiomeric series is required to identify the relative stereochemistry of the natural product. Due to the absence of optical rotation data for the natural product the absolute stereochemistry cannot be assigned.

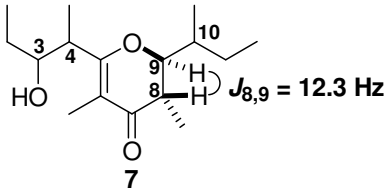


Figure 2.2 The structure of maurenone, featuring a tetra-substituted dihydropyrone moiety.

2.2.1 Research Aims

Polyketide derived secondary metabolites have been particularly valuable as potential drug candidates or lead compounds and therefore a thorough biological evaluation of maurenone (**7**) was desired. Due to the limited bioavailability of the natural product, a synthetic approach to each of the eight possible stereoisomers of one enantiomeric series of maurenone was sought. This would also provide the opportunity to assign the relative stereochemistry of the natural product by comparison of spectroscopic data from the natural product with the synthetic putative structures. The series of compounds **12**-**19**, indicated in Figure 2.3, containing the *S* configuration at C10 were targeted due to the commercial availability of optically pure (*S*)-2-methylbutan-1-ol which would be employed as a key starting material.

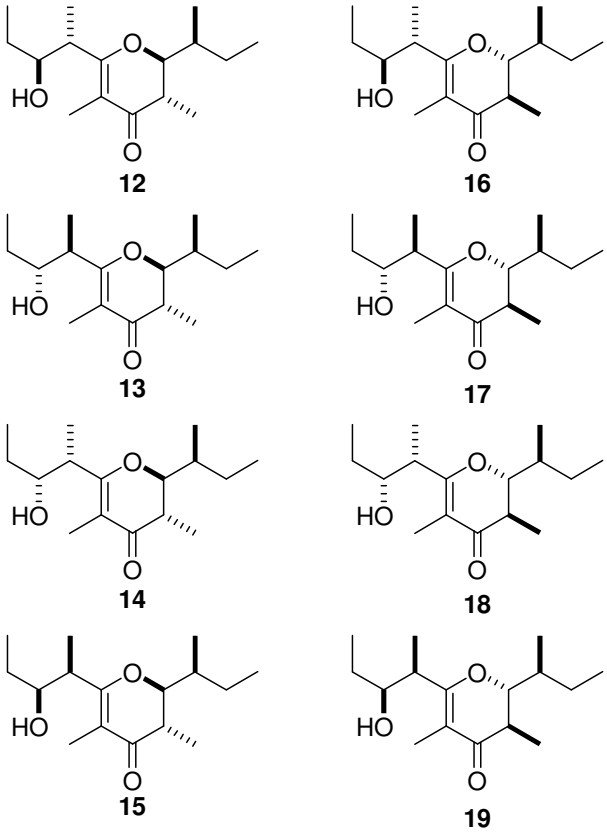
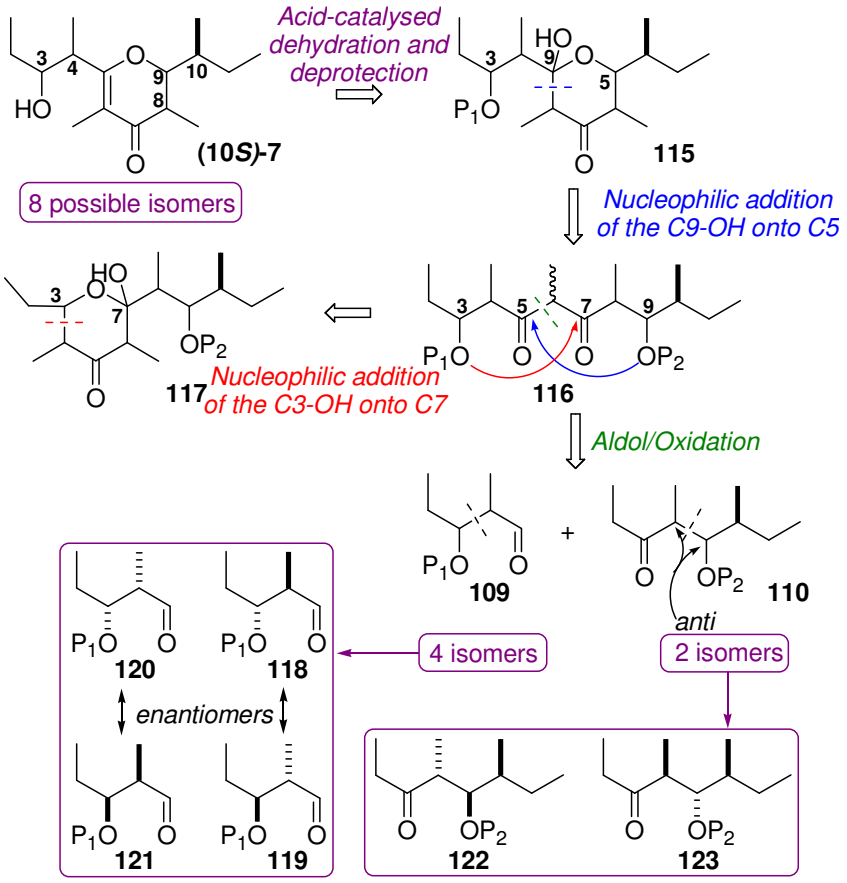


Figure 2.3 The eight putative isomeric structures of the natural product, maurenone.

2.2.2 Retrosynthetic Analysis of the Eight Stereoisomers

In order to achieve a convergent synthesis of the eight isomers (**12**-**19**), a strategy using a number of common intermediates and the minimum number of synthetic steps was desired. Scheme 2.1 outlines the retrosynthetic strategy for the planar maurenone structure with all of the required configurations at C3, C4, C8 and C9. The dihydropyrone (**10*S*)-7** can be envisaged to arise by acid-mediated deprotection of the masked C3 alcohol with concomitant dehydration of the corresponding hemiacetal moiety in precursor **115**. Formation of hemiacetal **115** was proposed to occur by selective deprotection and subsequent thermodynamically controlled cyclisation of dione **116**. The proposed cyclisation step utilises a biomimetic approach as cyclisation of linear polypropionates was thought to proceed under thermodynamic control in nature. For a detailed discussion of the spontaneous cyclisation of linear polyketides under thermodynamic control refer to Section 1.2.1. In addition, there are a number of literature examples of thermodynamically controlled, acid-catalysed, cyclisations of linear polypropionates supporting this synthetic plan.[25,31,27,202,203] As dione **116** has *pseudo* symmetry differential protection

of the C3 and C9 hydroxyl groups was critical in order to control the mode of cyclisation. The formation of desired hemiacetal **115** occurs *via* nucleophilic attack of the C9 hydroxyl onto the C5 carbonyl in dione **116** represented in blue. However, an alternative nucleophilic addition of the C3 hydroxyl onto the C7 carbonyl, represented in red, could potentially form undesired hemiacetal **117**. Therefore, in order to suppress formation of the undesired hemiacetal **117**, differential protection of the C3 and C9 hydroxyl groups was required. The C3 protecting group must be robust and capable of tolerating the conditions used to cleave the C9 protecting group. Dione **116** was envisaged to arise from an aldol/oxidation disconnection between C5 and C6 leading to aldehyde **109** and ketone **110**. Employing this strategy the eight isomers (**12**-**19**) of dihydropyrone **(10*S*)-7** can be prepared in a convergent, time efficient manner from four isomers of aldehyde **109** and two isomers of ketone **110**.



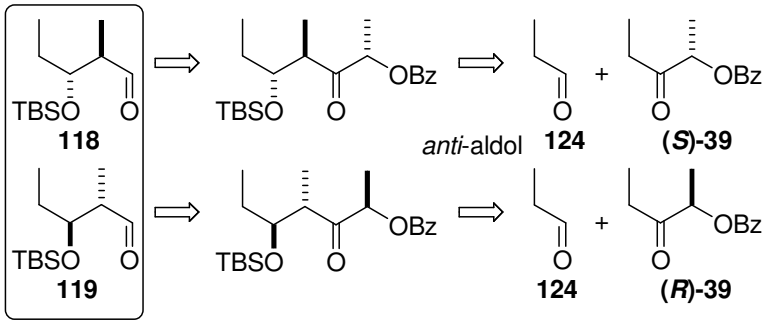
Scheme 2.1 A retrosynthetic strategy for the generic maurenone structure with all of the required configurations at C3, C4, C8 and C9.

A large array of protecting groups are commonly employed in the protection of free hydroxyl groups as discussed in Section 1.3.7. Silicon protecting groups were the

obvious choice due to their versatility, widely differing stabilities towards acidic and basic conditions and the relative ease of cleavage using a fluoride ion source.[194] The C9 hydroxyl was to be protected as the triethylsilyl (TES) ether while the C3 hydroxyl was to be protected as the *tert*-butyldimethylsilyl (TBS) ether. The TBS ether is much more robust than the TES ether due to the steric bulk of the *tert*-butyl group.[194] Thus, it was expected that selective cleavage of the TES ether could occur in a short time under acidic conditions.

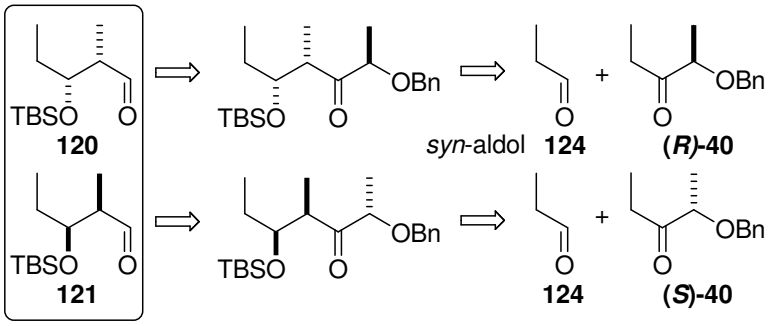
2.3 A Convergent Approach to Total Synthesis: Utilising Common Aldol Fragments

By exploiting the high π-facial selectivity in *syn*- and *anti*-aldol couplings of the lactate derived α-chiral ketones **39** and **40**,[71,75-77] introduced in Section 1.3.1.3.1 synthesis of all six of the common aldol fragments, aldehydes **118-121** and ketones **122** and **123** can be achieved. The enantiomeric *anti*-aldehydes **118** and **119** are available from the aldol reaction between benzyloxy protected ketones **(*S*)-39** and **(*R*)-39** and propionaldehyde (**124**) after protection, hydrolysis and oxidative cleavage. (Scheme 2.2) As discussed in Section 1.3.1.3.1, the benzoyloxy protecting group on the ketone gives rise to highly selective *E*-(O)-enolisation and the α-stereocentre dictates the π-facial selectivity.



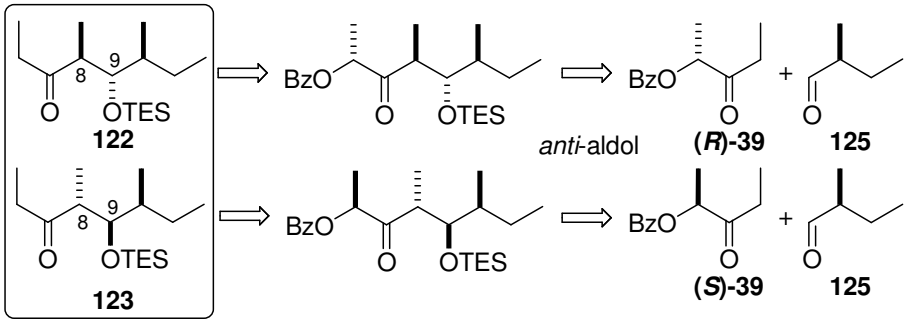
Scheme 2.2 Retrosynthetic analysis of the *anti*-aldehydes 118 and 119.

In a similar aldol coupling to that used for synthesis of the *anti*-aldehydes the enantiomeric pair of *syn*-aldehydes (**120** and **121**) are available from an aldol coupling of benzyl protected ketones **(*R*)-40** and **(*S*)-40** with propionaldehyde (**124**) followed by protection, reduction, hydrogenolysis and oxidative cleavage. (Scheme 2.3) In this instance, with the benzyl protecting group on the ketone, the *Z*-(O)-enolate geometry is achieved exclusively and again the α-stereocentre controls the π-facial selectivity of the enolate.



Scheme 2.3 Retrosynthetic analysis of the *syn*-aldehydes 120 and 121.

The two ketones **122** and **123** are prepared by an analogous, *anti*-selective aldol coupling between **(*R*)-39** and **(*S*)-39** and (*S*)-2-methylbutanal (**125**). (Scheme 2.4) In this instance the aldol coupling is double stereodifferentiating as both coupling partners possess stereogenic elements. However the π-facial preference of α-chiral ketones **(*R*)-39** and **(*S*)-39** are reported to dominate the facial preference of α-chiral aldehydes, such as aldehyde **125**, in double stereodifferentiating aldol couplings.[71]



Scheme 2.4 Retrosynthetic analysis of the ketones 122 and 123.

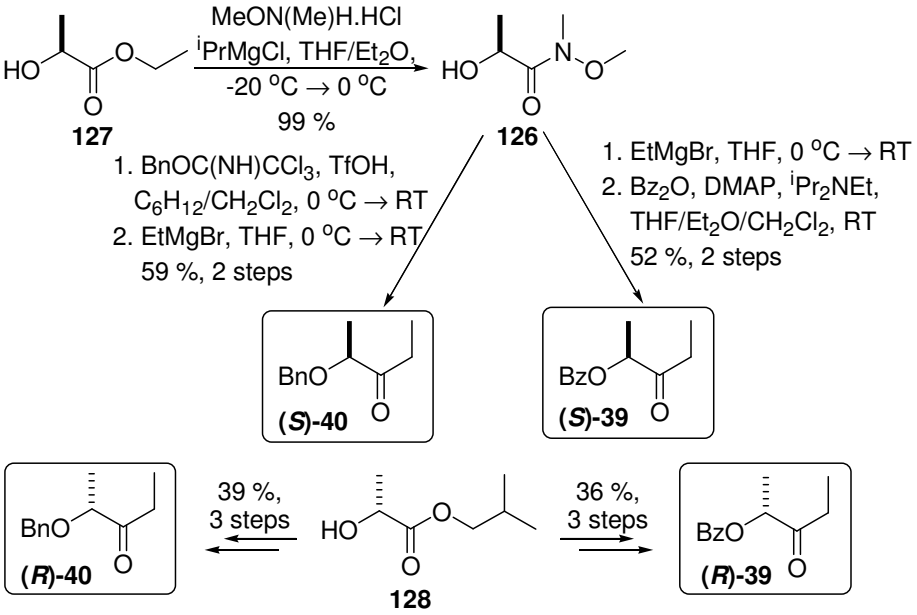
An advantage of this strategy is that common starting materials (i.e. ketones **(*S*)-39** and **(*R*)-39**) can be used in the synthesis of both aldehydes **118** and **119** and ketones **122** and **123**, making the synthesis more convergent and thus efficient. In addition, all eight possible isomers of maurenone are available from just 6 different aldol fragments; two ketones (**122** and **123**) and four aldehydes (**118-121**).

2.3.1 Constructing the Six Building Blocks

2.3.1.1 Synthesis of Common Precursors; The Lactate Derived α-Chiral Ketones

Lactate derived α-chiral ketones **39** and **40** were synthesised using the methods reported by Paterson and co-workers.[71,75-77] Both the benzoyloxy ketone **39** and the

benzyl ketone **40** were synthesised in three steps (Scheme 2.5) beginning with preparation of Weinreb amide **126** from ethyl-(*S*)-lactate (**127**) or isobutyl-(*R*)-lactate (**128**) using standard methods (dimethylhydroxyamine hydrochloride and isopropylmagnesium chloride). Grignard addition to amide **126**[204] using ethylmagnesium bromide and protection of the alcohol as the benzoate ester (benzoic anhydride, 4-dimethylaminopyridine and N,N-diisopropylethyl amine) gave benzyloxy ketone **39** (52 %, over 2 steps). Alternatively, the free hydroxyl of Weinreb amide **126** can be protected as the benzyl ether, then Grignard addition to the protected Weinreb amide **129** yields the benzyl ketone **40** (59 %, over 2 steps).

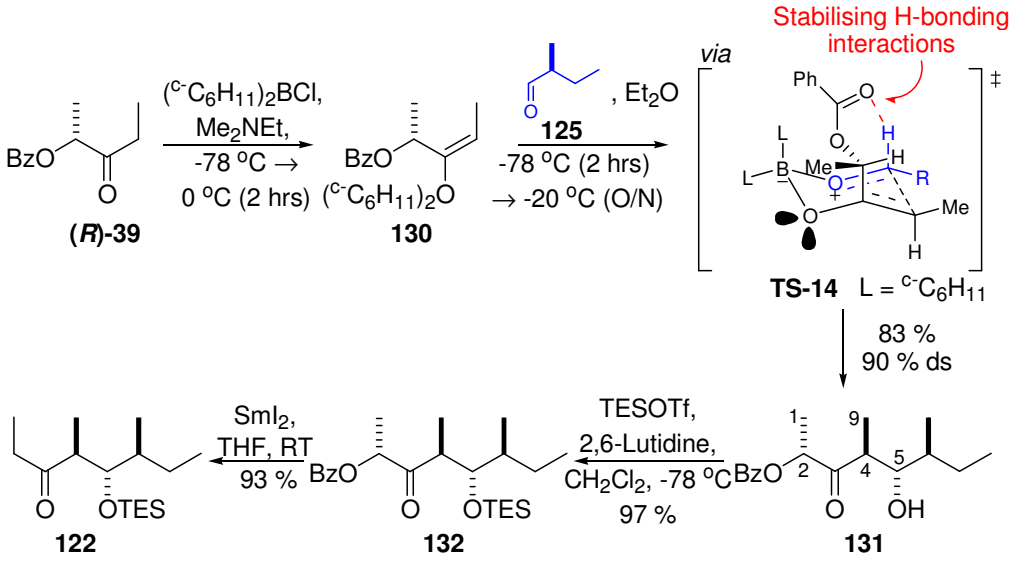


Scheme 2.5 Preparation of lactate derived α-chiral ketones 39 and 40.

2.3.1.2 Synthesis of the Ketone Fragments 122 and 123

Synthesis of the *anti, anti*-ketone **122**, outlined in Scheme 2.6, began with an asymmetric aldol reaction[71,75-77] between the dicyclohexylboron *E*-enolate **130** of α-chiral ketone **(*R*)-39** and the α-chiral aldehyde **(*S*)-125** (obtained by Swern[205] oxidation of (*S*)-2-methylbutan-1-ol). The enolate geometry and the π-facial preference of the ketone controls the formation of the C4 and C5 stereocentres in a mis-matched double stereodifferentiating aldol reaction to give *anti*-adduct **131** (83 % yield, 90 % ds). The π-facial selectivity of the enolate **130** can be rationalised by considering the most stable Zimmerman-Traxler transition state represented in Scheme 2.6. Stabilising H-bonding interactions between the axial proton from aldehyde **(*S*)-125** and the carbonyl of the benzoate ester facilitate reaction at the π-

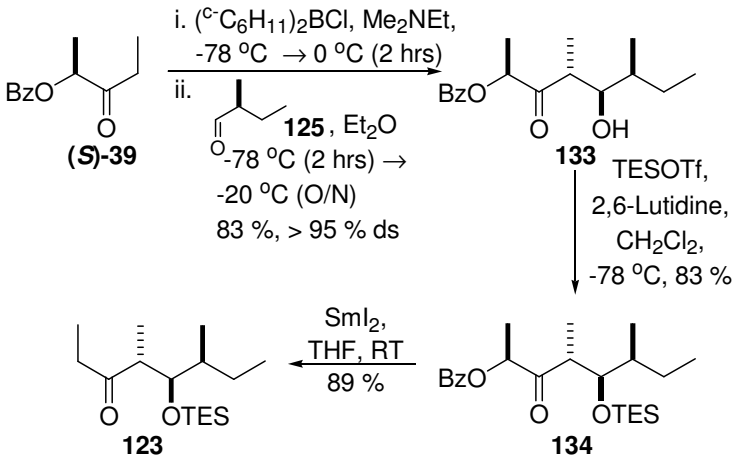
face shown. For a more detailed discussion of the alternative transition states refer to Section 1.3.1.3.1.[71,79] This transition state produces adduct **131** with a 1,3-*anti*-relationship between the C2 and C4 stereocentres. The 4,5-*anti*-relationship is dictated by the *E*-geometry of the enolate. The stereochemical assignment of the major aldol adduct, in this double stereodifferentiating aldol coupling, was based on literature precedent.[71] Although the inherent Felkin π-facial preference of aldehyde **(*S*)-125** suggests a 5,6-*syn*-relationship, the facial preference of the α-chiral ketone is reported to dominate the facial preference of the aldehyde. [71,75-77] Despite the double stereodifferentiating aldol reaction being mis-matched for the aldehyde the reaction diastereoselectivity is still high (90 % ds). Affirmation of synthesis of alcohol **131** was immediately obvious from the ^{1}H NMR spectrum due to the presence of a multiplet at 3.60-3.53 ppm due to the C5 proton and the doublet at 1.57 ppm due to the C9 protons. Other spectroscopic data confirmed that alcohol **131** had been synthesised. A small minor isomer component was evident in the NMR spectra however separation and stereochemical assignment was not achieved.



Scheme 2.6 Synthesis of *anti*, *anti*-ketone 122.

Silyl protection of the secondary alcohol **131** (TESOTF, 2,6-lutidine)[206] followed by controlled samarium diiodide (2-3 eq. SmI_2) mediated cleavage of the benzoate ester **132** gave the corresponding ketone **122** in good yield (93 %, 75 % over 3 steps).[75] Previous experience within the Perkins research group indicated that a TES ether may be sensitive to a large excess of SmI_2 (4 eq.). However when ester cleavage was monitored by TLC with controlled, portion-wise addition of SmI_2, ketone **122** was achieved in high yield.

The alternative *anti*, *syn*-ketone **123** was synthesised *via* compounds **133** and **134** (61 %, over 3 steps) in the same sequence to that described in Scheme 2.6, starting from (S)-2-benzoyloxypentane-3-one ((***S***)**-39**) as depicted in Scheme 2.7. The cyclic transition state is enantiomeric with that shown in Scheme 2.6, except for the configuration of the R group of aldehyde **(*S*)-125**. In this case the double stereodifferentiating reaction of α-chiral ketone **(*S*)-39** was matched with the Felkin[207] preference of α-chiral aldehyde **(*S*)-125** giving aldol adduct **133** with no detectable minor isomer (83 % yield, >95 % ds).

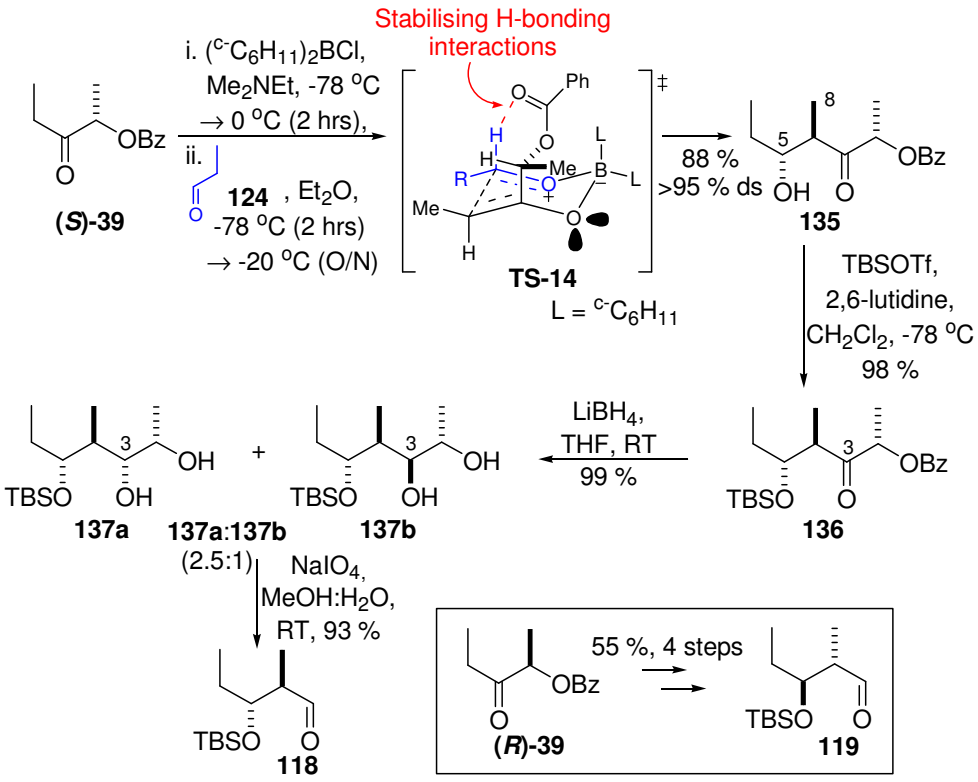


Scheme 2.7 Synthesis of the *anti*, *syn*-ketone 123.

2.3.1.3 Synthesis of the *anti*-Aldehyde Fragments 118 and 119

The synthesis of the *anti*-aldehyde **118**, described in Scheme 2.8, began with a similar substrate controlled *anti*-aldol coupling between the dicyclohexylboron *E*-enolate of α-chiral ketone **(*S*)-39** and propionaldehyde (**124**).[71,75-77] The most stable Zimmerman-Traxler transition state, **TS-14**, is analogous to that described for the synthesis of ketone **122**.[71,79] In this case the stereoselectivity of the aldol coupling with the achiral aldehyde is very high giving aldol adduct **135** with no minor isomer detected. Synthesis of alcohol **135** was verified by the presence of a ddd at 3.69 ppm due to the C5 proton and the doublet at 1.56 ppm due to the C8 protons. The generated alcohol was then protected as the TBS ether **136**[208] and reduction, of both the ketone and ester functionalities with $LiBH_4$ gave 1,2-diols **137a** and **137b** (ratio 2.5:1).[75] The $LiBH_4$ reduction of the ketone (C3) was not stereoselective, however this was of little concern as this stereocentre is lost in the subsequent oxidation. Separation of the two isomers by column chromatography and characterisation was

achieved. Oxidative cleavage of a mixture of both isomers using sodium periodate[75] gave the *anti*-aldehyde **118** in good yield (79 %, over 4 steps). Comparison of the spectral data with that reported in the literature confirmed synthesis of the desired aldehyde and thus verified the stereochemical outcome of the *anti*-aldol coupling reaction.[209] Synthesis of the enantiomeric aldehyde **119** was performed in an identical manner starting from (*R*)-benzoyloxypentan-3-one ((***R*)-39**) (55 %, over 4 steps).

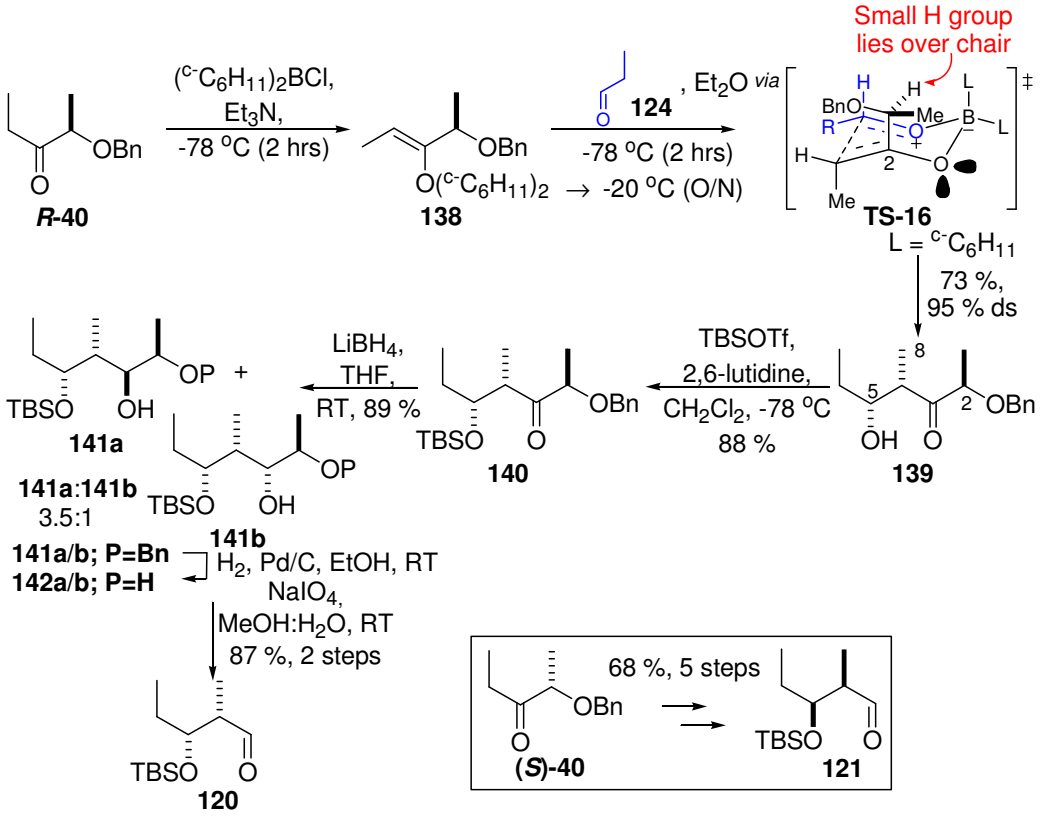


Scheme 2.8 Synthesis of the *anti*-aldehydes 118 and 119.

2.3.1.4 Synthesis of the *syn*-Aldehyde Fragments 120 and 121

The synthesis of *syn*-aldehyde **120** (Scheme 2.9) began with a substrate controlled aldol coupling between the dicyclohexylboron *Z*-enolate **138** of α-chiral ketone **(*R*)-40** and propionaldehyde (**124**) giving the *syn*-aldol adduct **139**.[75,71] Notably, the change in protecting group from Bz (in **39**) to Bn (in **40**) and using the modified enolisation conditions (($^{c}C_6H_{11})_2BCl$, NEt_3, -78 °C (2 hrs)) produces, the *Z*-enolate **138** selectively and thus the *syn*-aldol adduct **139** is obtained. The π-facial selectivity of enolate **138** can be justified by considering the most stable conformation of the Zimmerman-Traxler transition state, **TS-16**, depicted in Scheme 2.9.[71,210] For a more detailed discussion of the alternative transition states refer to Section 1.3.1.3.1.

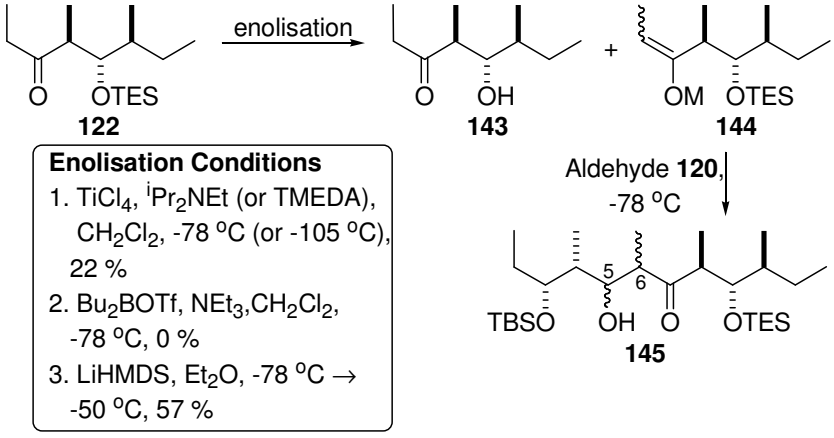
Reaction at the π-face shown is favoured as the smaller H group lies in the more sterically demanding position over the chair. Reaction at the other face would place the methyl group in this position which is clearly unfavourable. Confirmation of synthesis of alcohol **139** was again evident by ^{1}H NMR due to the presence of a ddd at 3.76 ppm due to the C5 proton and the presence of a doublet at 1.38 ppm due to the C8 protons. Oxidative cleavage, of this benzyl protected compound, to the aldehyde requires a modified sequence from that used for the *anti*-aldehyde (Scheme 2.8). The C5 hydroxyl was protected as the TBS ether **140**[208] and then carbonyl reduction ($LiBH_4$) gave alcohols **141a** and **141b** (ratio 3.5:1). Once again the reduction was not stereoselective however separation of the two isomers by column chromatography and subsequent characterisation was achieved. Hydrogenolysis of each isomer of benzyl ether **141** gave 1,2-diols **142a** (99 %) and **142b** (91 %) which were subsequently oxidised with $NaIO_4$ to give a single isomer of aldehyde **120** (97 %, 65 % over 5 steps).[75] Comparison of the spectral data with that reported in the literature confirmed synthesis of the desired aldehyde and thus provided evidence for the assigned stereochemical outcome of the *syn*-aldol coupling reaction.[211,212] The synthesis of the enantiomeric aldehyde **121**[213] was performed in an identical manner starting from (*S*)-benzylpentan-3-one (**(*S*)-40**) (68 %, over 5 steps).



Scheme 2.9 Synthesis of the *syn*-aldehydes 120 and 121.

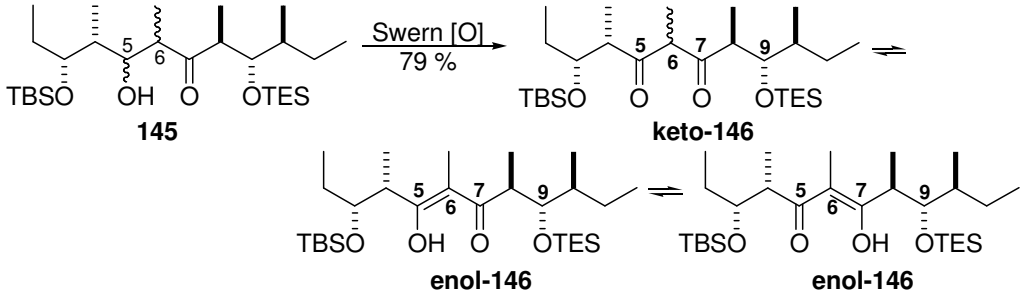
2.3.2 Assembling the Eight Isomers: Aldol Coupling and Cyclisation

The synthesis of all eight possible isomers of maurenone (**12**-**19**) was now possible by coupling each of the two ketone isomers (**122** and **123**) with the four aldehyde isomers (**118-121)** in eight double stereodifferentiating aldol couplings. Several different aldol strategies were investigated and are outlined in Scheme 2.10. Attempts to couple the titanium (IV) enolate **144** ($TiCl_4$ (5 min. complexation time), $^{i}Pr_2NEt$, -78 ^{o}C)[95] of ketone **122** with aldehyde **120** proved troublesome due to the desilylation of the ketone during enolisation. Formation of the desilylated adduct **143** was immediately evident from the ^{1}H NMR spectrum with the ethyl groups of the silyl ether noticeably absent. Small chemical shift differences for the other protons were also apparent, the most significant being the shift in the C*H*O proton from 3.8 ppm in the protected ketone to 3.4 ppm in the deprotected ketone. Modifications to the procedure such as lower reaction temperatures (-105 ^{o}C), shorter Lewis acid complexation times (2 min.) and an alternative base (TMEDA) were unsuccessful in generating the product in acceptable yields (22 %), although the diastereoselectivity was high (> 95 %). Similarly, attempts to generate the boron enolate **144** (Bu_2BOTf, NEt_3, -78 ^{o}C)[81] resulted in desilylation. Fortunately, higher yields (~ 60 %) were achieved by employing a lithium enolate. Treatment of ketone **122** with lithium bis(trimethylsilyl)amide[207] (Scheme 2.10) at -78 ^{o}C and stirring for 30 minutes before warming to -50 ^{o}C and stirring for a further 30 minutes, produced the lithium enolate **144**. Subsequent addition of aldehyde **120** at -78 ^{o}C and stirring for 2 hours gave the coupled product **145** in moderate yield (57 %) and diastereoselectivity (74 % ds). In this, and other cases, the isomers could be separated and characterised although assignment of the stereochemistry was not possible. Due to the *pseudo* symmetry of the aldol adducts it was difficult to assign the ^{1}H and ^{13}C NMR resonances to specific atoms. Therefore confirmation of synthesis of the isomeric aldol adducts **145**, was based on the four CH_3 doublets, resonating at around 1 ppm and three C*H*O protons (two doublet of doublets and one doublet of triplets) resonating at about 4 ppm in the ^{1}H NMR spectra. The ^{13}C NMR spectrum revealed three *CH*O carbons and one carbonyl resonance affirming the synthesis of the desired aldol adducts **145**.



Scheme 2.10 The search for suitable conditions to effect the double stereodifferentiating aldol coupling of the chiral ketone and aldehyde fragments.

Ultimately the configuration at C5 and C6 was of little significance as oxidation of the C5 hydroxyl to the ketone results in loss of this stereocentre and the C6 methyl group, now situated between two carbonyls groups, becomes readily epimerisable. Aldol adduct **145** was oxidised to the corresponding dione **146** under Swern conditions in reasonable yield (79 %) as represented in Scheme 2.11.[205]



Scheme 2.11 Oxidation of the aldol adducts results in epimerisation of C6.

The ^{1}H and ^{13}C NMR spectra (Figure 2.4 and Figure 2.5) of the desired dione **146** revealed a mixture of C6 epimers of keto-tautomer **146** with no evidence of the enol-tautomers. This mixture of C6 epimers of keto-tautomers **146** made structural assignment difficult, however, the presence of a quartet at ~ 4.0 ppm in the ^{1}H NMR spectrum corresponding to the C6 proton situated between the two carbonyl groups and the presence of two signals at ~210 ppm in the ^{13}C NMR spectrum corresponding to C5 and C7 confirmed that dione **146** had indeed been synthesised.

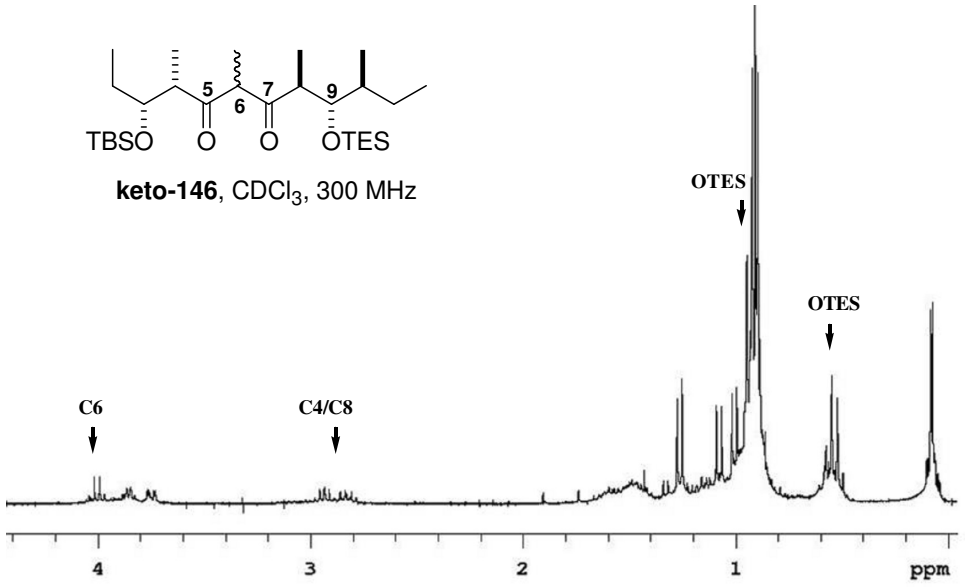


Figure 2.4 ^{1}H NMR spectrum of dione 146.

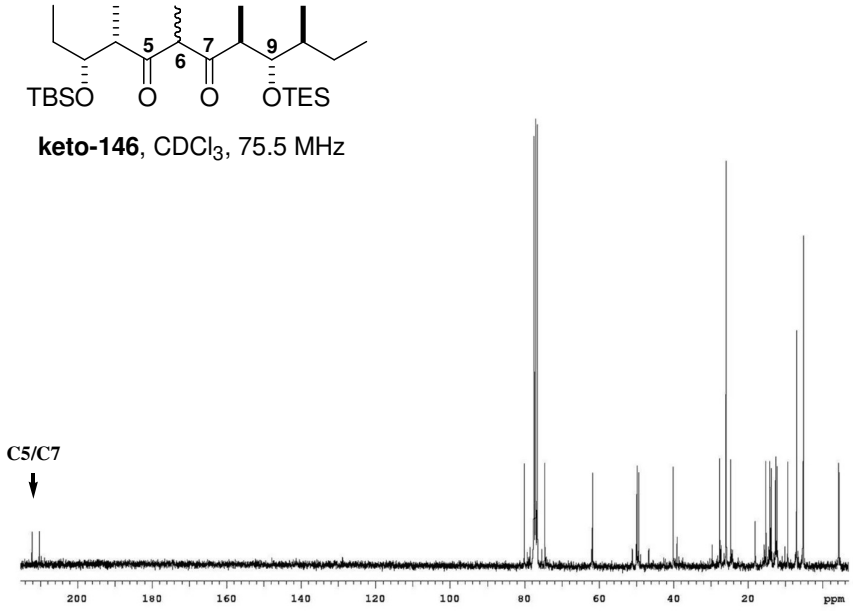
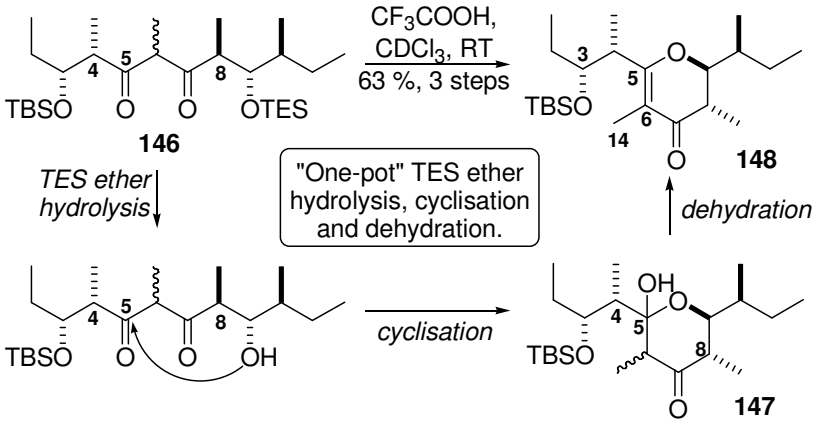


Figure 2.5 ^{13}C NMR spectrum of dione 146.

In order to investigate whether selective acid-promoted cleavage of the TES ether in the presence of the TBS ether was a viable option, a small amount of trifluoroacetic acid was added to the dione in $CDCl_3$. (Scheme 2.12) This was performed in an NMR tube to allow the reaction progress to be monitored by ^{1}H NMR. Over 40 minutes a reduction in the size of the peaks corresponding to the ethyl groups of the

TES ether was observed (refer to Figure 2.4). The simultaneous disappearance of the multiplet at ~ 2.9 ppm in the dione spectrum (corresponding to the protons on C4 and C8) and appearance of a new multiplet at ~ 2.45 ppm was observed. Finally, the appearance of a singlet at ~ 1.75 ppm thought to correspond to an allylic methyl group suggested that hemiacteal (**147**) formation had occurred and subsequent dehydration was occurring to give dihydropyrone **148** (Figure 2.6). After 40 minutes the complex dione spectrum, showing a mixture of C6 epimers of the keto-tautomer **146**, had simplified significantly due to the formation of one isomer of a cyclic product.



Scheme 2.12 Selective cleavage of the TES ether, promotes a cascade cyclisation/dehydration reaction sequence.

Purification of the product and subsequent NMR analysis confirmed earlier observations that cleavage of the TES ether and acid-promoted cyclisation to hemiacetal **147** had occurred, which spontaneously dehydrated under the acidic conditions to the dihydropyrone **148** (63 %, over 3 steps). This was immediately evident from the ^{1}H NMR spectrum, Figure 2.6, due to the presence of allylic methyl protons on C14 at 1.73 ppm and the absence of a signal for the C6 proton of hemiacetal **147**. The signals at 173.0 (C5) and 108.6 (C6) ppm in the ^{13}C NMR spectrum confirmed the presence of an enone system. (Figure 2.7) High resolution MS and UV spectral data were in agreement with this structural assignment. The coupling constant between the C8 and C9 protons was found to be 12.3 Hz, confirming the *trans*-relationship between these centres. The *trans*-relationship between the C8 and C9 protons also provides evidence that the aldol reaction described in Section 2.3.1.2, Scheme 2.6, was indeed *anti*-selective. While this had been assumed based on literature precedent this hadn't been confirmed until the cyclisation step.[75,71,76,77]

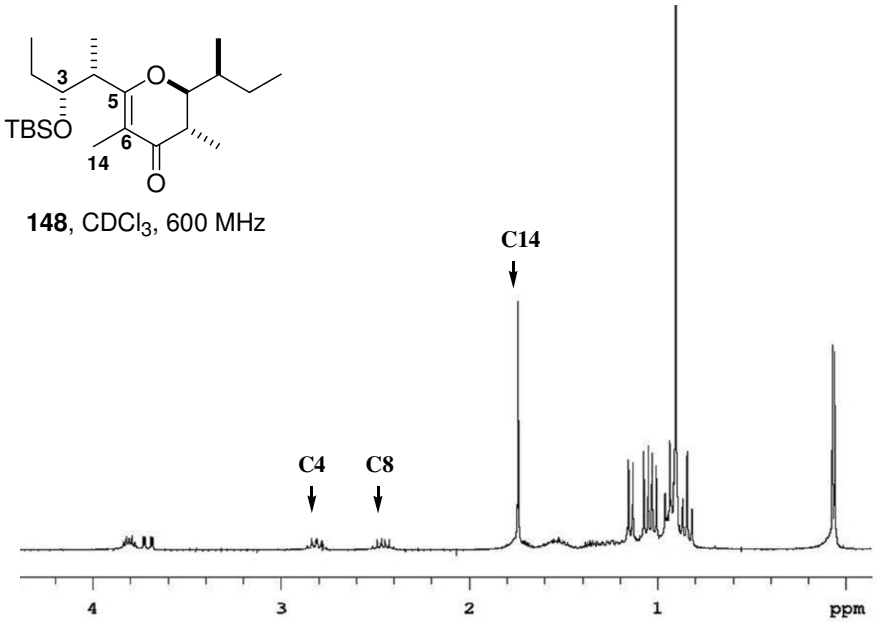


Figure 2.6 ^{1}H NMR spectrum of dihydropyrone 148.

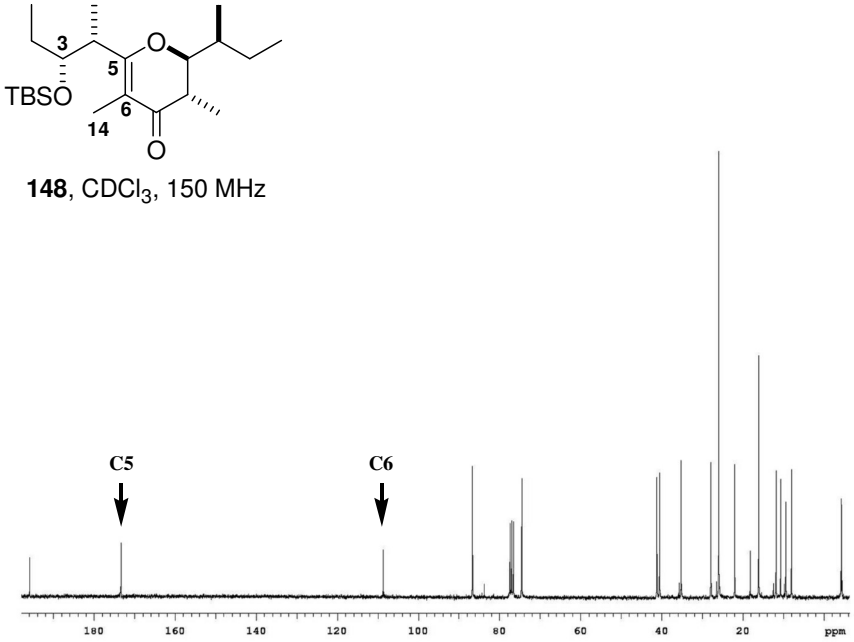
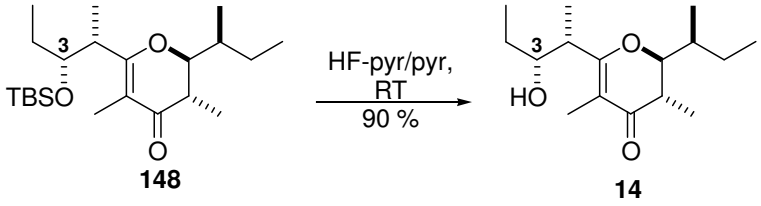


Figure 2.7 ^{13}C NMR spectrum of dihydropyrone 148.

In the proposed biosynthesis of maurenone (**7**), discussed in Section 1.2.1, Figure 1.10, it was suggested that thermodynamic cyclisation of a linear polypropionate precursor occurs to give the hemiacetal. Dehydration of the intermediate hemiacetal to the corresponding dihydropyrone was thought to occur spontaneously due to favourable thermodynamics. The spontaneity of the dehydration following

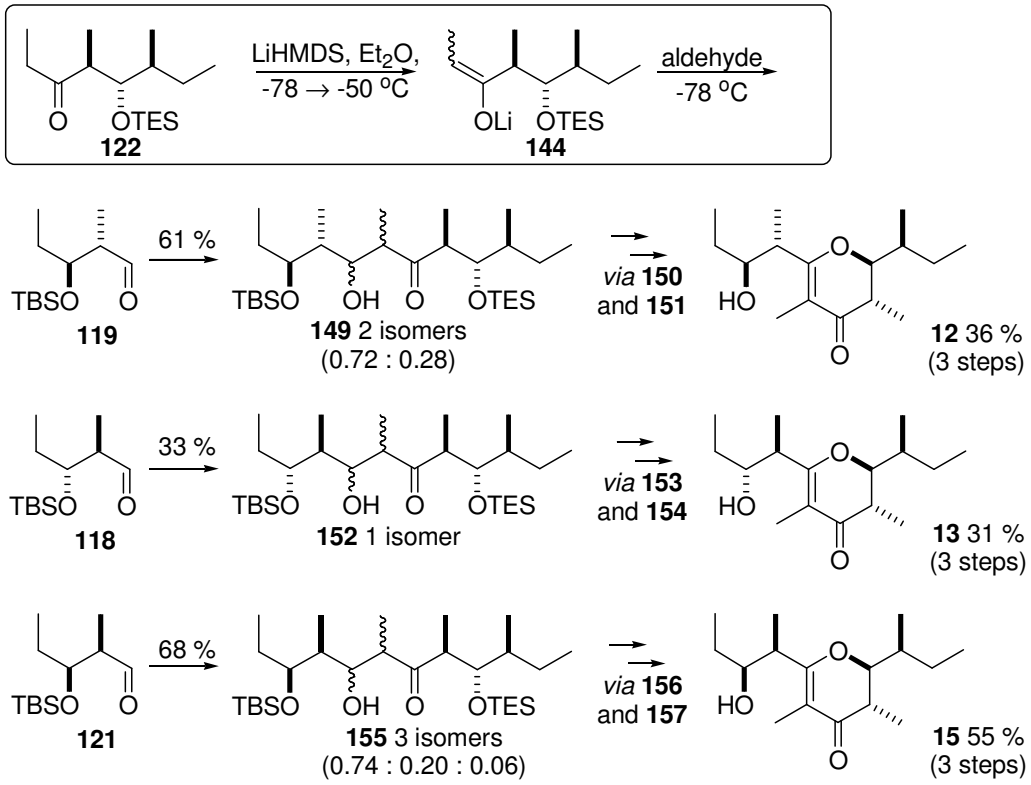
thermodynamic cyclisation suggests that the dihydropyrone is indeed lower in energy.

The final step involved liberation of the C3 alcohol with buffered HF-pyridine[198] as shown in Scheme 2.13, to give the dihydropyrone **14** in good yield (90 %, 25 % over the 4 steps described).



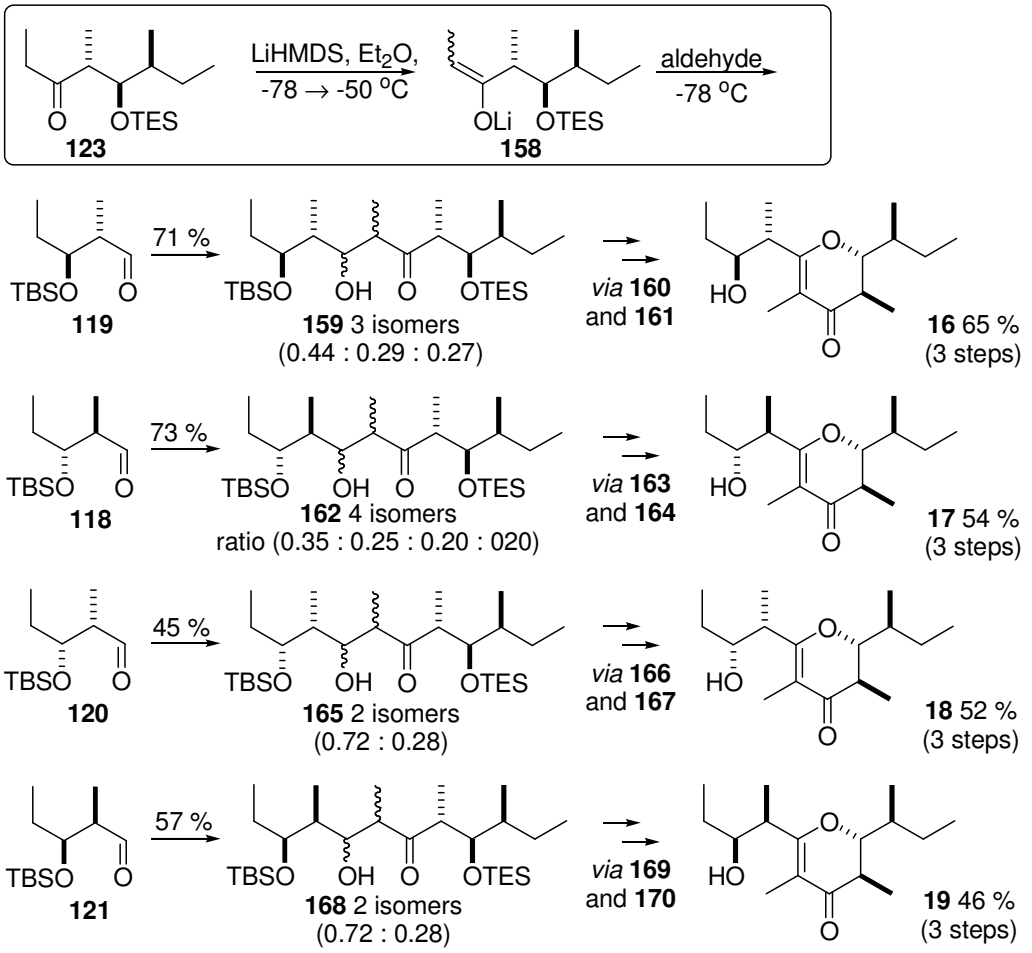
Scheme 2.13 Silyl ether cleavage to liberate the C3 hydroxyl group.

Using this approach synthesis of each of the possible isomers of maurenone in the 10*S* enantiomeric series was accomplished by coupling each of the ketones (**122** and **123)** with each of the *anti*- (**118** and **119)** and *syn*-aldehydes (**113** and **114**) in turn. Scheme 2.14 shows the reaction of the lithium enolate **144**, of ketone **122** with each of the remaining aldehydes (**118**, **119** and **121**) and the subsequent transformations which lead to the stereoisomers of maurenone (**12**, **13** and **15**).



Scheme 2.14 Aldol coupling reactions between the lithium enolate of ketone 122 with each of the remaining aldehydes (118, 119 and 121) and subsequent transformation into the stereoisomers of maurenone.

In an analogous manner, the lithium enolate **158**, of *anti*, *syn*-ketone **123** was coupled to each of the *anti*- (**111** and **112**) and *syn*- (**113** and **114**) aldehydes. The remaining four targeted stereoisomers (**16**-**19**) of maurenone were achieved.



Scheme 2.15 Aldol coupling reactions between the lithium enolate of ketone 123 with each of the aldehydes (118-121) and subsequent transformation into the stereoisomers of maurenone.

2.4 Natural Product Spectral Comparison

Stereochemical assignment of the natural product was carried out by comparison of the NMR spectra reported for the natural product with those obtained for the various isomers (**12–19**). There was found to be little difference between the ^{1}H NMR spectrum from one isomer to the next, although each of the stereoisomers was consistent with the ^{1}H NMR spectral data reported for the natural product. The ^{13}C NMR data revealed more significant differences between the isomers so attention turned to the ^{13}C NMR spectral data, represented in Table 2.1. An inconsistency was immediately noted in that C7 for the natural product was reported at δ = 208.2 ppm[30] while for all of the isomers **12-19**, C7 was found to be in the range δ = 195.5 - 195.7

ppm. The chemical shift of δ = ~195 ppm is consistent with previous findings for the presence of the γ-dihydropyrone carbonyl.[31,202,214-217] Thus, it is assumed that the signal at 208.2 ppm was misreported in the isolation paper. In addition, only 15 of the required 16 carbon signals were reported with the signal for the quaternary C6 at δ = ~109 ppm missing.[30]

Despite these inconsistencies the differences in the ^{13}C NMR spectra were highlighted in Figure 2.9 and Figure 2.11 by plotting the differences in chemical shift for each of the carbons of isomers **12-19** compared to that reported in the original isolation.* Figure 2.9 shows the comparison of the chemical shifts of the compounds **16-19** derived from *anti, syn*-ketone **123**. A significant difference was immediately obvious in the chemical shifts of a number of peaks for all four isomers derived from ketone **123**, most notably at C9, C11 and C16. (Figure 2.9) For these three carbons the Δδ is ± 2.3 - 4.8 ppm for the four compounds **16-19**. In addition isomers **17** and **18** both have notable differences for C1 (Δδ = +1.6 and +1.5 ppm) and C12 (Δδ = -1.6 and -1.9 ppm) and isomers **16** and **17** have differences at C13 (Δδ = +1.4 ppm). It is obvious that the majority of the carbon centres with poor chemical shift agreement with the natural product are derived from the *anti, syn*-ketone **123**. Figure 2.8 highlights the centres in the dihydropyrone originating in the *anti*, *syn*-ketone **123** which display the largest differences in chemical shift to the natural product. This indicates that the stereochemistry of this aldol coupling partner was not correct. On the basis of these considerable chemical shift differences, these four isomers (**16**-**19**) were ruled out for the natural product, maurenone.

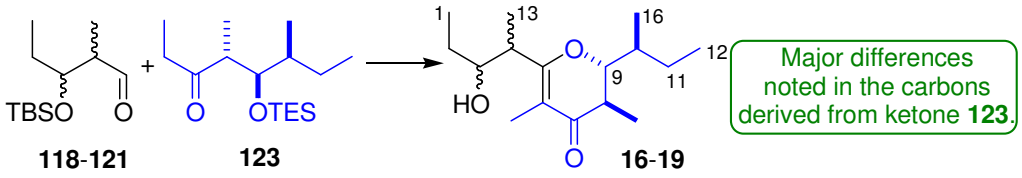
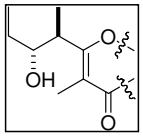
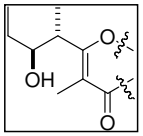
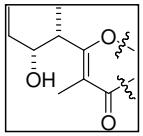
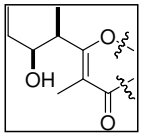


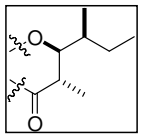
Figure 2.8 The carbon centres derived from the *anti*, *syn*-ketone 123, show the most obvious differences in chemical shift to the natural product.

* C6 and C7 were excluded from this comparison because of their absence from and apparent misreporting, respectively in the isolation paper.

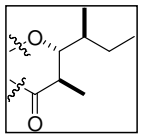
Table 2.1 ^{13}C NMR shifts of each of the isomers (12-19) and the natural product and the difference between each isomer and the natural product.

		Isomer 13		Isomer 12		Isomer 14		Isomer 15	
	Nat. Prod. [a,c]	δ [b,c]	Δδ	δ [b,c]	Δδ	δ [b,c]	Δδ	δ [b,c]	Δδ
1	10.3	12.0	1.7	10	-0.3	10.2	-0.1	10.2	-0.1
2	28.0	28.1	0.1	28.1	0.1	27.9	-0.1	27.8	-0.2
3	75.2	75.5	0.3	75.4	0.2	75.1	-0.1	74.8	-0.4
4	41.6	41.1	-0.5	41.4	-0.2	41.6	0.0	41.5	-0.1
5	172.9	172.4	-0.5	172.3	-0.6	173	0.1	173.1	0.2
6	*	109.9		109.7		108.6		108.5	
7	208.2	195.6	-12.6	195.6	-12.6	195.7	-12.5	195.7	-12.5
8	40.6	40.9	0.3	40.6	0.0	40.6	0.0	40.7	0.1
9	87.0	87.8	0.8	87	0.0	87	0.0	87.4	0.4
10	35.1	35.4	0.3	35.1	0.0	35.1	0.0	35.2	0.1
11	22.0	22.0	0.0	22.2	0.2	21.9	-0.1	21.9	-0.1
12	11.8	10.1	-1.7	11.7	-0.1	11.7	-0.1	11.9	0.1
13	13.2	14.7	1.5	14.7	1.5	13.3	0.1	12.9	-0.3
14	9.4	9.4	0.0	9.4	0.0	9.3	-0.1	9.2	-0.2
15	10.7	10.0	-0.7	11	0.3	10.6	-0.1	10.1	-0.6
16	16.2	16.2	0.0	16.3	0.1	16.1	-0.1	16.1	-0.1



	Isomer 17		Isomer 16		Isomer 18		Isomer 19	
	δ [b,c]	Δδ	δ [b,c]	Δδ	δ [b,c]	Δδ	δ [b,c]	Δδ
1	11.9	1.6	9.93	-0.4	11.8	1.5	10.2	-0.1
2	28	0.0	28	0.0	27.8	-0.2	28	0.0
3	75.3	0.1	75.3	0.1	74.8	-0.4	75.2	0.0
4	41.2	-0.4	41.2	-0.4	41.5	-0.1	41.8	0.2
5	172.6	-0.3	172.3	-0.6	173.2	0.3	173.2	0.3
6	109.8		109.8		108.6		108.7	
7	195.5	-12.7	195.5	-12.7	195.7	-12.5	195.7	-12.5
8	40.5	-0.1	40.6	0.0	40.7	0.1	40.5	-0.1
9	84.5	-2.5	84.5	-2.5	84.7	-2.3	84.2	-2.8
10	35.6	0.5	35.6	0.5	35.5	0.4	35.6	0.5
11	26.8	4.8	26.8	4.8	26.5	4.5	26.5	4.5
12	9.88	-1.9	11.9	0.1	10.2	-1.6	11.8	0.0
13	14.6	1.4	14.6	1.4	12.9	-0.3	13.4	0.2
14	9.4	0.0	9.4	0.0	9.2	-0.2	9.3	-0.1
15	9.9	-0.8	9.91	-0.8	9.5	-1.2	9.7	-1.0
16	12.3	-3.9	12.3	-3.9	12.4	-3.8	12.3	-3.9



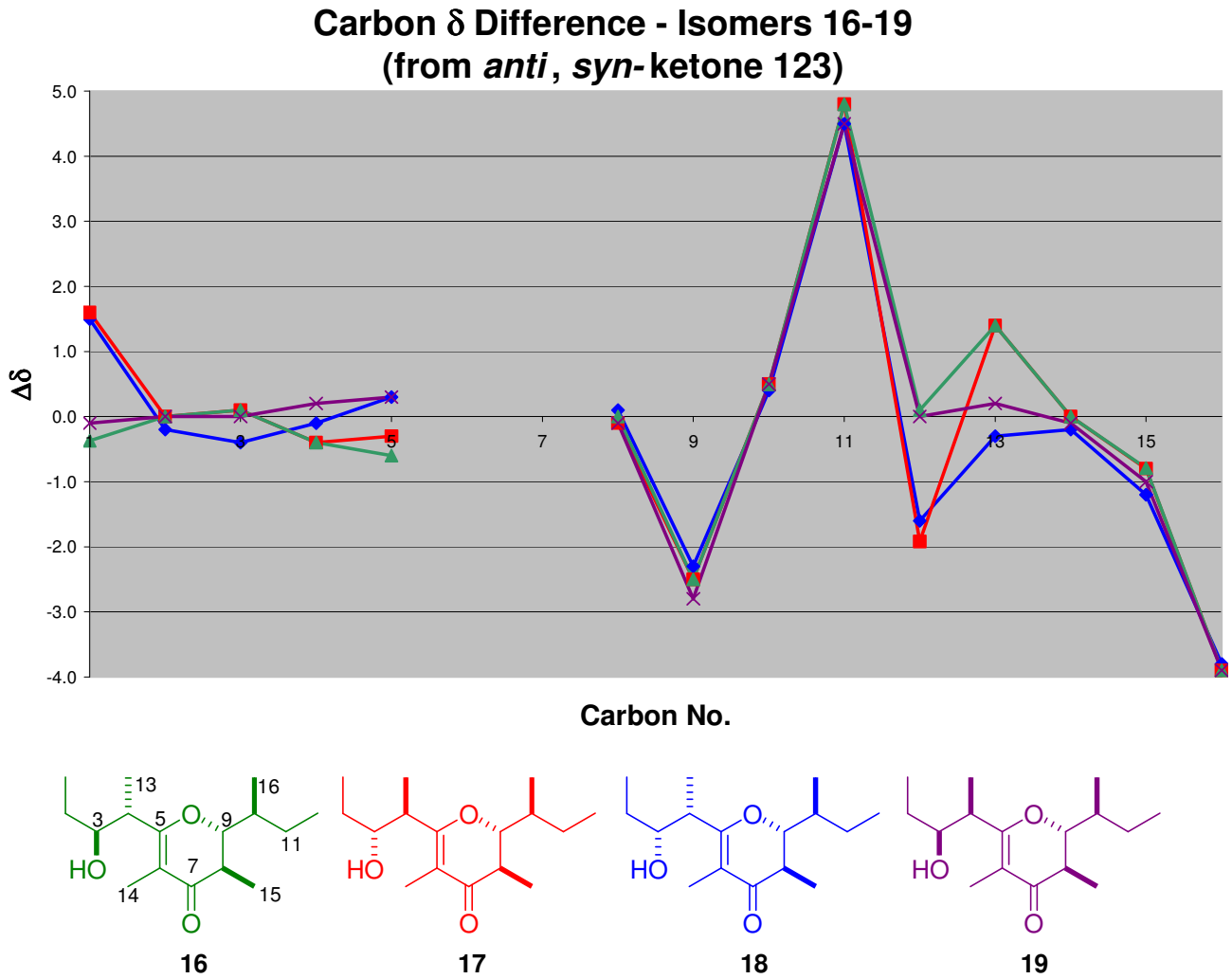
* Only 15 carbons were reported for the natural product not 16 as required (C6 is absent).

a Chemical shifts and coupling constants as reported in ref [30] (360 MHz).

b Varian Unity Inova 600 MHz NMR Spectrometer ($CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H- ^{1}H TOCSY.

c Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm.

Figure 2.9 Carbon δ Difference for Isomers 16-19 (from ketone 123).



Comparison of the chemical shift of the stereoisomers derived from *anti, anti*-ketone **122**, displayed in Figure 2.11, on the other hand show a much closer correlation with the natural product, maurenone (**7**). Isomer **13** showed the largest deviation with a maximum $\Delta\delta$ of ±1.7 ppm for C1 ($\Delta\delta$ = 1.7 ppm) and C12 ($\Delta\delta$ = -1.7 ppm) along with a number of other quite significant deviations (C4 and C5 $\Delta\delta$ = -0.5 ppm, C9 $\Delta\delta$ = 0.8 ppm, C13 $\Delta\delta$ = 1.5 ppm). Isomer **12** also showed substantial deviations (C5 $\Delta\delta$ = -0.6 ppm and C13 $\Delta\delta$ = 1.5ppm). It is apparent that a number of considerable variations in chemical shift are isolated to the centres derived from the *anti*-aldehyde isomers **118** and **119**, as indicated in Figure 2.10, so on this basis *anti*-aldehyde derived isomers **12** and **13** can be excluded.

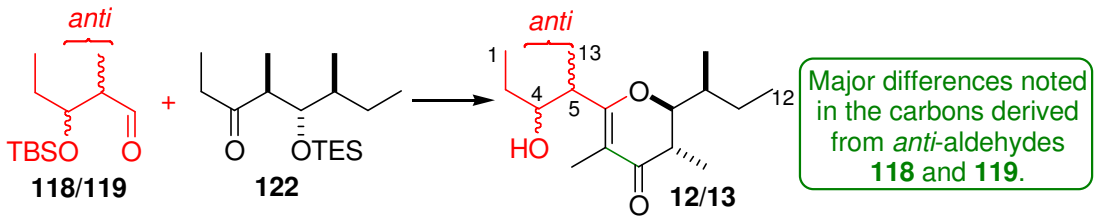
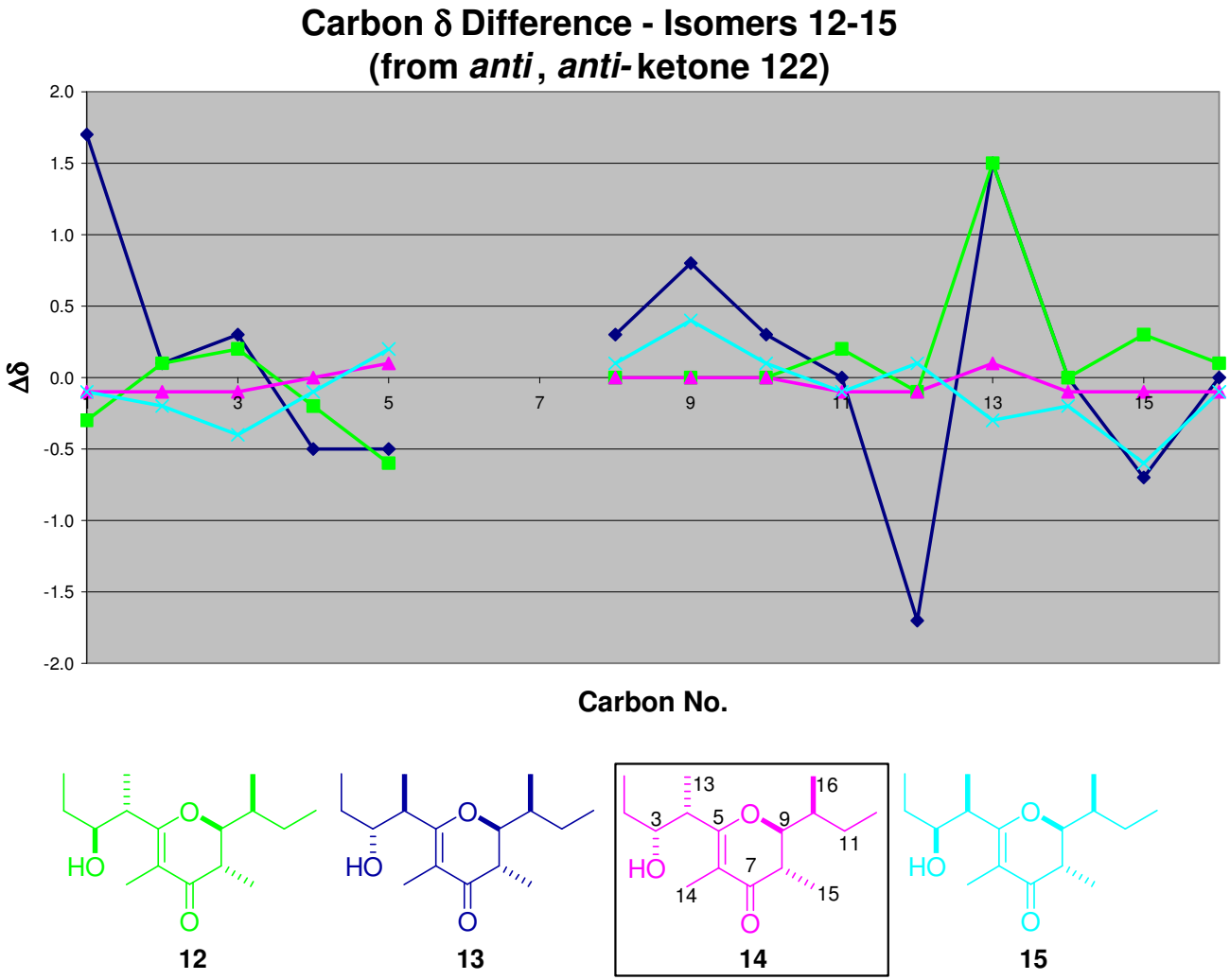


Figure 2.10 The carbon centres derived from the *anti*-aldehydes 118 and 119 showed the most significant differences in chemical shift.

The only two isomers remaining are the two *syn*-aldehyde derived isomers **14** and **15**. Small but consistent differences ($\Delta\delta$ = ± 0.1 - 0.6 ppm) in the chemical shift for isomer **15** are observed over a range of peaks. Isomer **14** alone, shows an almost perfect correlation ($\Delta\delta \leq$ ± 0.1 ppm) with all the peaks reported for maurenone (**7**) and on this basis the relative configuration of the natural product, maurenone (**7**) is assigned as shown for isomer **14**.

Figure 2.11 Carbon δ Difference for Isomers 12-15 (from ketone 122).



The ^{1}H and ^{13}C NMR data reported for the natural product and those obtained for isomer **14** are reported in Table 2.2 and show an excellent correlation. The mass spectral, IR and UV data for isomer **14** were also consistent with those reported for the natural product. Unfortunately the spectra obtained from the natural product were not available for a direct comparison to the synthetic analogue. As no optical rotation was reported for the natural product the absolute configuration of the natural product could not be assigned.

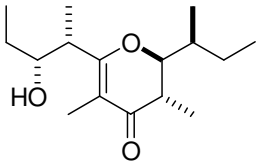
Table 2.2 ^{1}H and ^{13}C NMR data of isomer 14 and that reported for the natural product.

	maurenone [a]		Isomer 14 [b]	
Carbon no.	**δH , m, ^{3}J [Hz][c]**	**δC[c]**	**δH , m, ^{3}J [Hz][c]**	**δC[c]**
1	0.95, t, 7.4	10.3	0.96, t, 7.2	10.2
2	1.40, m	28.0	1.49 and 1.39, m	27.9
3	3.65, ddd, 7.8, 6.5, 3.3	75.2	3.65, ddd, 8.4, 6.6, 3.6	75.1
4	2.78, dq, 6.9, 6.5	41.6	2.77, apt qn, 7.2	41.6
5	-	172.9	-	173.0
6	-	-	-	108.6
7	-	208.2	-	195.7
8	2.49, dq, 12.3, 7.0	40.6	2.49, dq, 12.3, 6.6	40.6
9	3.80, dd, 12.3, 3.0	87.0	3.77, dd, 12.3, 3.3	87.0
10	1.74, m	35.1	1.73, m	35.1
11	1.50, m	22.0	1.57 and 1.25, m	21.9
12	0.98, t, 7.5	11.8	0.94, t, 7.2	11.7
13	1.22, d, 6.9	13.2	1.20, d, 7.2	13.3
14	1.74, s	9.4	1.73, s	9.3
15	1.08, d, 6.9	10.7	1.08, d, 6.6	10.6
16	1.05, d, 6.9	16.2	1.03, d, 6.6	16.1

[a] Chemical shifts and coupling constants as reported in ref [30] (360 MHz).
[b] Varian Unity Inova 600 MHz NMR Spectrometer ($CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY.
[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm.

2.5 Conclusion

In summary, a highly convergent synthesis of eight putative isomeric structures **12-19** for the natural product maurenone (**7**) was achieved by coupling two ketones, **122** and **123**, with four aldehydes, **118-121**. This synthesis used the lactate derived ketones **(*R*)-39** and **(*S*)-39** and **(*R*)-40** and **(*S*)-40** to generate four of the five required stereocentres in the final products. The spontaneous dehydration of each of the hemiacetals to dihydropyrones supports the suggestion that the dehydration is under thermodynamic control in nature. Comparison of the ^{1}H and ^{13}C NMR data reported for the natural product with that for the isomers enabled assignment of the structure of the natural product as isomer **14**.



(-)-maurenone

Figure 2.12 The assigned stereochemistry of (-)-maurenone.

Cyclisation of linear polyketide precursors is thought to occur under thermodynamic control producing the most stable cycloadduct. The proposed linear precursor **171** to the identified maurenone structure (**14**) possesses two nucleophilic hydroxyl groups and is represented in Figure 2.13. Therefore the linear precursor **171** may potentially cyclise in two directions; by nucleophilic addition of the C3 hydroxyl onto the C7 carbonyl (represented in red) or by nucleophilic addition of the C9 hydroxyl onto the C5 carbonyl (represented in blue). Examination of the most stable chair conformation of the cycloadduct **172**, obtained by nucleophilic addition of the C3 hydroxyl to the C7 carbonyl, reveals that the C4 methyl group occupies an axial position while the other alkyl groups occupy an equatorial position. In contrast the cycloadduct **173**, obtained by nucleophilic addition of the C9 hydroxyl to the C5 carbonyl, has a most stable chair conformation in which all of the alkyl groups occupy the equatorial position. Therefore, the favoured thermodynamic cyclisation mode for linear polyketide **171** is that in which the C9 hydroxyl adds to the C5 carbonyl producing hemiacetal **173** which has each of the alkyl groups in the more stable equatorial orientation. Dehydration of hemiacetal **173** produces dihydropyrone **14**, which matches the identified structure of the natural product maurenone, suggesting that formation of the natural product is under thermodynamic control. As a result, in this particular stereochemical orientation of the linear precursor,

differential protection of the C3 and C9 hydroxyl groups may not have been required to achieve the desired cycloadduct stereospecifically.

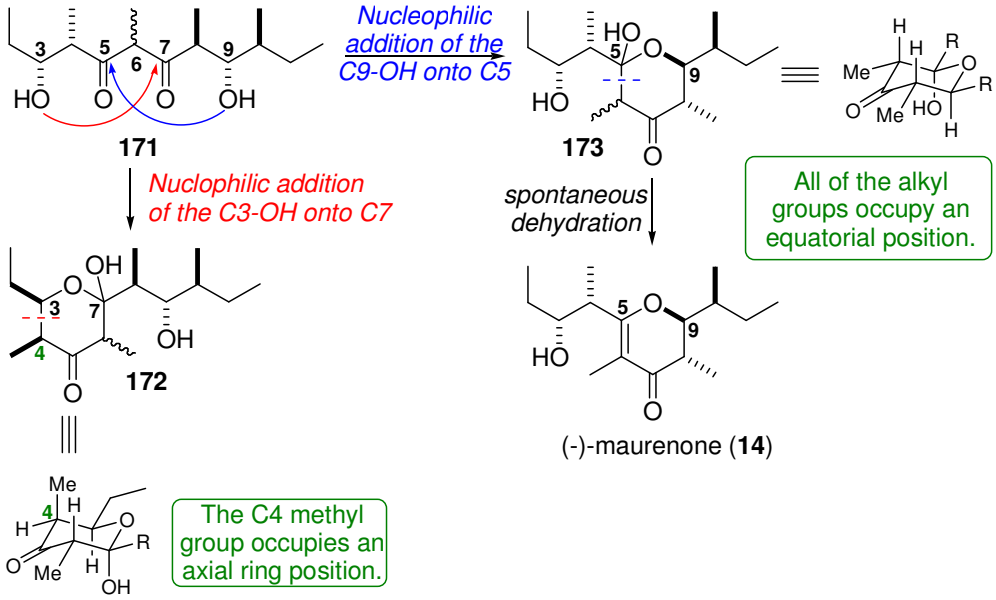


Figure 2.13 Potential cyclisation modes of the linear polyketide precursor to maurenone.

CHAPTER 3 INTRODUCTION TO THE SPICULOIC ACIDS

This chapter introduces the spiculoic acid family of novel polyketide derived secondary metabolites which were isolated from the Caribbean marine sponge, *Plakortis angulospiculatus*. The proposed biosyntheses of the spiculoic acids and the structurally similar plakotenin family of metabolites are compared and contrasted. Of particular interest is the IMDA cycloaddition reaction generating the [4.3.0] bicyclic core which is proposed to be enzyme catalysed. A brief review of synthetic studies reported in the literature by other research groups during the course of this investigation is presented. Finally the design of a model system, incorporating many of the functionalities of the natural products, is discussed. The model system was developed with the goals of investigating the feasibility of employing a thermally induced IMDA reaction to install the [4.3.0] bicyclic core and examining the factors affecting the stereochemical outcome of the cycloaddition reaction.

3.1 Marine Sponges, a Source of Unique Secondary Metabolites

Sponges are plentiful in the marine environment in widely differing habitats from polar seas to temperate and tropical waters. They are particularly prevalent in coral reefs where they occupy an important role in the ecosystem; being efficient filter-feeders, providing shelter for invertebrates and fish, harbouring nitrogen and carbon fixing symbionts, being aggressive competitors for space and being primary agents of carbonate bioerosion on coral reefs.[218]

Marine sponges have been the source of an abundance of secondary metabolites that have demonstrated the ability to interfere at a variety of stages of pathogenesis.[219] More than 5300 natural products have been isolated, displaying a diverse array of chemical structures and bioactivities, including *anti*-inflammatory, *anti*-tumour, immunosuppressive, neuro-suppressive, *anti*-viral, *anti*-malarial, antibiotic or *anti*-fouling.[219] Little is known about the ecological function of sponge secondary metabolites however a number of hypotheses have been proposed. *Anti*-fouling, *anti*-overgrowth and UV protective functions have been suggested, however the most commonly accepted theory to explain the function of these metabolites is in chemical defence.[220] Sponges are soft-bodied, sessile organisms lacking a morphological defence structure (i.e. shells or spines) and as a result, employ a chemical defence

system against predation and other ecological pressures. While knowledge of the mode of action of these secondary metabolites is fairly limited, several studies on the palatability of these compounds have indicated that some metabolites may be distasteful thus deterring predation.[221,218] An alternative proposal for the formation of secondary metabolites suggests that bacteria living symbiotically with the sponges may actually be producing these metabolites, not the sponges. Figure 3.1 illustrates two marine sponges which have been important sources of bioactive natural products.

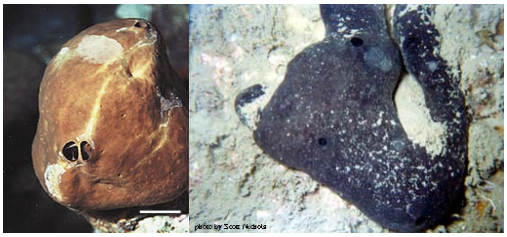


Figure 3.1 Examples of marine sponges; *plakortis angulospiculatus* and *plakortis simplex*.

The largest number and diversity of secondary metabolites from marine invertebrates have been isolated from sponges of the class Demospongiae.[222] In particular, sponges of the genus *Plakortis*, have yielded a plethora of bioactive substances including those of terpenoid and polyketide origins. They exhibit a variety of structural motifs including cyclic peroxides, peroxylactones, peroxyketals and aliphatic peroxy esters.[222] As a result, a surge in the numbers of *Plakortis* sponges under investigation, in both the search for new bioactive compounds and in probing the ecological functions of these compounds, has occurred since the early 1990's.

3.1.1 Isolation of Bioactive Marine Polyketides; the Spiculoic Acids

In 2004, as part of a study screening extracts from marine invertebrates for antimitotic and cytotoxic metabolites, Andersen and co-workers reported the isolation of two novel polyketide secondary metabolites from the methanol extract of the Caribbean marine sponge *Plakortis angulospiculatus*.[38] The crude extract showed potentially interesting cytotoxicity and fractionation led to the isolation of two metabolites; spiculoic acid A, which exhibited in *vitro* cytotoxicity against human breast cancer MCF-7 cell line, IC_{50} = 8 μg/mL, and spiculoic acid B which was inactive against the same cell line. Extensive 1D and 2D (^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HMBC, ^{1}H-^{1}H NOESY) NMR analysis in conjunction with HRMS

(ESI) indicated the two compounds were of polyketide origin and possessed the previously unreported spiculane carbon skeleton, which features a [4.3.0] bicyclic core, illustrated in Figure 3.2.

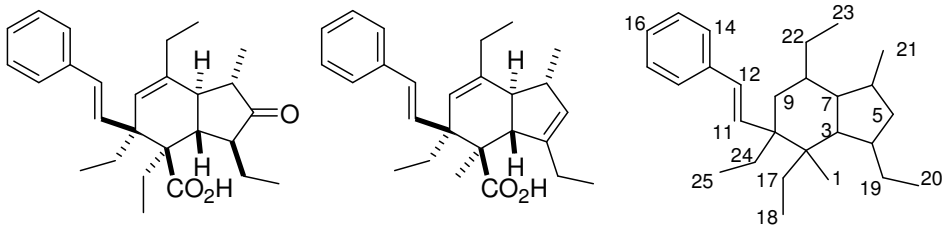


Figure 3.2 Sponge metabolites, spiculoic acid A (20) and B (21), exhibit a unique spiculane skeleton.

Shortly after the reported isolation of spiculoic acids A and B, Amade and co-workers reported the structurally related iso, *nor*- and *dinor*-spiculoic acid A, represented in Figure 3.3.[39] Containing the same [4.3.0] bicyclic core, these compounds differ from each other and spiculoic acid A only in the methyl/ethyl substitution around the bicyclic core. The relative stereochemistry is retained throughout the series. The in *vitro* activity of iso, *nor*- and *dinor*-spiculoic acid A was tested against three tumor cell lines.[39] Iso and *nor*-spiculoic acid A exhibited mild cytotoxicity against lung carcinoma A549 (GI_{50} ~ 15-20 μM) and colon carcinoma HT29 (GI_{50} > 25 μL) cell lines but were inactive against breast cancer MDA-MB-231 cell lines. *Dinor*-spiculoic acid was inactive against all three cell lines.

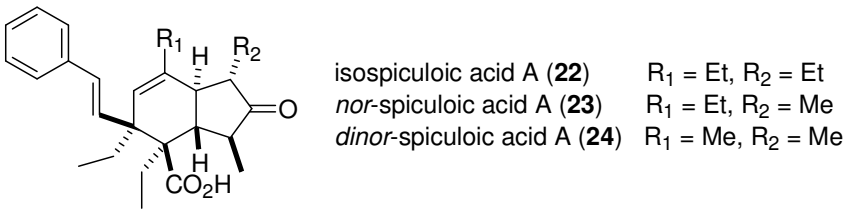
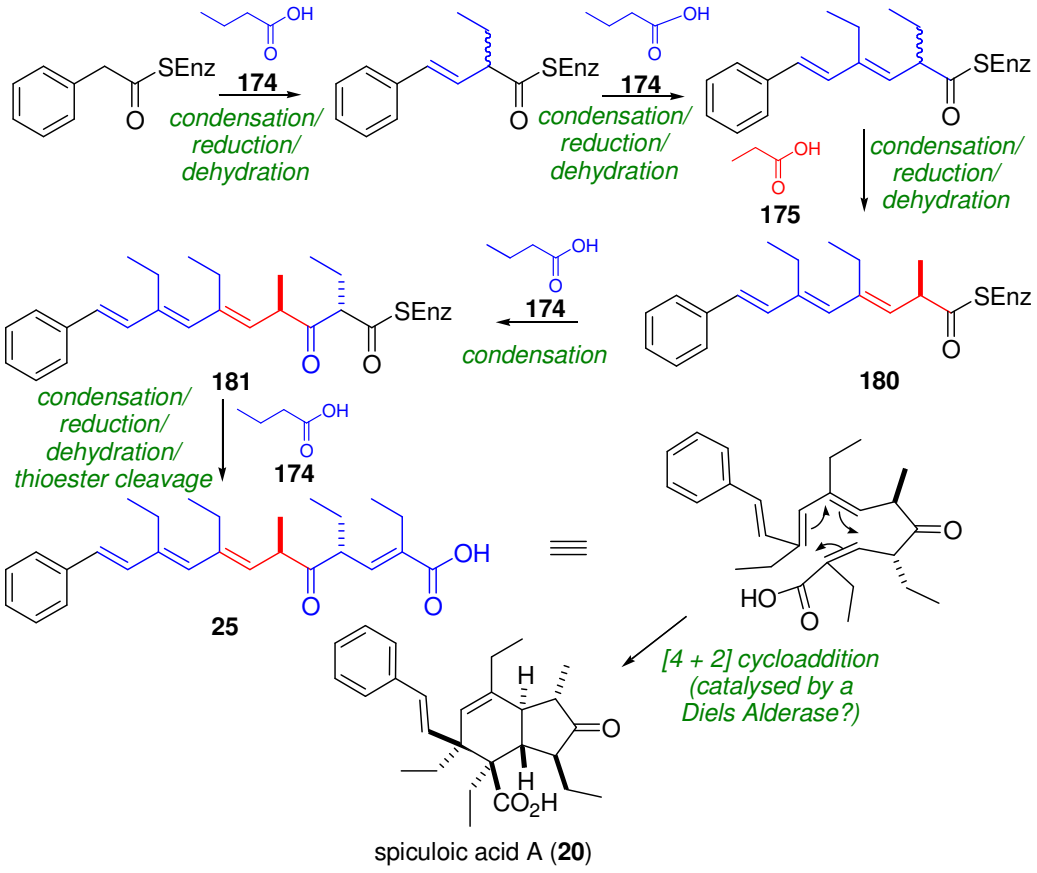


Figure 3.3 The structurally related iso, *nor*- and *dinor*-spiculoic acid A (22-24).

3.1.2 Biogenesis of the Spiculoic Acids

Andersen and co-workers suggested a polyketide origin to the biosynthesis of the spiculoic acid family of natural products, outlined in Scheme 3.1.[38] They proposed that the linear polyene precursor **25** is generated by successive condensation of butyrate and propionate units which undergo further enzyme facilitated reductions producing the olefinic functionalities. An enzyme catalysed, intramolecular [4 + 2]

cycloaddition reaction of the linear polyene precursor **25** installs the novel bicyclic skeleton. The differences in the structures of each of the members of the spiculoic acid family (i.e. methyl Vs ethyl substitution on the ring) arises during biosynthesis as a result of condensation of either butyrate or propionate units.



Scheme 3.1 The proposed biosynthesis of spiculoic acid A.

The proposed biosynthetic pathway of spiculoic acid A contains a number of noteworthy features that are relatively uncommon in polyketide biogenesis. The linear precursor **25** is made up of four butyrate building blocks (**174**, Scheme 3.1, in blue) and one propionate building block (**175**, Scheme 3.1, in red). Incorporation of butyrate units occurs infrequently in polyketide biosynthesis compared to the incorporation of acetate and propionate units. Interestingly, a significant number of natural products biosynthesised from butyrate units have been isolated from sponges of the genus *Plakortis*. Several examples shown in Figure 3.4 have been isolated from *Plakortis halichondrioides*,[223-226] *Plakortis simplex*[227] and *Plakortis lita*.[228]

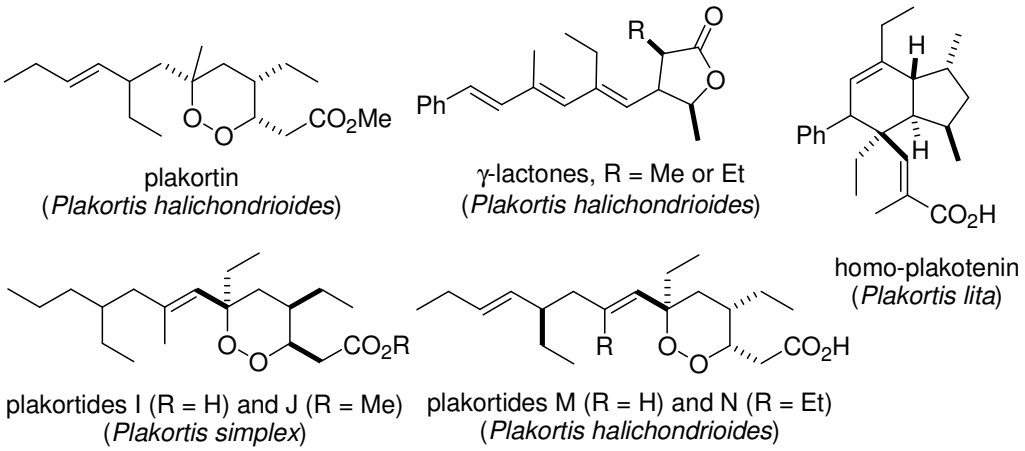


Figure 3.4 Natural products biosynthesised by the incorporation of butyrate units.

The proposed dehydration mechanism, giving the olefin functionalities in conjugation with the phenyl group, is also noteworthy. Figure 3.5 shows a schematic of the addition of the butyrate unit (**174**) and subsequent enzyme facilitated reduction and dehydration. Biosynthesis begins with a phenyl acetic acid starter unit (**176**) condensing with a butyrate unit (**174**) to give β-ketone **177**. Reduction followed by dehydration gives thioester **178**, where the olefin is in conjugation with the phenyl group, not the normally observed α,β-unsaturated ester **179**.

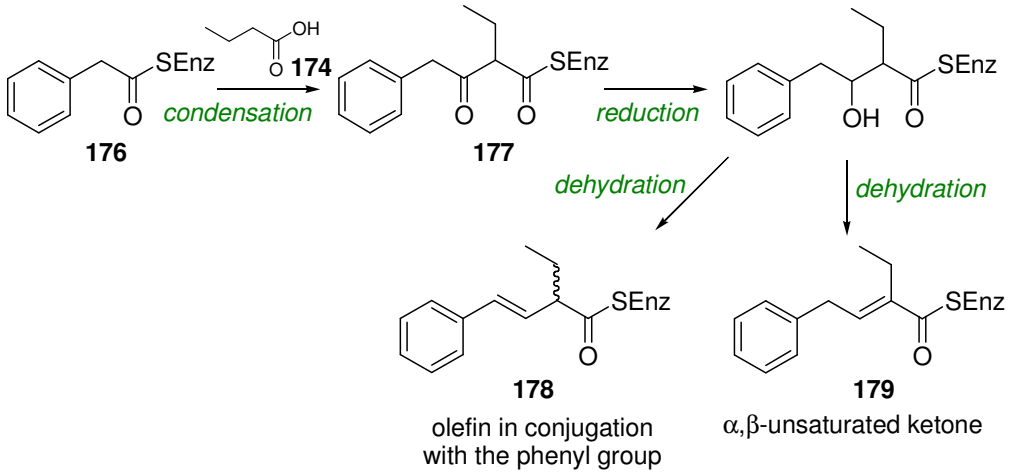


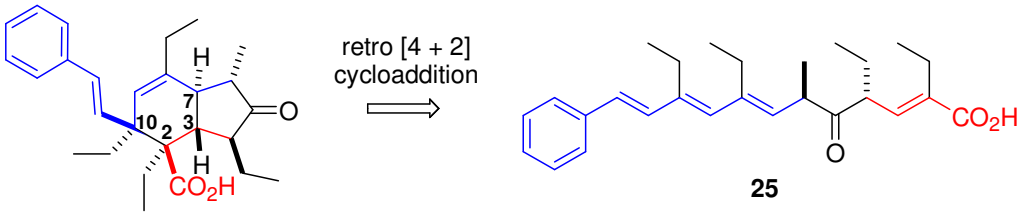
Figure 3.5 Dehydration mechanisms in the polyketide biosynthetic pathway.

After the first condensation, reduction and dehydration event has occurred this pattern is maintained for the incorporation of the following two carboxylate building blocks (butyrate and propionate units) producing a fully conjugated triene **180** (Scheme 3.1). Addition of the fourth building block (a butyrate unit) breaks this conjugation as the β-ketone **181** does not undergo reduction. The final condensation,

reduction and dehydration event adds a fourth butyrate unit however in this instance the usual α,β-unsaturated ester **25** is generated.

The final and perhaps most contentious step in the proposed biosynthesis, described in Scheme 3.1, is the Diels-Alderase catalysed, intramolecular [4 + 2] cycloaddition reaction. The spiculoic acids have all been isolated as single stereoisomers despite the fact that four stereocentres are created, two quaternary and two tertiary, in the cycloaddition step. This may suggest that an enzyme is involved in facilitating the cycloaddition reaction, locking the linear precursor in a particular reactive conformation. However it is possible that a non-enzyme mediated cycloaddition reaction may produce only one stereoisomeric product. Thus it is unclear whether the enzymes are involved in facilitating the cycloaddition reaction.

A certain degree of stereochemical control is imparted in the cycloadduct from the geometry of the starting material. The Cis Principle dictates conservation of the stereochemistry of the starting materials in the cycloadduct.[119] Thus, working back from the stereochemistry of the product, the geometry of linear precursor **25**, depicted in Scheme 3.2, is suggested. The *E*-dienophile geometry is transferred to the C2 and C3 stereocentres of the natural products which display a *trans*-relationship indicated in red. The diene geometry must be either *E*,*E* or *Z*,*Z* to produce the *trans*-relationship between the C7 and C10 stereocentres, indicated in blue.



Scheme 3.2 Retrospective determination of the olefin geometries in the linear precursor.

The linear precursor **25** can theoretically produce four stereoisomeric cycloadducts (**182**-**185**) upon [4 + 2] cycloaddition, illustrated in Figure 3.6. These stereoisomers arise due to the possibility of the cycloaddition reaction proceeding through four possible transition states, two endo and two exo, due to reaction at each of the two faces of the diene and dienophile. The stereochemistry matching the natural product arises from an endo transition state where reaction occurs to the top face of the diene and the bottom face of the dienophile, as highlighted in Figure 3.6.

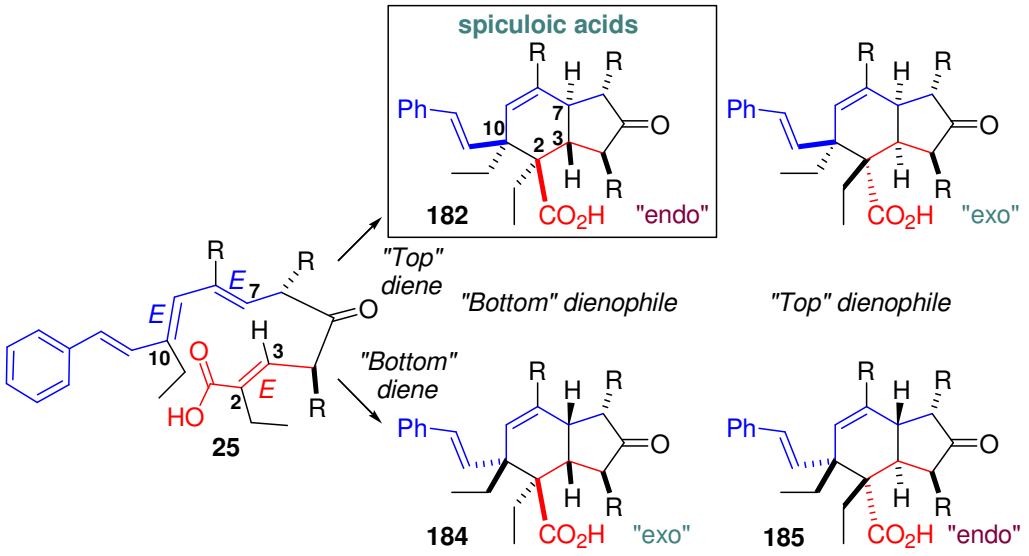
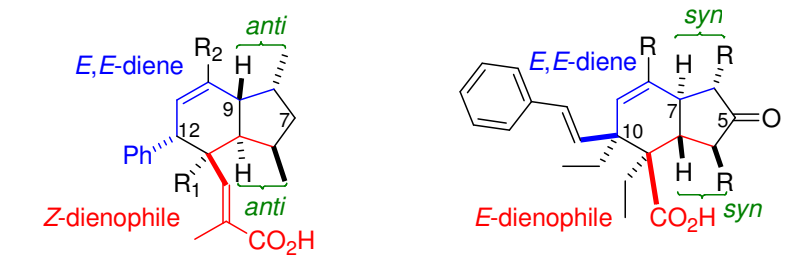


Figure 3.6 The possible cycloadducts from linear precursor 25.

There are countless examples in the literature of natural products which appear to be products of a Diels-Alder type cycloaddition reaction.[147,37] Evidence exists to suggest that in nature both enzymatic (i.e. Diels-Alderase promoted) and non-enzymatic Diels-Alder reactions are occurring, as discussed in Section 1.3.5.4. Rigorous proof of involvement of a Diels-Alderase in a particular system requires isolation and characterisation of the enzyme, which is a difficult and time consuming task. Biomimetic total syntheses can be performed to give an indication of whether the [4 + 2] cycloaddition is likely to be facilitated by enzymes, as discussed in Section 1.2.1.

3.1.3 The Plakotenins; a Structurally Related Family of Natural Products

A structurally similar family of secondary metabolites have been isolated from sponges of the genus *Plakortis*; plakotenin, homo- and *nor*-Plakotenin (**186**-**188**).[228,229] Figure 3.7 shows a comparison of the spiculoic acid and the plakotenin families of natural products. These compounds possess an analogous *trans*-fused [4.3.0] bicyclic core, however the ring appendages differ both in the type and orientation of the R groups.



plakotenin (**186**), R_1 = Et, R_2 = Me
homo-plakotenin (**187**), R_1 = Et, R_2 = Et
nor-plakotenin (**188**), R_1 = Me, R_2 = Me

spiculoic acids, R = Me or Et

Figure 3.7 Structural comparison of the spiculoic acid and plakotenin families of natural products.

The proposed biosynthesis of the spiculoic acids was derived from the biosynthesis suggested for the plakotenins.[229,230] Biosynthesis of the linear polyene precursors occurs *via* the PKS facilitated mechanism, described in Section 1.2, and subsequent IMDA cycloaddition reaction, which may or may not be facilitated by enzymes, occurs to install the bicyclic core. The Cis Principle implies that the geometry of the diene and dienophile will be conserved in the cycloadduct.[119] Thus the geometry of the diene in the plakotenins (and the spiculoic acids) must be either *E*,*E* or *Z*,*Z* in order to achieve the *trans*-relationship between the C9(C7) and C12(C10) stereocentres, indicated in Figure 3.7 in blue. The first difference between the two natural products is the geometry of the dienophile. As discussed in Section 3.1.2, the dienophile geometry must be *E* in the spiculoic acids, while in the plakotenins this geometry must be *Z* in order to achieve the *cis*-relationship between the C2 and C3 stereocentres, indicated in Figure 3.7 in red.

The final fundamental difference between the [4.3.0] bicyclic cores of the spiculoic acids and the plakotenins is the relative relationship between each of the protons at the ring fusion and the adjacent methyl centres in the five membered ring. In the spiculoic acids a *syn*-relationship exists while in the plakotenins the corresponding relationship is *trans*-, represented in Figure 3.7, in green. As the relative relationship between the stereocentres originating in the diene and those originating from the dienophile is dictated by the transition state geometry this suggests that the IMDA reaction forming each group of natural products is proceeding through different transition states. Figure 3.8 depicts all of the possible cycloadducts (**190**-**193**) available from cycloaddition of the proposed linear precursor to the plakotenins (**189**), with an *E*,*E*-diene and a *Z*-dienophile. The plakotenins, represented by

cycloadduct **193**, are achieved *via* an endo transition state, where the bottom face of the diene reacts with the top face of the dienophile. In contrast, the spiculoic acids (**20**-**24**) which are also produced *via* an endo transition state, are formed through reaction between the top face of the diene with the bottom face of the dienophile. The Endo rule predicts the endo transition state to be more stable than the exo transition state due to enhanced stabilisation provided by the π-orbital overlap of the activating ligands.[119]

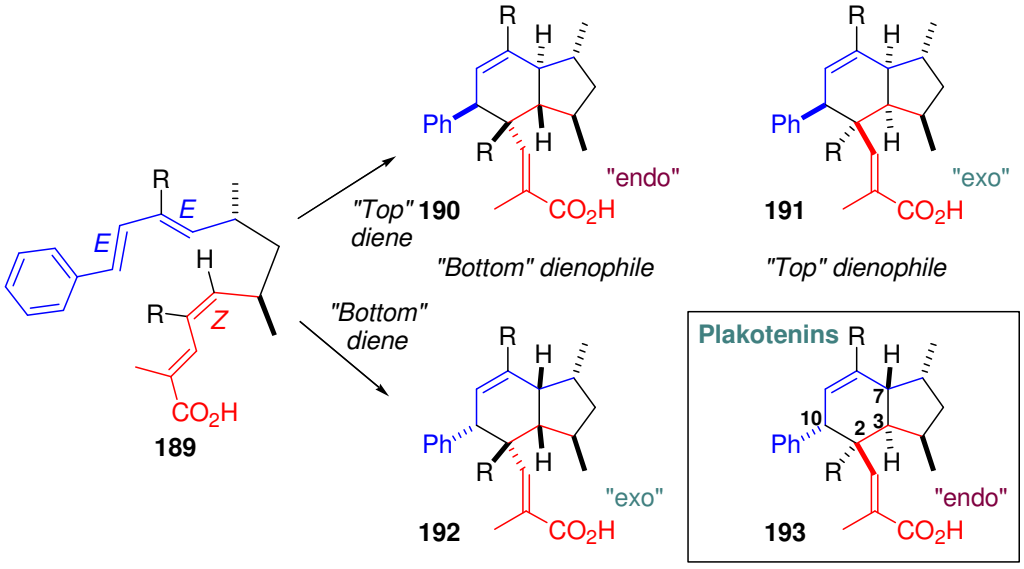


Figure 3.8 Possible cycloadducts from the linear precursor 189.

This raises an interesting question; why does the IMDA reaction of these structurally similar linear precursors proceed through alternative transition states to give the reported cycloadducts? If the reaction is occurring without enzyme involvement it may simply be that the alternative transition states have different energies due to the alternate geometries of the dienophile (*E* in the spiculoic acids and *Z* in the plakotenins) and the various functional groups within the linear precursors. If an enzyme is responsible for facilitating the cycloaddition reactions then analogous transition state geometries would be expected. In general, active sites of enzymes are capable of binding the substrates in a particular conformation stabilising the developing transition state. Due to the similar modes of biosynthesis of these two families of natural products, a similar binding orientation in the active site of the enzyme would be predicted. However, the opposite geometries of the dienophiles or the various functionalities within the linear precursors may be influencing the binding in the active site and thus the geometries of the stabilised transition states.

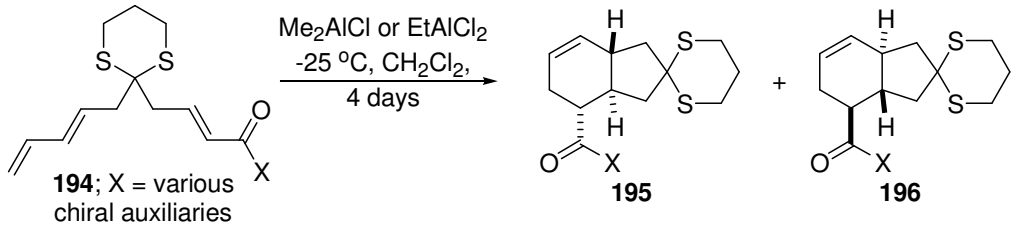
It must also be considered that while the linear precursors **25** and **189**, are proposed

to undergo IMDA cycloaddition reactions forming the spiculoic acids and plakotenins respectively, there is no proof to support this claim. Functional group modifications to the cycloadducts may be occurring post-cyclisation, not during biosynthesis by the PKS system, and thus the linear precursors may possess different functionalities. For example the linear precursors to the plakotenins may possess a carbonyl or hydroxyl group at C7 which is reduced to the methylene group following IMDA cycloaddition.

3.2 A Biomimetic Approach to the Total Synthesis of the Spiculoic Acids

The novel spiculane skeleton represents a challenging synthetic target due to the presence of six stereogenic centres (including two quaternary centres) and an array of different functionalities. Employing a biomimetic synthetic approach provided the opportunity to investigate the possible existence of a Diels-Alderase which, despite exhaustive efforts, remains fairly elusive and as a result insufficient information is known about its mode of action. Finally, the interesting bioactivity displayed by the spiculoic acid family of natural products added to their appeal as synthetic targets.

Prior to the development of the biomimetic strategy employed in this investigation, discussed in Chapter 4, there were no reports of synthetic efforts towards the spiculoic acids. Hoshino and co-workers had reported an investigation of an IMDA reaction in the formation of *trans*-hindranes in their synthetic studies towards the plakotenins.[231] They synthesised linear precursors **194** containing chiral auxiliaries as a method of imparting stereocontrol to the cycloaddition reaction which was catalysed by achiral Lewis acid catalysts, Me_2AlCl or $EtAlCl_2$, described in Scheme 3.3. *trans*-Hindranes **195** and **196** were achieved with high levels of stereoselectivity (96 % ee, following removal of the auxiliary) however these cycloadducts were structurally much simpler than the spiculoic acids and the plakotenins, possessing only three tertiary stereocentres.



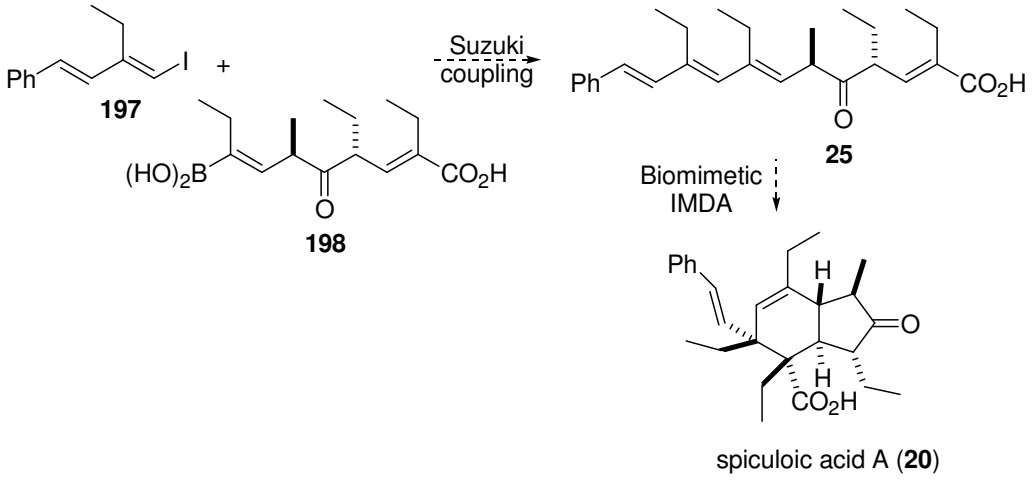
Scheme 3.3 Synthesis of *trans*-hindranes by Hoshino and co-workers, in 1999.

As no previous studies employing IMDA cycloaddition reactions in the synthesis of highly substituted [4.3.0] spiculane or hindrane skeletons were available investigation of a model system was proposed. During the course of investigations into the developed model system several reports of synthetic efforts towards the spiculoic acids appeared in the literature and will be discussed herein, before the designed model system will be presented.

3.2.1 Synthetic Studies Towards the Spiculoic Acids

3.2.1.1 Synthesis of a Model System

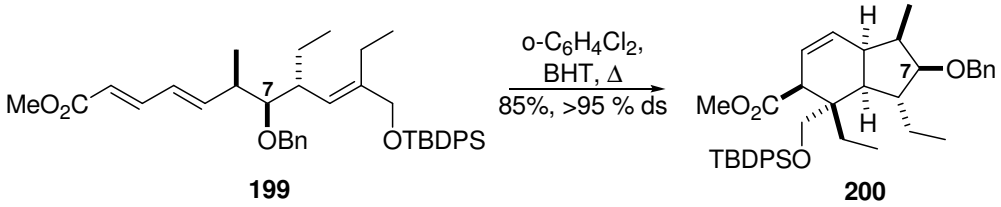
Kunda and co-workers reported their synthesis of a bicyclic core exhibiting several of the key functionalities present in the natural product.[232] Their original strategy, presented in Scheme 3.4, was to employ a biomimetic IMDA reaction in the construction of spiculoic acid A from linear precursor **25** which was to be synthesised *via* a Suzuki coupling reaction between iodide **197** and boronic acid **198**.



Scheme 3.4 The original strategy developed by Kunda and co-workers. [232]

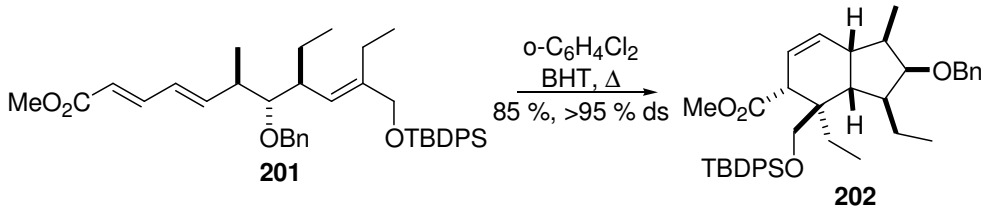
This methodology did not ultimately lead to the synthesis of spiculoic acid A because synthetic complications experienced with their approach to boronic acid **198** forced

Kunda and co-workers to target an alternative linear precursor **199**, depicted in Scheme 3.5.[232] While this alternative synthesis did allow them to establish that the IMDA approach could be employed to generate the [4.3.0] bicyclic core, through the synthesis of cycloadduct **200**, a number of key challenges remain to be conquered before a total synthesis can be achieved using this strategy.



Scheme 3.5 The alternative linear precursor synthesised by Kunda and co-workers underwent a [4+2] cycloaddition reaction to give cycloadduct 200, possessing a [4.3.0] bicyclic core. [232]

Closer examination of the structure that Kunda and co-workers claim to have synthesised reveals a number of discrepancies with their stereochemical assignment.[232] Initial examination revealed that the C7 stereochemistry defined in the linear triene precursor **199** was not accurately transposed in cycloadduct **200**. However, upon closer inspection, Baldwin and co-workers identified an anomaly in the assigned stereochemistry of a key intermediate epoxide achieved by stereoselective, Sharpless epoxidation using D-tartaric acid diethyl ether.[233] As a result of the erroneous assignment of the linear precursor **199** the stereochemical assignment depicted for cycloadduct **200**, based on NOE correlations, was also incorrect. Baldwin and co-workers resolved the stereochemical inconsistencies reporting their results of an extensive analysis of the data of Kunda and co-workers.[233] Scheme 3.6 shows the revised stereochemical assignment of both the linear precursor **201** (originally **199**, in Scheme 3.5) and the cycloadduct **202** (originally **200**, in Scheme 3.5).



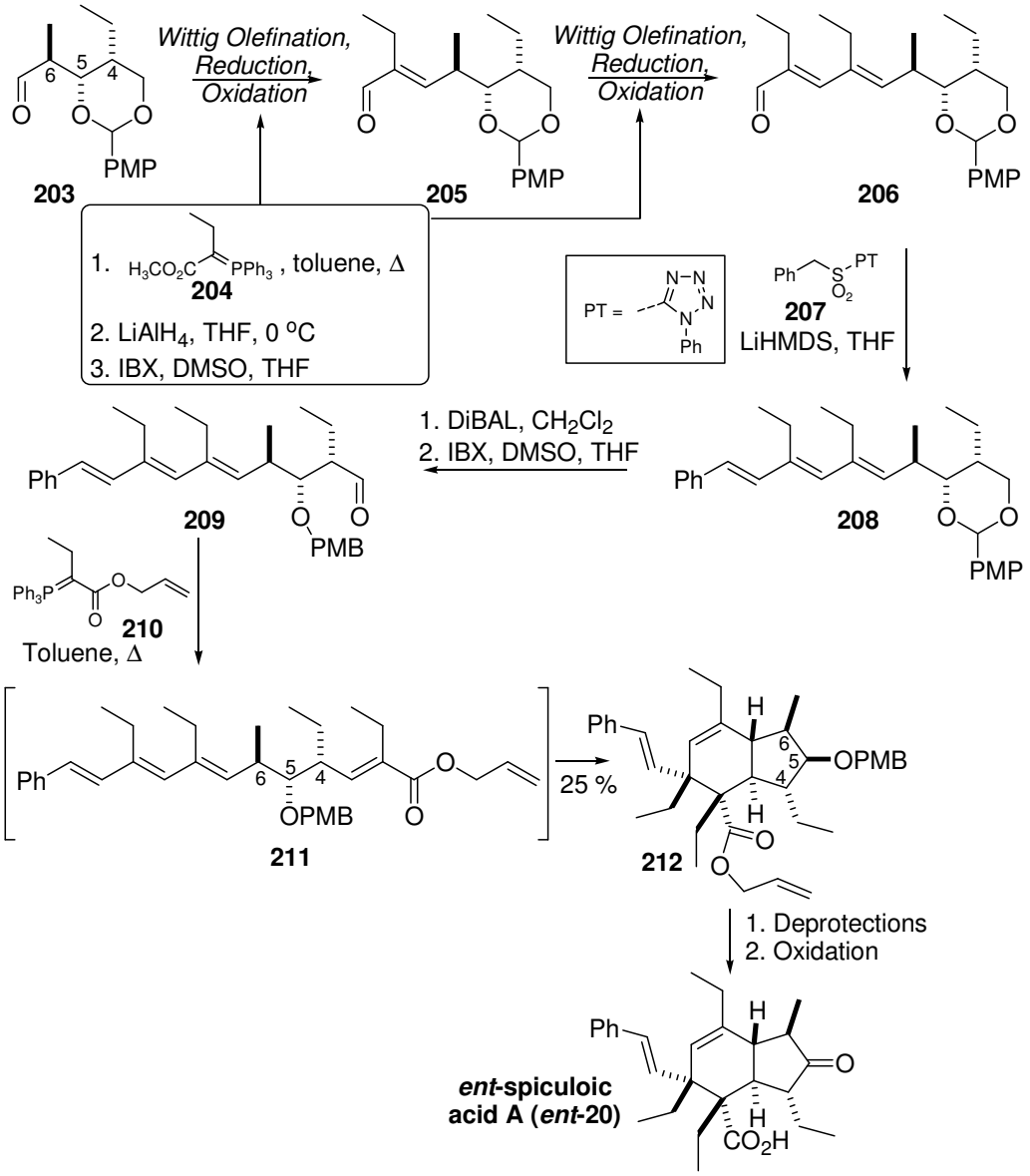
Scheme 3.6 Baldwin and co-workers structural reassignment of the analogue synthesised by Kunda and co-workers. [233]

The revised structure **202**, while containing the desired [4.3.0] bicycle, does not possess the stereochemistry desired for the natural product. It has a *cis*- rather than a

trans-relationship at the ring fusion and the relative orientation between the six stereocentres is not consistent with the stereochemistry required in the natural product. Furthermore, the model is not an accurate representation of the natural product because linear precursor **201** has an electron withdrawing group on the diene, facilitating an inverse electron demand IMDA reaction, while in the natural product the electron withdrawing group is on the dienophile, facilitating a normal electron demand IMDA reaction.

3.2.1.2 A Total Synthesis of Spiculoic Acid A

In 2006, Baldwin and co-workers reported the total synthesis of *ent*-spiculoic acid A, and thus the establishment of the absolute configuration, employing a biomimetic synthetic approach.[234] The key intermediates and synthetic transformations are shown in Scheme 3.7.



Scheme 3.7 The total synthesis of *ent*-spiculoic acid A, reported by Baldwin and co-workers. [234]

Employing extensively developed, highly stereoselective aldol strategies utilising chiral oxazolidinone derivatives, Baldwin and co-workers synthesised chiral aldehyde **203** which possessed the two desired stereocentres for the linear precursor as well as an additional stereocentre at C5. Chiral aldehyde **203** was coupled *via* a Wittig olefination to stabilised ylide **204** giving the corresponding ester which was

reduced to the alcohol and subsequently oxidised to aldehyde **205**. This Wittig olefination/reduction/oxidation sequence was repeated to give the doubly conjugated aldehyde **206**. Julia/Kocienski olefination of the aldehyde **206** using benzyl sulfone **207** gave the fully conjugated triene **208**. Selective removal of the protecting group from the primary alcohol only and subsequent oxidation gave aldehyde **209** which was coupled to ylide **210** by heating in toluene. Cyclic product **212** was isolated from the reaction mixture in relatively low yield (25 %) indicating that linear precursor **211** spontaneously undergoes a thermal IMDA cycloaddition reaction under these conditions. A final sequence of deprotection and oxidation reactions gave *ent*-spiculoic acid A (***ent*-20**), confirmed by comparison of NMR and optical rotation data with that reported for the natural product. While Baldwin and co-workers report the synthesis of *ent*-spiculoic acid A *via* a thermal IMDA reaction, they failed to comment on the stereoselectivity of the cyclisation reaction, simply stating a 25% yield of the adduct **212** leading to *ent*-spiculoic acid A. As a result no conclusions can be drawn about the thermal stereoselectivity of the IMDA reaction and the implications of this on the possible existence of a Diels-Alderase in the natural system.

3.2.2 Design of a Model System

At the beginning of this project no synthetic studies of the spiculoic acids had been reported and the novel spiculane skeleton represented an exciting challenge. A biomimetic approach to synthesis of the spiculane skeleton was proposed to investigate the possible involvement of a Diels-Alderase in the biosynthesis of the spiculoic acids. Due to the structural complexity of the spiculane skeleton, cyclisation of the linear polyene precursor **25** would result in the generation of four new stereocentres (including two quaternary centres) in one synthetic step. As discussed in Section 3.1.2, Figure 3.6, the linear precursor to the spiculoic acids can react through four different transition states producing a total of four possible stereoisomeric cycloadducts from the IMDA reaction. In order to explore the stereochemical outcome of the cycloaddition reaction a model system was proposed. As the studies described in Section 3.2.1, were undertaken in parallel to the model system discussed herein, they were not considered in the development of this model system.

The model system **113** was designed as a hybrid between the spiculoic acid and

plakotenin families of natural products, with the view of potentially applying this approach to the synthesis of both groups of natural products. While the model system contains many of the functionalities present in the natural products, it is significantly simplified to enable time and cost effective synthesis and to limit potential synthetic complications arising from steric hindrance or labile functionalities. Figure 3.9 shows the linear precursors leading to spiculoic acid A (**20**) and plakotenin (**186**) and the related model system (**113**) proposed to probe the stereoselectivity of the cycloaddition reaction.

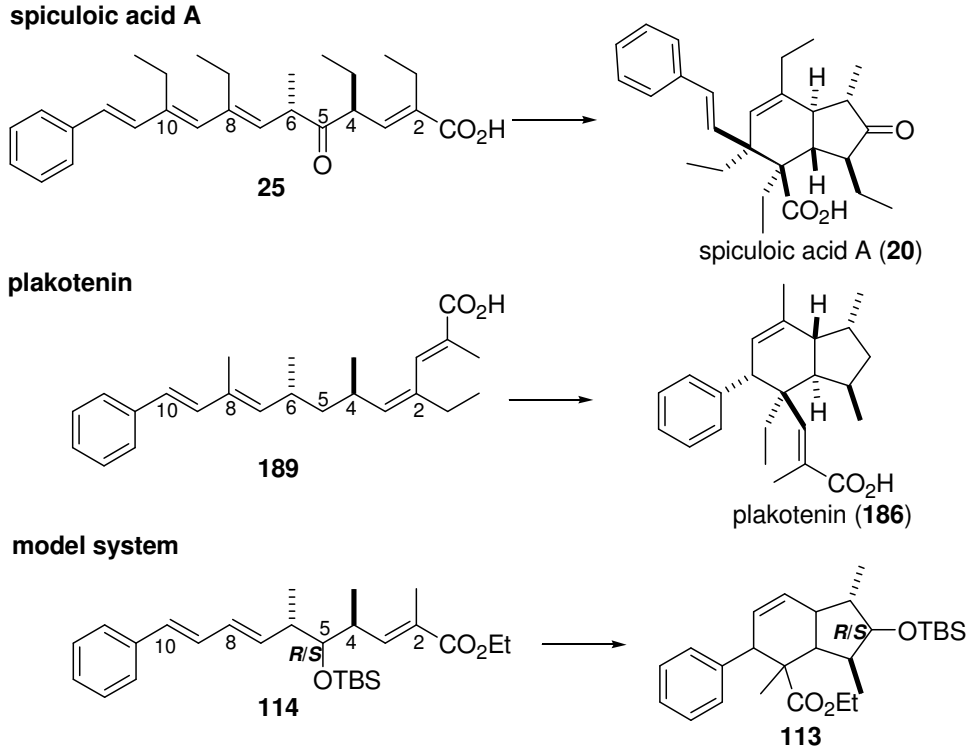


Figure 3.9 The two model systems (5*R*/5*S*-113) developed based on the spiculoic acid and plakotenin natural products.

In the proposed model system, the substituents at C8 and C10 were omitted while the ethyl group at C4 was replaced with a methyl group. The simple –Ph group, of the plakotenins, was selected in favour of the –CH=CH-Ph group of the spiculoic acids. The considerably simpler dienophile component of the spiculoic acids was preferred over that of the plakotenins however a slight modification was made, substituting the C2 ethyl group for a methyl group. In addition, the carboxylic acid functionality was replaced with the ethyl ester which would still facilitate a normal electron demand IMDA reaction. The C5 carbonyl was desired however it was masked as the *tert*-butyldimethylsilyl ether to prevent undesirable side reactions. Although this introduces an additional stereocentre into the linear precursor, flexibility is

introduced to the system because the [4 + 2] cycloaddition reaction can potentially be attempted on three different species; the C5 silyl ether, the C5 hydroxyl or the C5 carbonyl containing linear precursors. This may provide the opportunity to examine the affect of the C5 substituent on the selectivity of the cycloaddition reaction. In addition, it was proposed that this approach would enable further investigation of the stereoselectivity of the IMDA reaction, examining the affect of the configuration of the C5 stereocentre (*R* Vs *S*) which is not present in the natural product.

3.3 Conclusion

A model system has been designed in order to investigate synthetic methodologies to achieve the proposed linear polyene precursors to the natural products, the spiculoic acids and the plakotenins. The proposed model system incorporates a number of linear precursors, differing in the stereochemical orientation of the C5 substituent (OH or OTBS) or possessing the carbonyl at this centre. By examining the stereoselectivity of the thermally induced IMDA reaction of these linear precursors it is proposed that a thorough understanding of the factors influencing the stereochemical outcome may be achieved. This information may be used to develop a biomimetic strategy towards the spiculoic acids and the plakotenins. A biomimetic total synthesis is hoped to provide evidence to support or refute the suggested involvement of a Diels-Alderase enzyme in the cycloaddition reaction in the natural systems.

CHAPTER 4 THE MODEL SYSTEM; SYNTHESIS AND STEREOCHEMICAL ASSIGNMENT OF THE IMDA CYCLOADDUCTS

This chapter describes the synthesis of the linear precursors (**114**) for the proposed model system utilising two highly diastereoselective substrate-controlled aldol reactions: an *anti*-boron aldol reaction, controlled by the π-facial preference of (*S*)-2-benzoyloxypentan-3-one ((***S*)-39**), and a *syn*-titanium aldol reaction, under the stereocontrol of a chiral N-acylthiazolididinethione (**43a**). Installation of the diene and dienophile components was achieved using standard Wittig, H.W.E. and "modified" Julia olefination conditions. A thorough stereochemical analysis of the cycloadducts of the thermally induced IMDA reaction, employing 2D NMR techniques, is described. Comparison of the IMDA cycloadducts from each of the linear precursors provided an insight into the factors influencing the stereochemical outcome of the cycloaddition reaction.

4.1 Retrosynthetic Analysis of the Model System

In Chapter Three a model system, developed in order to investigate the factors affecting the stereochemical outcome of the IMDA reaction, was introduced. The model system (**113**) combined structural features of both the spiculoic acid and the plakotenin families of natural products, illustrated in Figure 4.1.

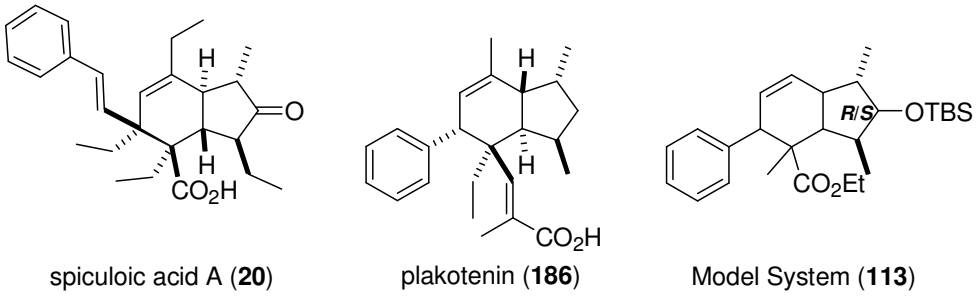
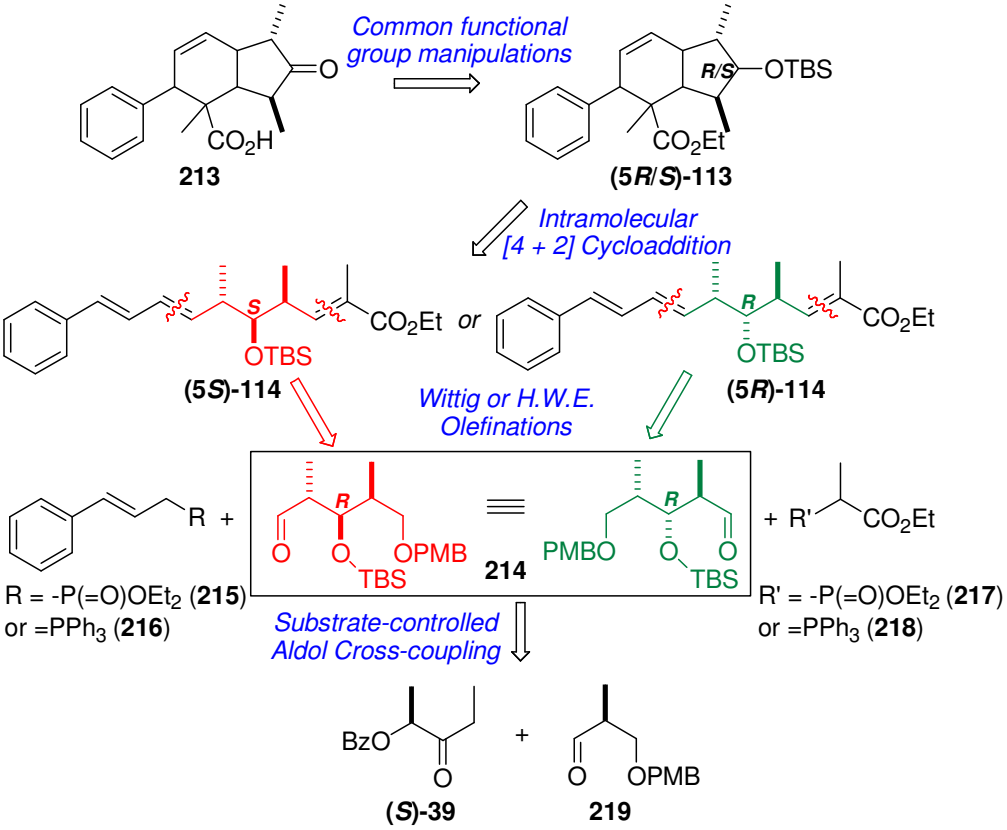


Figure 4.1 The model system, (5*R/S*)-113, contains structural similarities with spiculoic acid A (20) and plakotenin (186).

A number of approaches were considered in the development of a synthetic strategy, outlined in Scheme 4.1, for synthesis of the proposed linear triene (**114**) to the cycloadducts (**5*R/S*)-113**. Retrosynthetically, the molecule could be disconnected at the double bonds to be constructed by olefination reactions such as H.W.E.,[97] Wittig[97] or Julia (and modifications)[111] olefination reactions. Alternatively, the molecule could be disconnected at the single bonds to be constructed *via* the many palladium- and nickel-catalysed cross-coupling reactions introduced in the 1970's.[235]

Ultimately the desire to complete the model synthesis in a time and cost efficient manner lead to the decision to design a strategy employing both H.W.E. and Wittig olefination reactions due to the ready availability and relatively low cost of the reagents required. Scheme 4.1 shows the retrosynthetic breakdown of the model system into either commercially available or readily synthesisable blocks.



Scheme 4.1 The retrosynthetic analysis of the proposed model systems 113.

The synthesis and thorough stereochemical analysis of cycloadducts **113** and **213**, obtained *via* an IMDA reaction of linear triene precursors **(5*R*)-114** and **(5*S*)-114**, and subsequent protecting group removal and oxidation state changes, was the focus of this investigation. The linear trienes **(5*R*/*S*)-114**, differing only in the orientation of the C5 stereocentre, will be referred to as Model System One (5*S* stereochemistry) and Model System Two (5*R* stereochemistry). Linear trienes **(5*S*)-114** and **(5*R*)-114** could be derived from Wittig[31,236] or H.W.E.[237,238] olefination reactions of central chiral fragment **214** with ylide's **216** and **218** or phosphonate's **215** and **217**. A degree of flexibility exists within this approach because both olefination reactions are potential candidates for installation of the diene and dienophile components of the system. An additional feature of this proposed synthesis is the possibility of synthesising the linear triene **114** with both *R* and *S* stereochemistry at C5, by simply

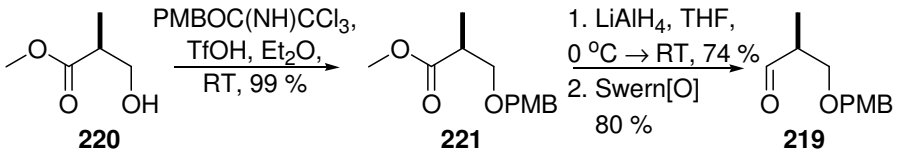
altering the order of attachment of the diene and dienophile components to aldehyde **214**, as represented in Scheme 4.1 in red and green. Control of the stereotriad in central fragment **214** is achieved through a substrate-controlled aldol coupling of known chiral aldehyde **219**[239] and lactate derived α-chiral ketone **(*S*)-39**, introduced in Section 1.3.1.3.1.[77,75,71] This ketone has been previously employed in the synthetic studies towards the structural elucidation of (-)-maurenone described in Section 2.3. The synthetic pathway, proposed in Scheme 4.1, should provide access to all of the desired linear precursors; C5, with both *R* and *S* orientations, and variations of the C5 substituent, OTBS, OH and =O, in a relatively time and cost efficient manner. Following synthesis of these linear precursors a thorough investigation of the stereochemical outcome of the thermal IMDA reaction of each is intended.

In order to simplify the discussion, synthesis of the linear precursors and stereochemical evaluation of the cycloadducts from each model system will be addressed separately. Model System One, with 5*S* stereochemistry is examined in Section 4.2, while Model System Two, with the 5*R* stereochemistry is investigated in Section 4.4.

4.2 Synthesis of Model System One

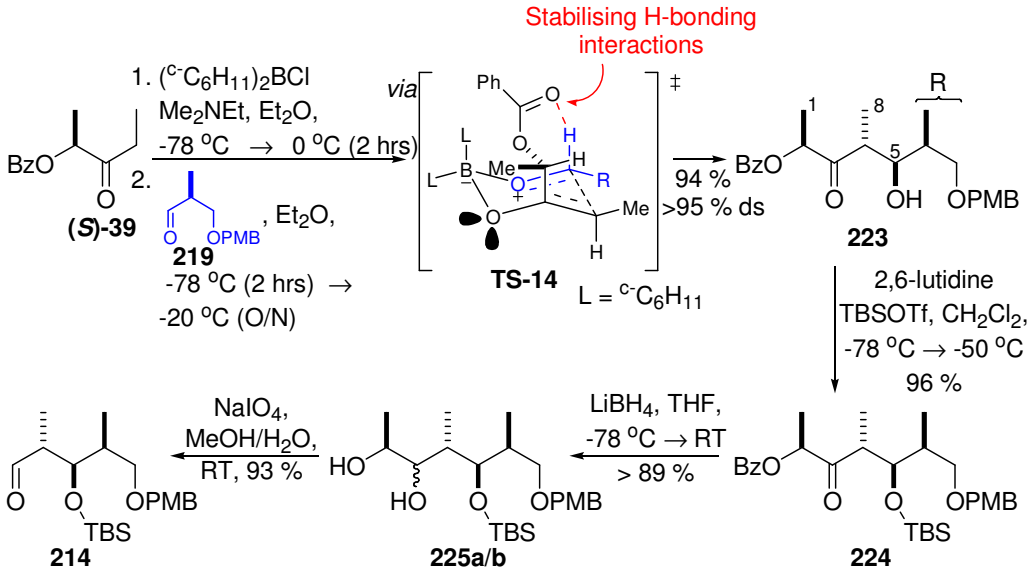
4.2.1 Synthesis of Aldehyde 214

The central aldehyde fragment **214**, containing the desired stereotriad, was proposed to be synthesised *via* a substrate-controlled aldol coupling between ketone **(*S*)-39** and aldehyde **219**. Synthesis of lactate derived α-chiral ketone **(*S*)-39** from ethyl-(*S*)-lactate has previously been described in Section 2.3.1.1. α-Chiral aldehyde **219** was synthesised according to literature procedures from the commercially available (*S*)-Roche ester ((*S*)-methyl 3-hydroxy-2-methylpropionate, **220**).[239] The three step sequence involved protection of the primary alcohol as the PMB ether **221**, $LiAlH_4$ reduction of the methyl ester and Swern oxidation[205] of the generated alcohol **222** to aldehyde **219**, as described in Scheme 4.2.



Scheme 4.2 Synthesis of α-chiral aldehyde 219.

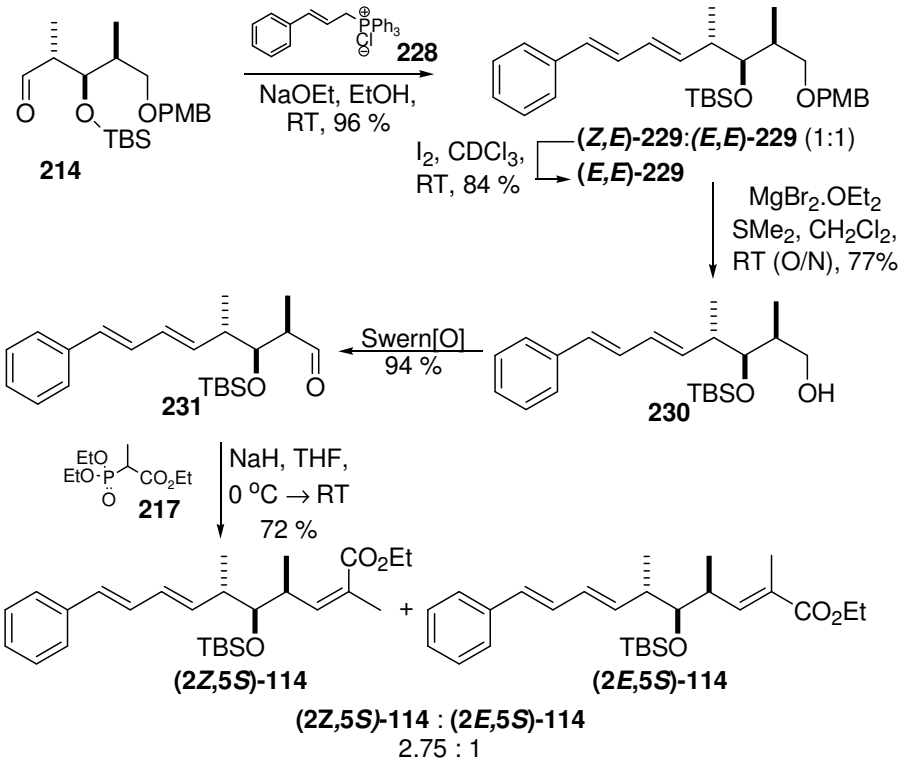
An asymmetric, substrate-controlled aldol coupling[71,75-77] between the *E*-dicyclohexylboron enolate of α-chiral ketone **(*S*)-39** and α-chiral aldehyde **219** gave *anti*-aldol adduct **223** (94 %). The double stereodifferentiating aldol reaction was highly diastereoselective (>95 % ds) as the adduct **223** satisfies both the facial preference of the α-chiral ketone **(*S*)-39** and the Felkin[57] preference of α-chiral aldehyde **219**. As discussed in Section 1.3.1.3.1, the stereoselectivity of the aldol addition arises due to the enhanced stability of transition state **TS-14** brought about by the H-bonding interactions between the benzoate carbonyl and the C1 proton in the aldehyde, as seen in Scheme 4.3. Formation of the alcohol **223** was indicated by the doublet of doublets at 4.07 ppm due to the C5 proton and the doublet at 1.21 ppm due to the C8 methyl. A minor isomer was observed in the purified aldol product however as the quantity of the minor isomer was relatively insignificant separation and assignment of the stereochemistry was not undertaken. The stereochemistry of aldol adduct **223** was assigned based on literature precedent.[71,75-77] The secondary hydroxyl group was protected as the *tert*-butyldimethylsilyl ether **224**[208] and the reduction of both the ketone and ester functionalities with $LiBH_4$ gave inseparable 1,2-diols **225a/b** (ratio ~2:1).[71,75-77] Oxidative cleavage using sodium periodate[71,75-77] gave the aldehyde **214** in good yield (>75 % over 4 steps).



Scheme 4.3 Synthesis of central chiral fragment 214.

4.2.2 Synthesis of the Linear Precursors (2*E*,5*S*)-114 and (2*Z*,5*S*)-114 and Subsequent Cyclisation

Synthesis of a full linear precursor **(5*S*)-114** was now possible through a two directional Wittig/H.W.E. olefination approach using central chiral fragment **214**, as proposed in Scheme 4.4. A Wittig coupling[236] of ylide **216** (available in a four step sequence from cinnamaldehyde; $NaBH_4$ reduction to the alcohol **226**,[240] conversion to the allyl chloride **227**,[241] formation of the phosphonium salt **228**[236] and deprotonation[236]) with chiral aldehyde **214** produced an inseparable mixture of **(*E,E*)-229** and **(*Z,E*)-229** isomers (96 %, 1:1 **(*E,E*)-229**:**(*Z,E*)-229**). Ylide **216**, generated in situ by addition of ethoxide to a stirring solution of the phosphonium salt **228** and aldehyde **214** at room temperature, was bright red in colour. After stirring the reaction mixture at room temperature for five days the colour was lost indicating completion of the reaction. Isomerisation of **(*Z,E*)-229** to the thermodynamically favoured **(*E,E*)-229** was achieved using catalytic I_2.[242-244] In this reaction an iodine atom adds to the olefin and the resulting radical isomerises to the thermodynamic product. The use of $CDCl_3$ as the solvent for the isomerisation reaction allowed the progress to be monitored by ^{1}H NMR. This was necessary due to the similar R_f values of the two isomers by TLC making monitoring the reaction by this method ineffective. The reaction endpoint was obvious by ^{1}H NMR because the initially complex spectrum displaying two of each of the expected resonances, at similar chemical shifts, simplified significantly to give only one set of expected signals. The four vinyl resonances were all observed in the downfield region between 6.74 and 5.80 ppm due to the deshielding effect of extended conjugation within the system.[245] Assignment of the stereochemistry of the double bonds as *E,E* was based on the large coupling constants between the vinyl protons (J_{ab} = 15.9 and 15.3 Hz) indicating an *E*-relationship.[245] Double bonds with *Z*-geometry generally have coupling constants ~ 7-11 Hz in magnitude.[245]

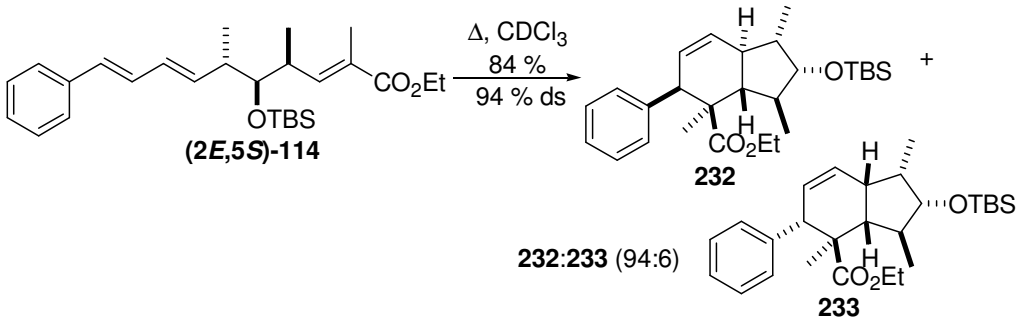


Scheme 4.4 Synthesis of the linear precursors (2*E*,5*S*)-114 and (2*Z*,5*S*)-114.

Cleavage of the PMB ether proved troublesome due to the sensitivity of diene **(*E*,*E*)-229**. Conventional methods (DDQ [246] and CAN[247]) resulted in decomposition of the starting material and attempts at achieving cleavage using a variety of acids (eg *p*-TsOH, TFA and amberlyst resin) yielded only starting material. Fortunately, alcohol **230** was synthesised (77 % yield) using a method reported by Iwasaki and co-workers where the Lewis acid, $MgBr_2.OEt_2$, binds to the ether oxygen facilitating an S_N2 displacement by SMe_2 upon stirring this mixture in CH_2Cl_2 at room temperature for 24 - 48 hours.[248] The *para*-methoxybenzyl group is removed as the water soluble sulfonium ion making this method particularly attractive as it eliminates potential problems of separating the PMB alcohol from the reaction product **230**, a problem which plagues other commonly used methods of PMB ether cleavage.

Oxidation of alcohol **230** *via* Swern oxidation gave the desired aldehyde **231** in good yield (94 %).[205] A H.W.E. coupling between commercially available phosphonate **217** and aldehyde **231** (stirring at room temperature for 30 min.) gave the linear triene as a separable mixture of (**2*E*,5*S*)-114** and (**2*Z*,5*S*)-114** (ratio 1:2.75).[237] The stereochemistry of each triene was assigned retrospectively, following stereochemical assignment of the IMDA reaction cycloadducts. Upon purification

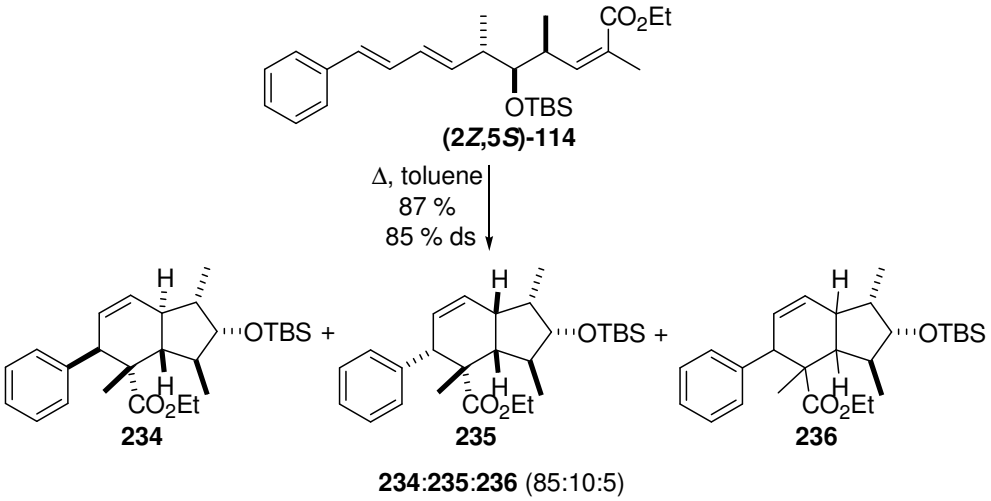
and separation on silica gel linear triene (**2*E*,5*S*)-114** spontaneously begins to undergo the IMDA cyclisation and heating gently to 50 °C drives the reaction to completion. Two isomeric products, **232** and **233** (84 % yield, ratio 94:6, 94 % ds), were produced which were separable by column chromatography. The stereochemical assignment of the cycloadducts, as shown in Scheme 4.5, is described in Section 4.3.2. Due to the spontaneity of the cyclisation, attempts to perform the IMDA reaction with the C5 hydroxyl or the C5 carbonyl in place were not possible. The propensity for the linear triene (**2*E*,5*S*)-114** to undergo a spontaneous IMDA cycloaddition reaction meant that a ^{1}H NMR spectrum of the pure triene could not be obtained. Instead the ^{1}H NMR spectrum showed evidence of a mixture of the linear triene **(2*E*,5*S*)-114** and the cycloadducts, obvious because of the multiple vinyl signals corresponding to both the linear triene and the cycloadducts. However, this spectrum rapidly resolved to reveal only two vinyl signals, between 5.5 ppm and 6.0 ppm, corresponding to the formation of the cyclohexene moiety, for each of the two stereoisomeric products.



Scheme 4.5 IMDA cycloaddition of (2*E*,5*S*)-114.

The linear triene **(2*Z*,5*S*)-114** was much more stable than **(2*E*,5*S*)-114**, and thus ^{1}H and ^{13}C NMR spectra of the pure triene could not be measured. The ^{1}H NMR spectrum of **(2*Z*,5*S*)-114** indicated that five vinyl protons were present, with resonances between 5.7 ppm and 6.7 ppm, which could be assigned to the specific vinyl protons with the assistance of the 2D ^{1}H-^{1}H COSY spectrum. In addition, a vinyl methyl doublet (^4J = 1.5 Hz) at 1.9 ppm confirmed the installation of the dienophile component. Further evidence supporting synthesis of the linear triene **(2*Z*,5*S*)-114** was provided by the ^{13}C NMR spectrum which revealed 10 resonances due to vinyl carbon centres between 146 ppm and 126 ppm, assigned to the four non-equivalent aromatic carbons and the six vinyl carbons.

Although the **(2*Z*,5*S*)-114** triene was more stable than the **(2*E*,5*S*)-114** triene, heating under reflux in toluene overnight promoted the cycloaddition reaction which produced a mixture of three isomeric IMDA adducts **234**-**236** (87 %, ratio 85:10:5, 85 % ds). These three isomers, represented in Scheme 4.6, were not able to be separated by column chromatography at this stage, however following silyl ether cleavage separation was achieved. Stereochemical assignment of the major isomer **234** was achieved from the NMR spectra of the mixture while retrospective assignment of isomer **235** (10 % ds) was achieved following TBS cleavage and is discussed in Section 4.3.2.2. The alcohol derived from the minor component **236** (5 % ds) was isolated in very small amounts and was impure despite several attempts at purification and thus stereochemical assignment of this adduct was not achieved.



Scheme 4.6 IMDA cycloaddition of (2*Z*,5*S*)-114.

Each of the stereoisomeric IMDA cycloadducts, **232**-**234**, produce similar ^{1}H and ^{13}C NMR spectra displaying similar chemical shifts and multiplicities. A discussion of the spectra of each stereoisomer has not been included however tables containing the assignment of each of the ^{1}H and ^{13}C NMR resonances in these isomers, assisted by 2D NMR experiments, are available in Chapter 7, Appendix 1 (**232**), Appendix 4 (**233**) and Appendix 7 (**234**). A description of the assignment of the ^{1}H and ^{13}C NMR resonances for the major adduct **232** is discussed herein as an example of the process used in the assignment of all of the isomers. The ^{1}H NMR spectrum of the major adduct (**232**) arising from cyclisation of **(2*E*,5*S*)-114** is shown in Figure 4.2.

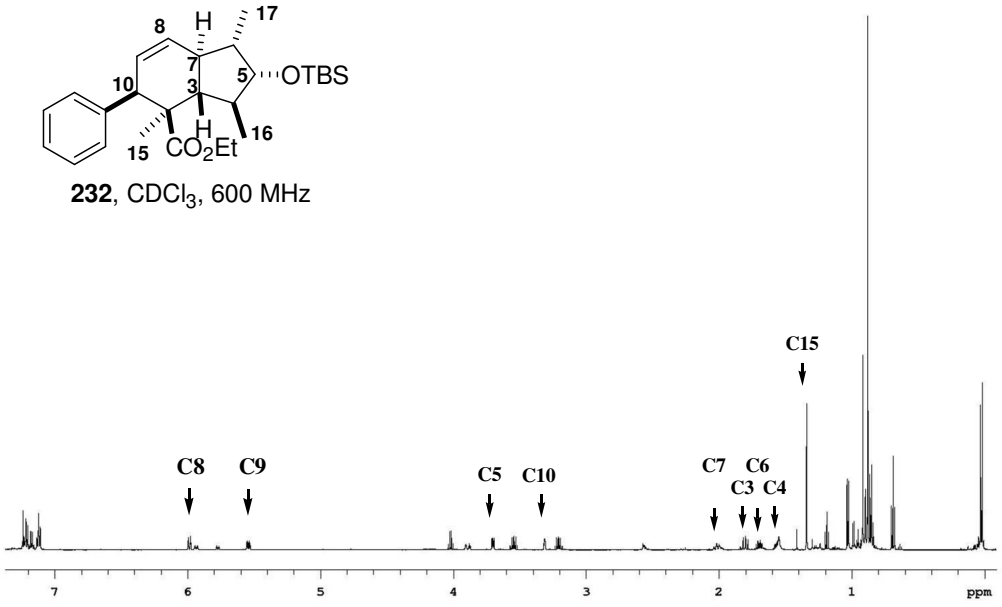
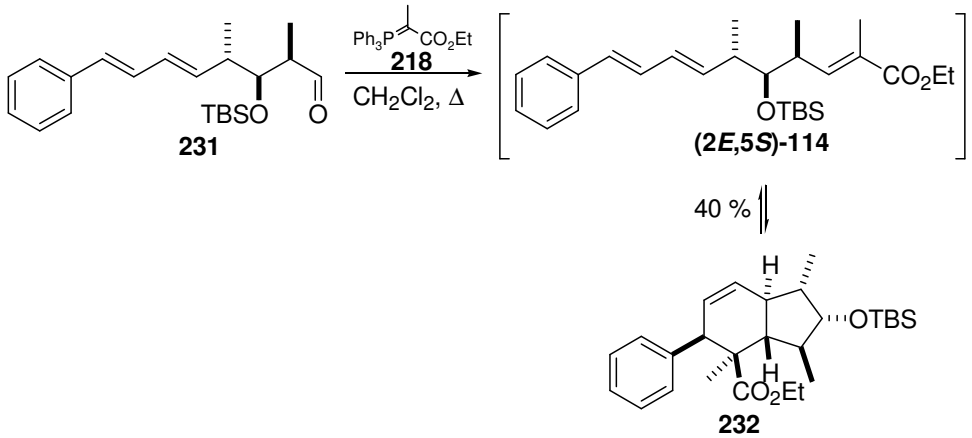


Figure 4.2 ^{1}H NMR spectrum of cycloadduct 232 showing the structural assignment.

The presence of two vinyl proton signals assigned to the C8 and C9 protons, at 5.99 ppm and 5.54 ppm, immediately implied formation of the cyclohexene. The appearance of a broad multiplet at 3.31 ppm was attributed to the C*H*Ph (C10 proton) resonance. The vinyl methyl doublet was replaced by a singlet at 1.34 ppm due to the C15 methyl attached to the quaternary C2 carbon centre. The protons at the ring fusion, on C3 and C7, and the C4 and C6 protons all resonated between 1.57 ppm and 2.02 ppm, with high variability in the chemical shifts between the stereoisomers. However, the multiplicity, coupling constants and ^{1}H-^{1}H COSY correlations allowed ready assignment of each resonance to a particular proton. The C7 proton has a particularly unique splitting pattern which resembled a ddddd, due to long range coupling to the C9 and C10 protons, however second order effects added further complications to the splitting. The C3 proton, adjacent to the quaternary C2 centre, was simply a doublet of doublets while the C4 and C6 centres were obviously doublet of doublet of quartets. Figure 4.2 reveals a doublet of doublets at 1.80 ppm due to the C3 proton while the ddddd's corresponding to the C7 proton resonated at 2.02 ppm. The doublet of doublet of quartets attributed to the C4 and C6 protons resonated at 1.57 and 1.70 ppm, respectively. The ^{13}C NMR spectrum confirmed the formation of cycloadduct **232** with only six resonances in the vinyl region due to the two unsaturated carbons of the cyclohexene and the four non-equivalent carbons from the phenyl group. A description of the stereochemical assignment of each of the IMDA cycloadducts, based on analysis of ^{1}H-^{1}H ROESY and ^{1}H-^{1}H NOESY NMR

spectra, is addressed in Section 4.3.2.

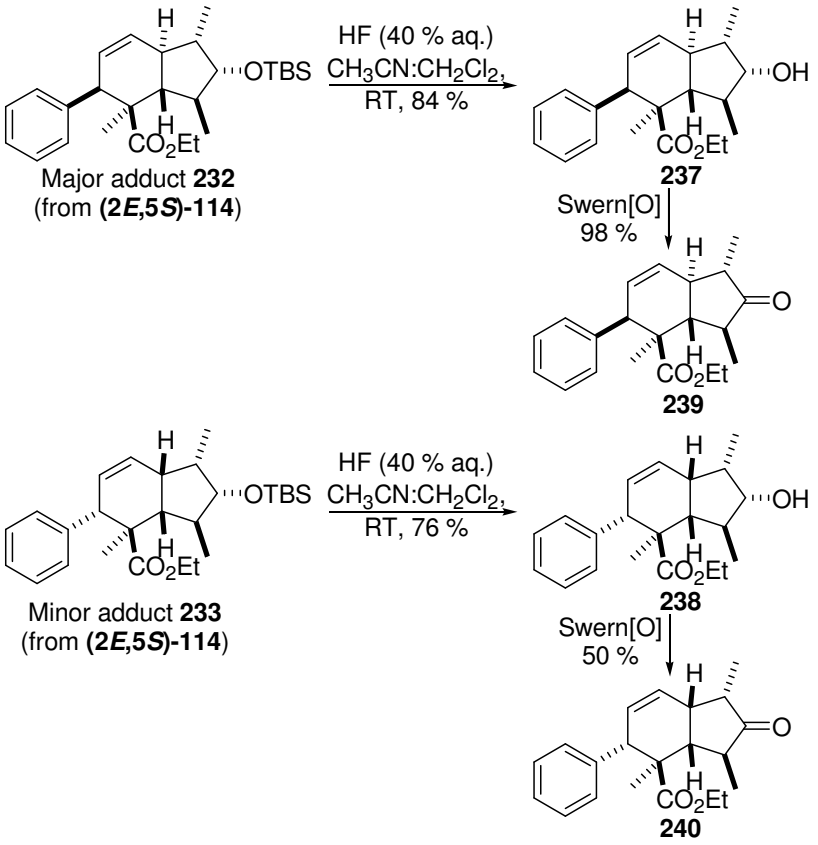
A Wittig olefination reaction was also attempted to install the dienophile component with the hope of replicating the high *E*-stereoselectivity reported for reactions with commercially available ylide **218**.[31] As described in Scheme 4.7, the ylide **218** and aldehyde **231** were heated under reflux in CH_2Cl_2 for 5 days producing only one IMDA adduct (40 %, incomplete reaction). The presence of only one cycloadduct indicated that under these conditions the olefination reaction was highly stereoselective as was the spontaneous IMDA reaction that followed. The NMR data of the IMDA adduct matched that of the cycloadduct **232**, the major isomer from the diene (**2*E*,5*S*)-114** isolated from the H.W.E. olefination. This suggests that the Wittig olefination occurred in a highly *E*-selective manner as anticipated. As isolation of the intermediate triene **(2*E*,5*S*)-114** was not achieved, the stereoselectivity of the Wittig olefination was inferred from the stereochemistry of the IMDA adduct **232**. Section 4.3.2.1 contains a detailed discussion of the stereochemical assignment of cycloadduct **232**. Intriguingly only cycloadduct **232** was isolated from the cycloaddition reaction which occurred at 40 ^{o}C in CH_2Cl_2 over 5 days, while the reaction promoted at 50 ^{o}C in $CDCl_3$ over several hours, gave two stereoisomeric products, **232** and **233**. This could be attributed to the higher temperature promoting formation of cycloadducts **233** through an alternative transition state. Another proposal is that the longer reaction time required for the Wittig olefination compared to the H.W.E. olefination enables equilibration of the D.-A. cycloadducts suggesting that the cycloaddition reaction may be reversible.



Scheme 4.7 Installation of the dienophile *via* a Wittig olefination producing cycloadduct 232.

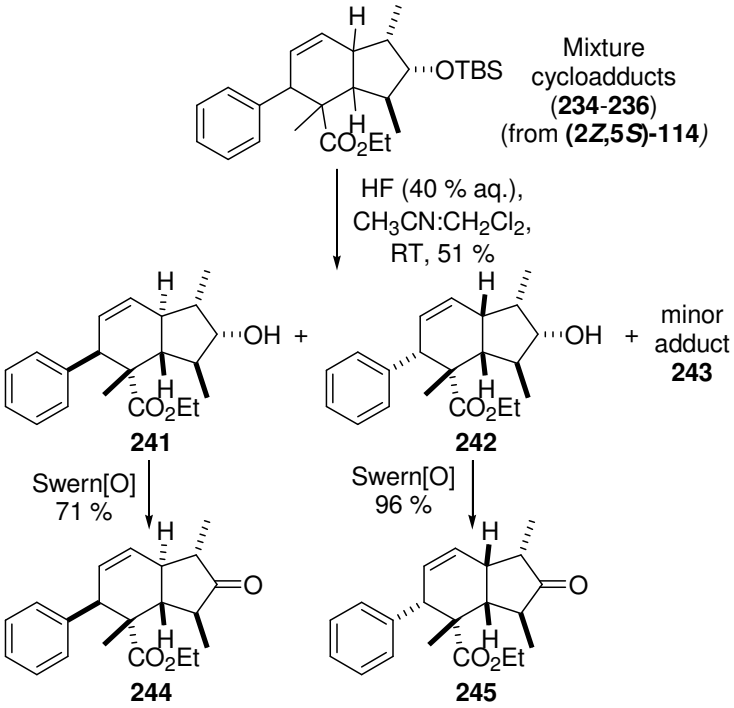
Each of the isomeric IMDA adducts underwent cleavage of the silyl ether with aqueous HF/CH_3CN:CH_2Cl_2 in 1-3 hours to give the corresponding alcohols.[197,249] HF-Pyr/Pyr[198] and TBAF[196] were very slow to react and the reaction was incomplete after days or weeks under these conditions. Subsequent oxidation under Swern conditions gave the ketones.[205] Unfortunately, despite exhaustive effort, liberation of the acid functionality, the final step in the model synthetic scheme, was unsuccessful. Various attempts at effecting the ester hydrolysis (TFA, KOH, H_2O_2/LiOH,[250] $Ba(OH)_2$,[251] NaI/TMSCl,[252] K^{t}BuO[253]) all failed with starting material recovered in each case.

The two cycloadducts **232** and **233**, separated following IMDA cycloaddition of the triene **(2*E*,5*S*)-114,** were subjected to silyl ether cleavage yielding alcohols **237** (84 %) and **238** (76 %). Swern oxidation of the alcohols yielded ketones **239** and **240**, in 98 % and 50 % yields respectively, represented in Scheme 4.8.



Scheme 4.8 Deprotection and oxidation of the cycloadducts 232 and 233, from the (2*E*,5*S*)-114 linear precursor.

The previously inseparable cycloadducts (**234**-**236**), from IMDA cycloaddition of triene **(2*Z*,5*S*)-114**, were able to be separated after silyl ether cleavage (51 %) and the two principal stereoisomers, **241** and **242**, fully characterised, as illustrated in Scheme 4.9. As previously mentioned the minor component **243** was present in only small quantities and a pure sample was unattainable. The alcohols **241** and **242** were then oxidised under Swern conditions to ketones **244** and **245**, in 71 % and 96 % yields respectively.



Scheme 4.9 Deprotection and oxidation of the cycloadducts 234-236, from the (2*Z*,5*S*)-114 linear precursor.

A thorough stereochemical analysis of each of the cycloadducts **232** and **233**, isolated from the IMDA cycloaddition reaction of the triene **(2*E*,5*S*)-114,** was performed. In order to confirm the stereochemical assignment was correct the analysis was repeated on the corresponding alcohols **237** and **238** and ketones **239** and **240**. The stereochemical assignment of these cycloadducts is discussed in Section 4.3.2.1.

Similarly, the stereochemical assignment of the major cycloadduct **234** isolated from the IMDA reaction of the triene **(2*Z*,5*S*)-114** was achieved (within the mixture of isomers) and was confirmed by analysis of the corresponding alcohol **241** and ketone **244**. The stereochemical assignment of the minor adduct **235** (10 % ds) could only be

performed retrospectively from the corresponding alcohol **242** and ketone **245**. The stereochemical analysis of **242** and **245** is described in detail in Section 4.3.2.2.

4.3 Stereochemical Assignment of the IMDA Adducts

The stereochemistry of both the diene and dienophile components involved in the IMDA reaction are transferred to the cycloadducts as discussed in Section 1.3.5. However, as both the planar diene and planar dienophile components can undergo cycloaddition at both faces, the potential exists for the formation of four stereoisomeric cycloadducts. Assignment of the stereochemistry of each of the cycloadducts would thus provide information on the reaction pathway indicating which faces of the planar components are reacting. This information could be used to predict the potential outcome of a thermal IMDA reaction of linear precursors to the natural products which would be useful in designing a synthetic approach.

In addition to investigating synthetic strategies which may be employed in the total synthesis of the spiculoic acids, a major goal of the synthesis of these model systems was to investigate the stereoselectivity of the thermal IMDA reaction. The original goal was to determine what affect, if any, the orientation of the C5 stereocentre (*R* Vs *S*) or the nature of the C5 substituent (OTBS, OH or =O) had on the stereochemical outcome of the IMDA reaction. The linear triene precursors **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114**, demonstrated a high propensity to spontaneously cyclise under the conditions of the Wittig reaction and even when the milder H.W.E. conditions were employed, cyclisation occurred relatively quickly upon purification by column chromatography, NMR analysis in $CDCl_3$ or upon storage in the refrigerator. As a result analysis of the stereochemistry of the cycloadducts arising from cyclisation of the linear precursors with a C5 OH or a C5 =O was not possible. However it was possible to make comparisons between the cycloadducts from the **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** linear precursors, to examine the affect of the dienophile geometry on the stereochemistry of the cycloadducts. Analysis of the stereochemical outcome of cyclisation of the linear precursors **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** (Figure 4.3) is discussed here. In addition the linear precursor **(2*E*,5*R*)-114**, was also synthesised enabling the affect of the orientation of the C5 stereocentre on the cycloaddition reaction to be examined. The synthesis of the **(2*E*,5*R*)-114** linear precursor and subsequent analysis of the stereoselectivity of the thermally induced IMDA reaction

is described in Section 4.4.

Model System 1

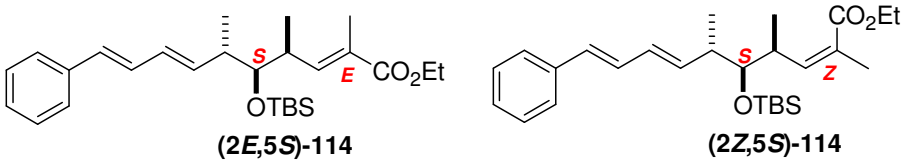


Figure 4.3 Linear trienes (2*E*,5*S*)-114 and (2*Z*,5*S*)-114, differ only in the dienophile geometry.

In order to assign the stereochemistry of each cycloadduct extensive 1D and 2D NMR analysis was performed. Initially each of the ^{1}H and ^{13}C resonances in the 1D spectra were assigned to specific atoms within the spiculane skeleton on the basis of the following spectroscopic data; chemical shift, splitting patterns, coupling constants, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC data. This information corresponds to "through bond" magnetic interactions between connected atoms (generally 1-2 bonds but in conjugated systems longer range magnetic interactions can be observed).[245] The stereochemical assignment of each cycloadduct was possible by examining the 2D ^{1}H-^{1}H ROESY or ^{1}H-^{1}H NOESY spectra which reveal information about the "through space" magnetic interactions of the protons in close proximity (typically 2-5 Å).[245] In this investigation the ^{1}H-^{1}H ROESY or ^{1}H-^{1}H NOESY spectra provide information about the relative spatial arrangement around the [4.3.0] bicyclic core. As the three carbon centres C4-C6 were synthesised in a stereocontrolled fashion the absolute stereochemistry of the cycloadduct could be deduced by considering the ^{1}H-^{1}H ROESY and ^{1}H-^{1}H NOESY correlations between the centres of known orientation (C4-C6) and the newly formed stereogenic centres. In practical terms this means that by first examining the ^{1}H-^{1}H ROESY or ^{1}H-^{1}H NOESY correlations involving these known stereocentres, it was possible to move around the ring inferring stereochemical information about the other centres. Tables containing the complete set of NMR data collected and assigned for each of the IMDA cycloadducts, the corresponding alcohols and the corresponding ketones for Model System One are available in Chapter 7, Appendix 1-Appendix 11. Each table contains the assignments of each of the ^{1}H and ^{13}C NMR resonances, the ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBC data supporting these assignments and the ^{1}H-^{1}H ROESY or ^{1}H-^{1}H NOESY data used to identify the stereochemistry of the adducts.

4.3.1 Modelling Studies

Upon identification of the stereochemistry of each of the IMDA adducts, computer modelling studies (Spartan '04 for Macintosh, Wavefunction, Inc., Irvine, CA) were undertaken to predict the low-energy conformation of each stereoisomer. Each isomer was submitted to a conformational search, performed at the Molecular Mechanics level using MMFF and the conformations identified were subjected to an equilibrium geometry analysis at the semi-empirical level using AM1. This produced a number of conformations with different energies. In most cases the lowest energy conformation was sufficient to explain the correlations observed in the ^{1}H-^{1}H NOESY or ^{1}H-^{1}H ROESY spectra.

The spiculane skeleton, containing the [4.3.0] bicyclic core with one site of unsaturation, is quite rigid significantly restraining conformational flexibility. In most instances the conformational differences between the stereoisomers were minimal. The most noteworthy differences were observed between isomers possessing a *trans*-fused Vs a *cis*-fused bicyclic core. In all systems the cyclohexene ring adopts a *pseudo* chair conformation which is slightly flattened due to the double bond and the conformational restraints imparted by the fused 5-membered ring. The isomers containing a *trans*-fused ring system were generally very rigid within the bicyclic core with the most obvious differences between the alternative conformers resulting from movement of the appendages (i.e. Ph, CO_2Et, OH or OTBS). This can be rationalised by examination of the bonding within the fused ring system, depicted in Figure 4.4. When the cyclohexene ring adopts the *pseudo* chair conformation the 5-membered ring lies in a favoured *pseudo* equatorial orientation in which the two rings of the bicycle are relatively co-planar. The C3 and C7 protons at the ring fusion therefore adopt the *pseudo* axial orientations. The fused 5-membered ring locks the conformation of the cyclohexene ring physically preventing the ring from flipping, inverting the stereocentres.

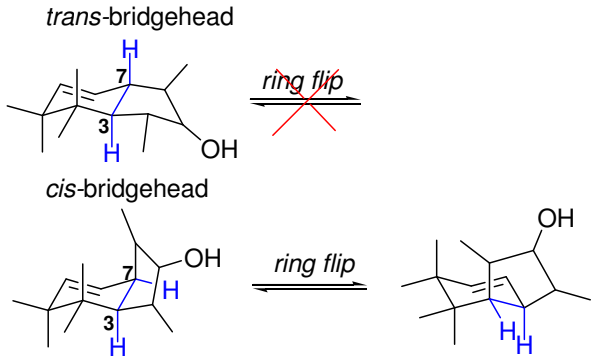


Figure 4.4 Comparison of the *trans*- and *cis*-fused bicycles.

In contrast, the *cis*-fused ring system experiences significantly more conformational flexibility, due to movement within the appendages as well as movement within the bicyclic core. In this instance, with the cyclohexene ring in a *pseudo* chair conformation, the fused 5-membered ring occupies both a *pseudo* axial and a *pseudo* equatorial orientation at the two carbon centres of attachment. As a result the bicyclic core has a concave shape. The *pseudo* chair conformation of the cyclohexene ring is free to ring-flip altering the orientation of the substituted groups from *pseudo* axial to *pseudo* equatorial. The energy difference between these conformations is significantly dictated by the orientation of the bulkier phenyl, ethyl ester and OTBS substituents. In some cases, if both the phenyl and ethyl ester lie in a *pseudo* equatorial position, no conformations resulting from a ring-flip were predicted by the computational analysis.

It was clear from the modelling studies that when the protons at the ring fusion have a *trans*-relationship a large dihedral angle of ~180^{o} occurs between the overlapping orbitals. When overlap is 180^{o} this is known as an *anti*periplanar arrangement and orbital overlap is most efficient resulting in a large coupling constant.[245] When the protons at the ring fusion have a *cis*-relationship the dihedral angle between the protons is close to 0^{o} due to concave nature of the bicyclic core. This is known as a *syn*coplanar arrangement and orbital overlap is less efficient than in the *anti*periplanar arrangement resulting in a slightly smaller coupling constant. Therefore the coupling constant between the protons at the ring fusion in a *cis*-orientation would be expected to be slightly less than for the *trans*-orientation. The absolute values of J^{0} and J^{180} are dependent on the substituents on the carbon atoms and in this system experimental results indicated that J^{180} is 11-13 Hz, while J^{0} is closer to 9-11 Hz.

4.3.2 Model System One - Stereochemical Assignment of Cycloadducts 232-235

As reported in Section 4.2.2, the diene component of the linear precursors **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** was achieved stereoselectively in the *E*,*E* orientation by employing an I_2 catalysed thermodynamic isomerisation. Installation of the dienophile component of the linear precursor *via* a H.W.E. olefination reaction, produced both **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** stereoisomers. Cyclisation of **(2*E*,5*S*)-114** produced two isomeric cycloadducts **232** and **233** (ratio 94:6), which were separated by column chromatography and the stereochemistry investigated. Upon cyclisation, **(2*Z*,5*S*)-114** produced three isomeric cycloadducts **234**-**236** (ratio 85:10:5) which were not separable until after cleavage of the silyl ether. The three deprotected isomers **241**-**243** were separated by column chromatography and the stereochemistry of **241** and **242** was determined.

As a comparison, the dienophile component was also installed *via* the corresponding Wittig olefination reaction producing only one cycloadduct. NMR analysis of the cycloadduct revealed data matching that observed for the major product **232** from **(2*E*,5*S*)-114**. It could be deduced that the Wittig reaction was highly stereoselective forming only the *E*-alkene with no evidence of the *Z*-alkene.

4.3.2.1 Diels-Alder Adducts from Linear Precursor (2*E*,5*S*)-114

Although four cycloadducts are possible from linear precursor **(2*E*,5*S*)-114**, only two isomeric products were formed. All of the possible products of the IMDA cycloaddition reaction arising from the four possible facial combinations are represented in Figure 4.5. Considering that the double bond geometry is conserved in the cycloadducts, the relative geometry between the C2 and C3 stereocentres from an *E*-dienophile is such that the ethyl ester and the C3 hydrogen have a *cis*-relationship. Similarly, the C10 and C7 stereocentres must have the protons on the same face due to the conformational restraints that the *E*,*E*-diene imparts on the newly formed stereocentres.

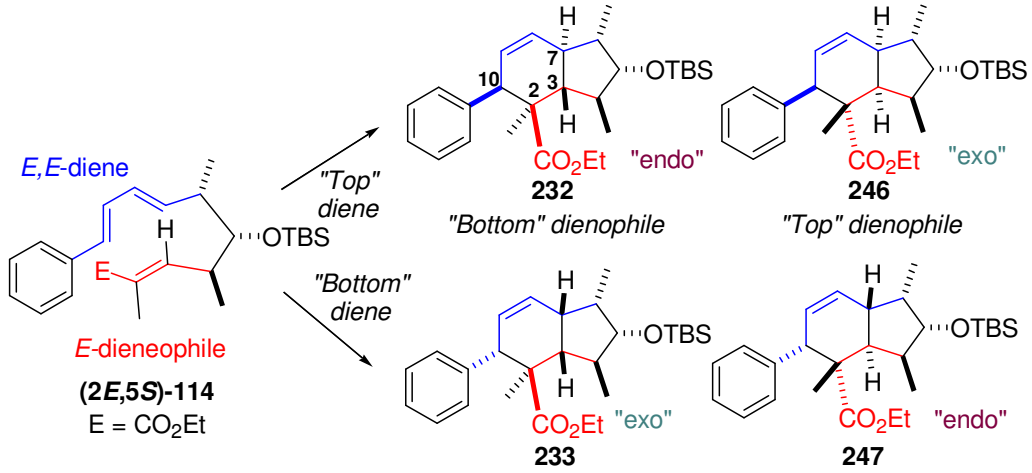


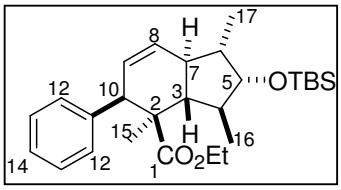
Figure 4.5 Possible cycloadducts available from linear precursor (2*E*,5*S*)-114.

4.3.2.1.1 Assignment of the Major D.-A. Adduct 232

Beginning with the major D.-A. adduct **232**, the ^{1}H-^{1}H ROESY correlations in Table 4.1 were considered in order to define the stereochemistry as illustrated. A stepwise approach to assignment of the stereochemistry at each centre was employed as depicted in Figure 4.6.

Table 4.1 ^{1}H-^{1}H ROESY correlations and stereochemical assignment of cycloadduct 232.

^{1}H No.	^{1}H-^{1}H ROESY [a]
3	H4*, H7*, H16, ArH
4	H3*, H15, H16*
5	H6*, H16
6	H5*, H7*, H17*
7	H3*, H6*, H15, H17
8	H9*, H17
9	H8*, H10*, H17 (wk)
10	H9*, H15, ArH
15	H4, H7, H10
16	H3, H4*, H5
17	H6*, H7, H8, H9 (wk)
ArH	H3, H10



[a] NMR spectrometer (600 MHz, $CDCl_3$).
* Indicates ^{1}H-^{1}H COSY correlations.

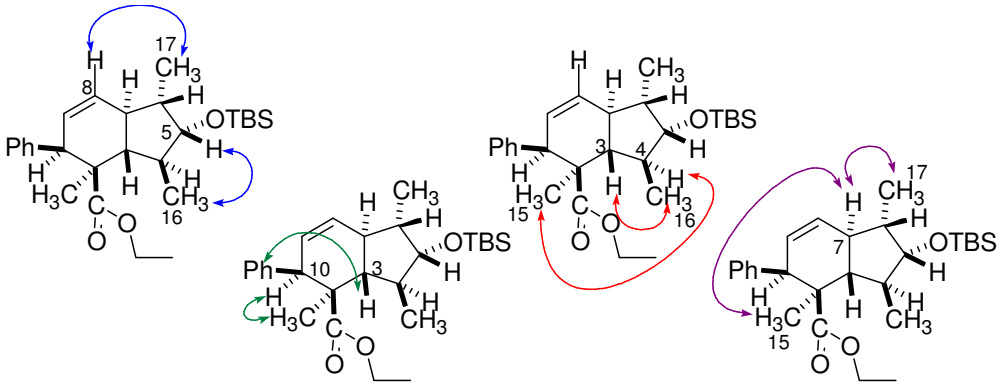


Figure 4.6 Stepwise analysis of the ^{1}H-^{1}H ROESY correlations used in the stereochemical assignment of cycloadduct 232.

The ROESY correlations between the stereocentres of known orientation are represented in blue and confirm the relative relationship of these centres. The C5 proton correlates to the C16 protons which are on the same face and the C17 protons correlate to the planar C8 proton on the double bond. The correlations, in red, between the protons of known stereochemical orientation and the undefined stereocentres allow the absolute stereochemical assignment of these centres. A correlation between the protons at the ring fusion (on C3 and the C16) indicated the C3 configuration shown. Similarly, a correlation between the C4 and C15 protons suggested the absolute stereochemistry at C2, as shown. This relative relationship between the C2 and C3 stereocentres is expected due to conservation of the geometry of the *E*-dienophile in the cycloadduct.

Moving around the ring system, further inferences about the stereochemistry of the unknown centres can be made by considering the correlations in green. The C3 proton correlates to the aromatic protons and the C15 protons correlate to the C10 proton providing supporting evidence for the depicted absolute stereochemistry of C10. Finally, the correlations in purple, between the C7 proton and both the C15 and C17 protons, suggest the absolute stereochemistry at C7 is as shown. The relative relationship between C7 and C10 is predicted due to conservation of the geometry of the *E*,*E*-diene in the cycloadduct. Based on this stereochemical assignment the ring fusion geometry was found to be *trans*, which was supported by the large coupling constant, ^{3}J = 11.2 Hz. As mentioned in Section 4.3.1, a large coupling constant (11-13 Hz) is indicative of a *trans*-ring fusion due to the efficient orbital overlap with a dihedral angle of near 180^{o}.

The low energy conformer for the assigned stereochemistry is shown in Figure 4.7. The relatively planar bicyclic core is evident due to the *trans*-relationship at the ring fusion. As a result of this planarity, all of the observed ^{1}H-^{1}H ROESY correlations were readily accounted for based on the orientation of the substituents attached to the ring (i.e. above or below the plane) and their proximity. The low energy conformer is therefore in good agreement with the spectroscopic data providing strong supporting evidence for the assigned stereochemistry. Correlations to the CH_3 groups of the *tert*-butyldimethylsilyl ether or the CH_2CH_3 of the ester may be expected, however these are not observed due to the high degree of flexibility of the ring appendages evident upon examination of the other predicted conformations.

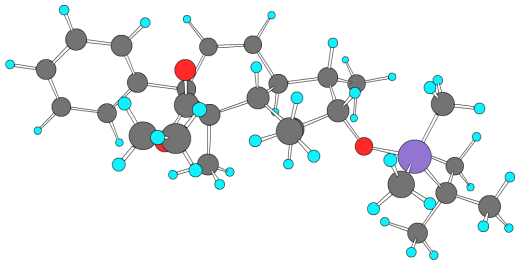
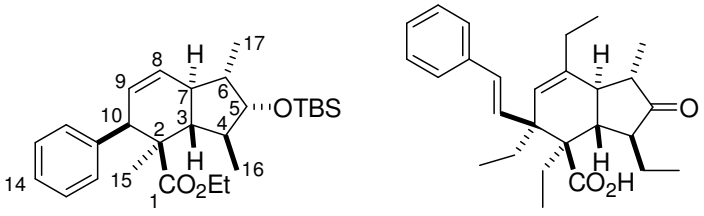


Figure 4.7 The low energy conformer of the major cycloadduct 232.

Comparison of the stereochemistry assigned on the basis of the ^{1}H-^{1}H ROESY NMR data and supported by examination of the low energy conformer with the possible IMDA adducts in Figure 4.5, indicates that the endo adduct **232** was formed through reaction of the top face of the diene with the bottom face of the dienophile. In addition, the stereochemistry of cycloadduct **232** matches the stereochemistry of the corresponding centres in the natural products, as represented in Figure 4.8. This suggests that a thermal IMDA reaction of a linear precursor to the natural products, possessing a C5 OTBS ether, may produce a cycloadduct with the desired stereochemistry as the major product.



spiculoic acid A (**20**)

Figure 4.8 Comparison of the assigned stereochemistry of cycloadduct 232 with the stereochemistry of the natural products.

In order to confirm the stereochemical assignment of major cycloadduct **232**,

cleavage of the silyl ether was performed and the resulting alcohol **237** subjected to a full stereochemical analysis as described for cycloadduct **232**. The alcohol **237** was subsequently oxidised to the ketone **239** and the stereochemical analysis repeated. The ^{1}H-^{1}H ROESY correlations observed for alcohol **237** and ketone **239** are illustrated in Figure 4.9, with the full tables of NMR data available in Appendix 2 and Appendix 3. As the correlations observed replicate those already discussed, and thus confirm the stereochemical assignment of cycloadduct **232**, a full description of the analysis will not be undertaken. The low energy conformers predicted for each of these structures also reveal flat bicyclic cores, analogous to that of cycloadduct **232**. As expected for an adduct with a flat bicyclic core, each of the observed correlations occur across either the top or bottom face, not between faces, further supporting the stereochemical assignment.

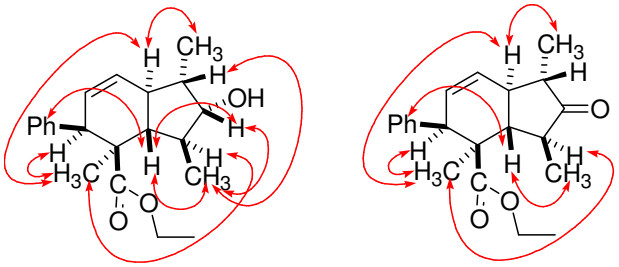


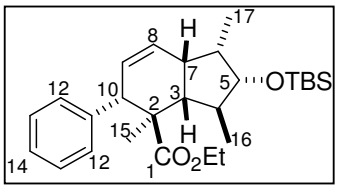
Figure 4.9 The ^{1}H-^{1}H ROESY correlations of alcohol 237 and ketone 239 support the stereochemical assignment of cycloadduct 232.

4.3.2.1.2 Assignment of the Minor D.-A. Adduct 233

Analysis of the minor IMDA cycloadduct **233** was performed in the same manner to that described for the major cycloadduct **232**. The ^{1}H-^{1}H NOESY correlations in Table 4.2 enabled the assignment of the stereochemistry of the cycloadduct **233**, as represented, by working around the bicyclic core exploring the ^{1}H-^{1}H NOESY correlations between nearby groups, as shown in Figure 4.10.

Table 4.2 ^{1}H-^{1}H NOESY correlations and stereochemical assignment of cycloadduct 233.

^{1}H No.	^{1}H-^{1}H NOESY [a]
3	H6 (wk), H7*, H10, H15 (v. wk), H16
4	H5*, H15, H16*
5	H4*, H6*, H16, H17, SiC(CH$_3$)$_2$*
6	H3 (wk), H5*, H15 (v. wk), H16 (wk), H17*
7	H3*, H8*, H9, H10, H16 (wk), H17 (wk)
8	H7*, H9*, H10, H17, ArH
9	H7, H8*, H10*, ArH
10	H3, H7, H8, H9*, H15 (wk), ArH (st)
15	H3 (v. wk), H4, H6 (v. wk), H10 (wk), ArH(st)
16	H3, H4*, H5, H6 (wk)
17	H4, H5, H6*, H7 (wk)
Ar	H8, H9, H10, H15 (st)



[a] NMR spectrometer (600 MHz, C_6D_6).
* Indicates ^{1}H-^{1}H COSY correlations.

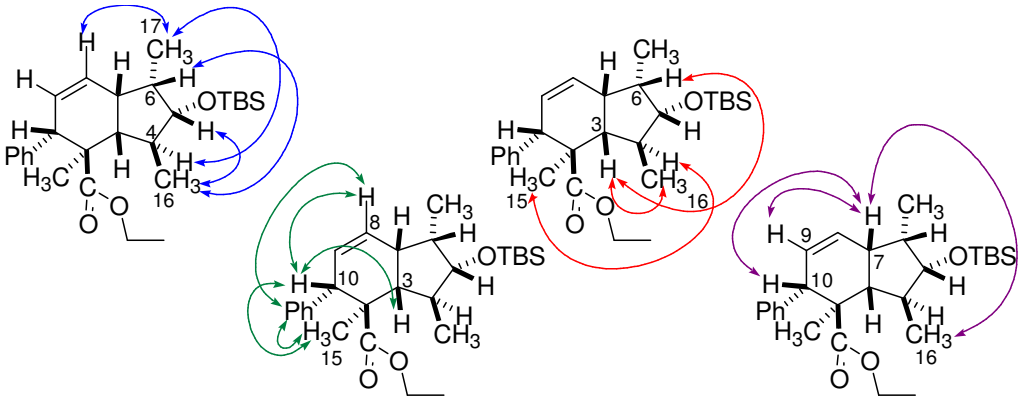


Figure 4.10 Stereochemical assignment of the minor cycloadduct 233, based on a stepwise analysis of the ^{1}H-^{1}H NOESY correlations.

The correlations between the centres of known orientation are again represented in blue, confirming the relative stereochemistry between these centres. Just as for the major isomer **232**, correlations between C3 and both the C16 and C6 (although relatively weak) protons and similar correlations between the C4 and C15 protons, indicated in red, reveal the absolute stereochemistry at C2 and C3 as depicted. Again, the stereochemistry of the *E*-dienophile has been conserved in the product confirming this relative relationship.

The stereochemistry of the C10 carbon centre was identified based on the correlations shown in green. The C15 protons show strong correlations to the aromatic protons and weak correlations to the C10 protons. Based on the relative strength of these correlations the C15 and aromatic protons were determined to lie on the same face. This is further evidenced by a correlation between the C3 and C10 protons. Finally only the C7 centre remained to be assigned, with correlations involving this centre represented in purple. A correlation between the C7 proton and both the C10 and C16 protons indicated that the C10 and C7 protons are on the same face which is predicted due to conservation of the stereochemistry of the *E,E*-diene. The absence of a C15 to C7 correlation, which was evident in the ^{1}H-^{1}H ROESY spectrum from cycloadduct **232**, supports this absolute assignment of C7. In this instance the geometry of the C3 and C7 protons at the ring fusion is *cis* which is substantiated by the magnitude of the coupling constant, ^{3}J = 10.3 Hz, which is slightly smaller in magnitude than that observed for the *trans*-relationship in the major adduct **232** (^{3}J = 11.2 Hz). As discussed in Section 4.3.1, this is expected because orbital overlap in a *syn*coplanar arrangement is slightly less efficient than in

the *anti*periplanar arrangement resulting in a marginally smaller coupling constant.[245]

The stereochemical assignment of this isomer was complicated by a number of weak correlations which appear to be conflicting. These correlations, which are represented in red in Figure 4.11, occur between protons on opposite faces of the bicyclic core and are thus unpredicted.

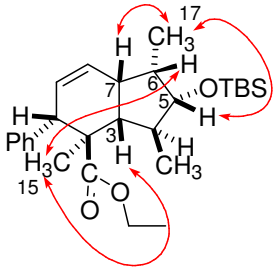


Figure 4.11 The weak correlations observed in cycloadduct 233, appear to conflict with this stereochemical assignment.

By examination of the low energy conformers for the assigned stereochemistry of cycloadduct **233**, attempts can be made to rationalise these observations. All of the predicted conformations for this isomer have the bulky ethyl ester and phenyl groups in a *pseudo* equatorial conformation, with no evidence of the ring-flipped conformation which would place these groups in the more sterically demanding axial orientation. The conformer with the lowest energy, shown in Figure 4.12, reveals the bicyclic core has a concave shape due to the *cis*-ring fusion. This explains many of the unexpected correlations because the orientation of the appendages on the ring are effected by the concave nature of the bicyclic core. For instance the C5 proton was found to correlate to both the C16 and C17 protons which is not expected if the bicyclic core if flat, however the *cis*-ring fusion results in a slight twisting of the 5-membered ring bringing the C5 proton into close proximity to both of these centres, 2.4 Å (C16) and 3.3 Å (C17). Similarly, the C7 proton, which is on the opposite face to the C17 methyl group, shows a correlation to the C17 protons due to the twisting of the 5-membered ring, resulting in an interatomic distance of 3.5 Å between these centres. Two unexpected, albeit very weak, correlations between the C15 protons and both the C3 and C6 protons were also observed. Examination of the low energy conformer however shows that while these protons are expected to be quite remote, the concave shape of bicyclic core causes the C15 methyl to be tucked underneath the ring. This results in interatomic distances of the C15 protons to the C3 and C6 protons of 3.7 Å and 4.3 Å respectively explaining these weak correlations.

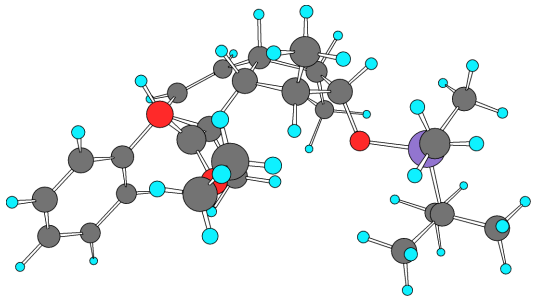


Figure 4.12 The lowest energy conformer of cycloadduct 233 reveals the concave shape of the bicyclic core brought about by the *cis*-ring fusion.

Comparison of the stereochemistry assigned on the basis of the ^{1}H-^{1}H NOESY data and the predicted low energy conformer with the possible IMDA reaction adducts, in Figure 4.5, indicates that the exo adduct **233** was formed through reaction of the bottom face of the diene with the bottom face of the dienophile. As each of the cycloadducts **232** and **233** is formed *via* a different transition state, endo Vs exo, this suggests that the inherent endo/exo selectivity is dominated by the stereocontrol imparted by the C4-C6 stereotriad.

In order to confirm the stereochemical assignment a thorough stereochemical assignment of the corresponding alcohol **238**, achieved by cleavage of the TBS ether, and ketone **240**, the product of the subsequent oxidation, was performed. The NMR data collected is available in Appendix 5 (for alcohol **238**) and Appendix 6 (for ketone **240**). The ^{1}H-^{1}H NOESY correlations observed for alcohol **238** and the ^{1}H-^{1}H ROESY correlations observed for ketone **240**, illustrated in Figure 4.13, support the stereochemical assignment of cycloadduct **233**. A systematic analysis of the stereochemistry of these cycloadduct will not be undertaken here as the observed correlations simply reinforce the correlations and stereochemical assignment previously discussed.

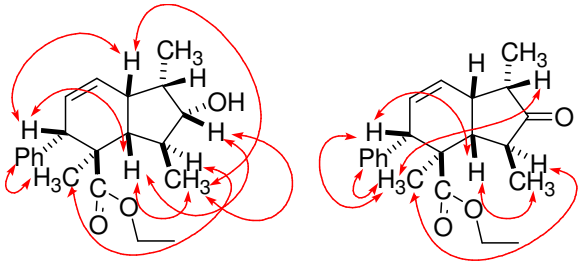


Figure 4.13 The ^{1}H-^{1}H NOESY correlations for alcohol 238 and ^{1}H-^{1}H ROESY correlations for ketone 240 support the stereochemical assignment of cycloadduct 233.

4.3.2.2 Diels-Alder Adducts from Linear Precursor (2*Z*,5*S*)-114

The stereochemistry of the cycloadducts resulting from IMDA cyclisation of linear precursor **(2*Z*,5*S*)-114** were also investigated. Figure 4.14 reveals that once again four different stereoisomeric products are theoretically possible. Conservation of the stereochemistry within the linear precursor **(2*Z*,5*S*)-114** reveals that the *E,E*-diene imparts a *cis*-relationship between the C7 and C10 protons (shown in blue) and the dienophile with the *Z*-geometry imparts a *trans*-relationship between the C2 ethyl ester and the C3 hydrogen (shown in red) in each of the possible cycloadducts.

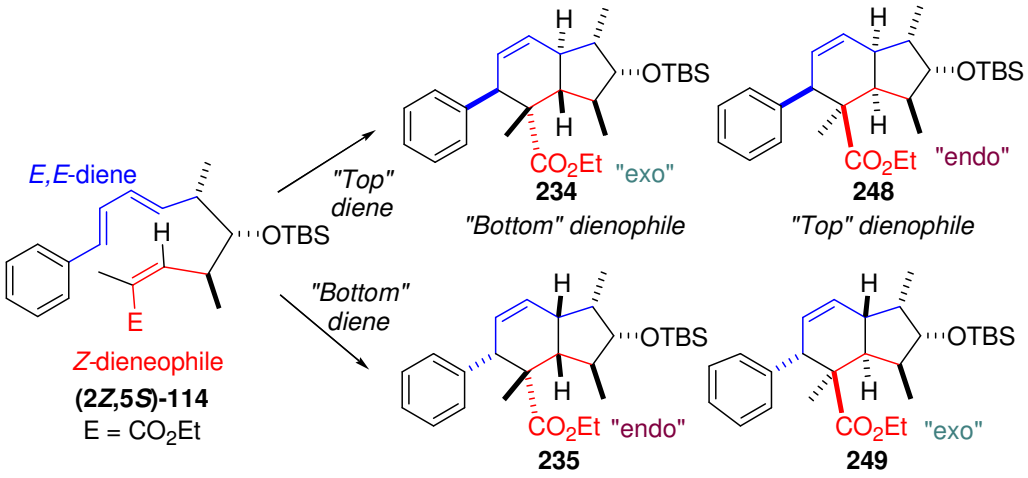


Figure 4.14 The possible cycloadducts available from linear precursor (2*Z*,5*S*)-114.

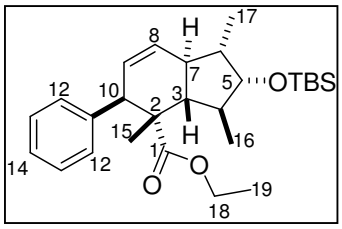
NMR analysis of the IMDA reaction mixture indicated that three of the four possible cycloadducts were produced; **234**, **235** and **236** (undefined stereochemistry) (ratio 85:10:5). Stereochemical assignment was achieved for isomers **234** and **235** (in the case of adduct **235** the stereochemical assignment was performed retrospectively from alcohol **242**). Separation of the three cycloadducts was not achieved following the IMDA cyclisation, however, following silyl ether cleavage the resulting alcohols were separable by column chromatography. A full stereochemical assignment of the major adduct **234** within the mixture was achieved with the silyl ether in place and will be discussed first. A discussion of the stereochemical assignment of the minor (10 % ds) alcohol **242** will follow. The stereochemistry of the other minor (5 % ds) component of the mixture, alcohol **243**, was not achieved due to low purity and quantity of material after repeated attempts at chromatographic separation.

4.3.2.2.1 Assignment of the Major D.-A. Adduct 234

The ^{1}H-^{1}H ROESY correlations in Table 4.3 were used in the stereochemical assignment of cycloadduct **234** as shown.

Table 4.3 ^{1}H-^{1}H ROESY correlations and assigned stereochemistry of cycloadduct 234

^{1}H No.	^{1}H-^{1}H ROESY [a]
3	H7*, H15, H16, ArH
4	H16*
5	H6*, H16
6	H5*, H17*
7	H3*, H17
8	H9*
9	H8*, H10*
10	H9*, ArH
15	H3, ArH
16	H3, H4*, H5
17	H6*, H7, H8
Ar	H3, H10, H15



[a] NMR spectrometer (600 MHz, C_6D_6).
* Indicates ^{1}H-^{1}H COSY correlations.

Sequential examination of the ^{1}H-^{1}H ROESY correlations, as described in Figure 4.15, enabled the absolute stereochemical assignment of each of the centres. The ^{1}H-^{1}H ROESY correlations between centres of known orientation are shown in blue and confirm the relative relationship between these stereocentres.

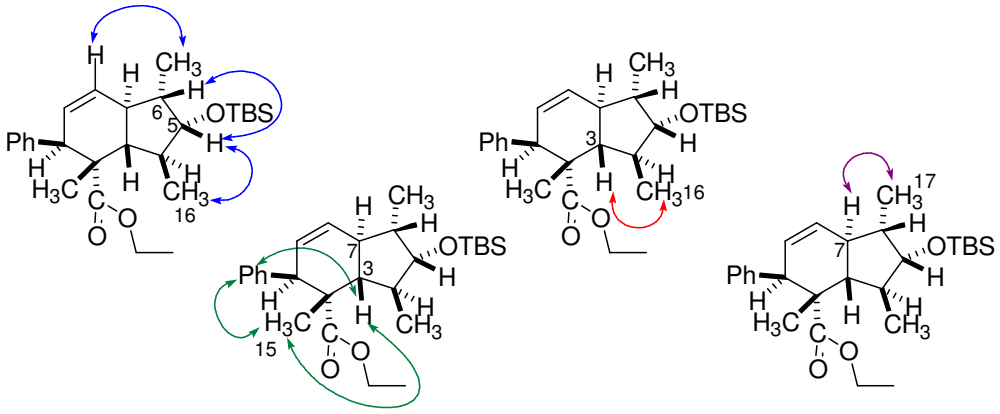


Figure 4.15 A stepwise analysis of the ^{1}H-^{1}H ROESY correlations enabled the stereochemical assignment of cycloadduct 234.

By first examining the correlations involving the stereocentres of known orientation, the stereochemistry at the C2, C3, C7 and C10 stereocentres could be determined by working around the ring. Just as for the isomers from the *E*-dienophile, a strong correlation between the C3 and C16 protons, in red, identified the stereochemistry at C3. The stereochemistry of the C2 and C10 stereocentres were assigned on the basis of the green correlations. The C3 proton correlates to both the C15 protons and the aromatic protons indicating that these three groups lie on the same face of the

bicyclic core. Support for this assignment is provided by an additional correlation between the C15 and aromatic protons. The relative relationship between the C2 and C3 stereocentres is as predicted from a *Z*-dienophile, with the C2 ethyl ester and the C3 hydrogen in a *trans*-relationship, providing reinforcing evidence for this stereochemical assignment.

Complications arose in the assignment of the stereochemical orientation of C7. The C7 proton correlated only to the C8 proton, in blue, and the C17 protons, in purple. Analysis of both of the cycloadducts from the linear precursor **(2*E*,5*S*)-114**, cycloadducts **232** and **233**, revealed that a correlation between the C7 and C17 protons may be observed when these groups lie on the same or opposite faces of the bicyclic core. This indicates that this is not a reliable correlation upon which to base the C7 stereochemical assignment. However, the coupling constant between the C3 and C7 protons, ^{3}J = 11.4 Hz, is indicative of an *anti*periplanar arrangement of the overlapping orbitals, or a *trans*-relationship. Additionally, the absence of correlations between C7 and the C5, C15 or C16 protons, all of which could be reasonably expected if the ring fusion geometry was *cis*, provided further evidence for a *trans*-relationship. The final piece of evidence supporting the stereochemical assignment of C7, was that the C7 and C10 protons lie on the same face, which is predicted from the conservation of the stereochemistry of the *E*,*E*-diene.

Examination of the low energy conformer, represented in Figure 4.16, reveals a relatively planar bicyclic core, similar to that observed for cycloadduct **232** which also possessed a *trans*-ring fusion. The ester group adopts a *pseudo* axial orientation in all of the predicted conformers. As expected, all of the observed correlations occur on either the top or bottom face of the planar bicyclic core and can thus be readily explained based on the predicted low energy conformer, supporting the proposed stereochemical assignment.

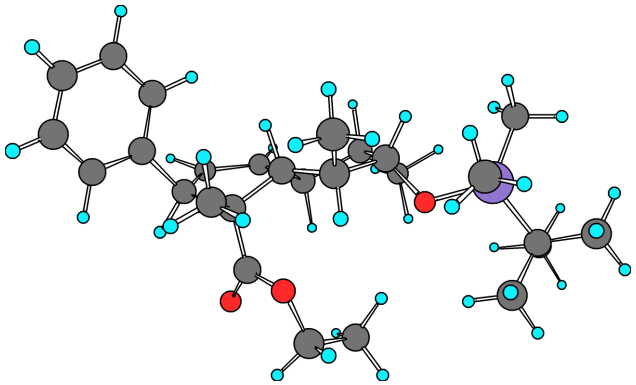


Figure 4.16 The low energy conformer of cycloadduct 234, reveals a planar bicyclic core.

Comparison of the stereochemistry assigned on the basis of the ^{1}H-^{1}H ROESY NMR data with the possible cycloadducts represented in Figure 4.14, indicates that the major isomer is the exo product, formed through reaction of the top face of the diene with the bottom face of the dienophile. Interestingly, the stereochemistry of the major cycloadducts **232** and **234**, from the two linear precursors **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** respectively, differ only at the C2 stereocentre. This indicates that the two cycloaddition reactions are proceeding *via* reaction at the same faces of the addends with the orientation of the dienophile controlling the C2 stereocentre. However, due to the different dienophile geometry cycloadduct **232**, from linear precursor **(2*E*,5*S*)-114**, forms through an endo transition state while cycloadduct **234**, from linear precursor **(2*Z*,5*S*)-114**, forms through an exo transition state. Therefore it can be inferred that any inherent endo/exo selectivity is dominated by the steric effects of the C4-C6 stereocentres.

Again, in order to confirm the stereochemical assignment, the stereochemistry of the corresponding alcohol **241** and ketone **244** was investigated. (NMR data for **241** and **244** can be found in Appendix 8 and Appendix 9). A thorough analysis of the ^{1}H-^{1}H ROESY correlations obtained for alcohol **241** and ketone **244** will not be described however the correlations are represented in Figure 4.17. Most of the observed correlations are identical to those discussed for cycloadduct **234**, indicated in red. Some correlations were not previously observed but provide further evidence for the assigned stereochemistry (such as correlations between C3 and C6 as well as between C4 and C7 shown in green). However, a number of correlations involving the C15 protons, shown in blue, appear to contradict the stereochemical assignment. The C15 protons correlate to both the C4 protons and the C10 protons which are on the opposite face of the planar bicyclic core. In order to explain these unexpected

correlations the low energy conformers predicted for alcohol **241** and ketone **244** were examined. Just as for cycloadduct **234**, the ethyl ester lies in a *pseudo* axial position while the C15 methyl group adopts a *pseudo* equatorial position in the low energy conformation for both alcohol **241** and ketone **244**. As a result of this equatorial orientation and the 6-membered ring having a slightly flattened chair conformation the C15 methyl protons are in relatively close proximity to both the C4 (2.5 Å) and C10 (2.9 Å) protons which lie on the opposite face of the bicyclic core. The low energy conformations of each of these cycloadducts have not been included as the orientation of the bicyclic core is similar to that of the TBS protected cycloadduct represented in Figure 4.16.

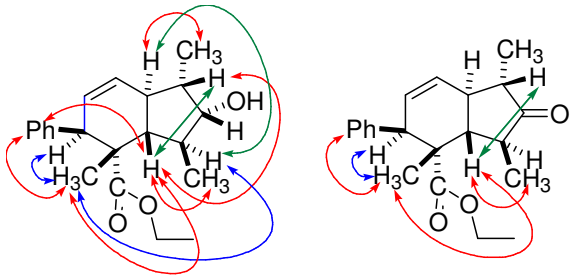


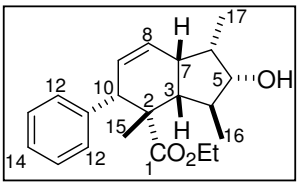
Figure 4.17 ^{1}H-^{1}H ROESY correlations for alcohol 241 and ketone 244, are consistent with the stereochemical assignment cycloadduct 234.

4.3.2.2.2 Assignment of the Minor D.-A. Adduct 235 (retrospectively from alcohol 242)

As mentioned in Section 4.2.2, separation of the IMDA cycloadducts (**234**-**236**) was not achieved, however after cleavage of the TBS ether separation of the alcohols, **241**-**243**, was possible by column chromatography. Therefore the NMR analysis of the minor cycloadducts was achieved on alcohols **242** (10 % ds) and **243** (5 % ds). Unfortunately cycloadduct **243** was not pure enough to undertake a stereochemical assignment however cycloadduct **242** was thoroughly analysed. Examination of the ^{1}H-^{1}H NOESY correlations described in Table 4.4, enabled the stereochemical assignment of alcohol **242** to be made as shown.

Table 4.4 ^{1}H-^{1}H NOESY correlations and subsequent stereochemical assignment of alcohol 242.

^{1}H No.	^{1}H-^{1}H NOESY [a]
3	H4*, H6 (wk), H7*, H15, H16, ArH
4	H3*, H15 (wk), H16*
5	H4 (wk),* H6*, H16, H17 (wk), OH
6	H3 (wk), H5*, H7*, H16 (wk), H17*
7	H3*, H6*, H8*, H9, H10 (wk), H17 (wk)
8	H7*, H9*, H10, H17 (wk)
9	H7, H8*, H10*
10	H7 (wk), H8, H9*, H15, ArH
15	H3, H4 (wk), H10, ArH
16	H3, H4*, H5, H6 (wk)
17	H5 (wk), H6*, H7 (wk), H8
Ar	H3, H10, H15



[a] NMR spectrometer (600 MHz, $CDCl_3$).
* Indicates ^{1}H-^{1}H COSY correlations.

The ^{1}H-^{1}H NOESY correlations were examined, as illustrated in Figure 4.18, starting with those involving the centres of known orientation, in order to deduce the stereochemistry of alcohol **242**. The correlations in blue are between the centres of known orientation and confirm the relative stereochemical relationship between these centres. The weak correlation between the C4 and C5 protons was dominated by a stronger correlation between the C16 and C5 protons.

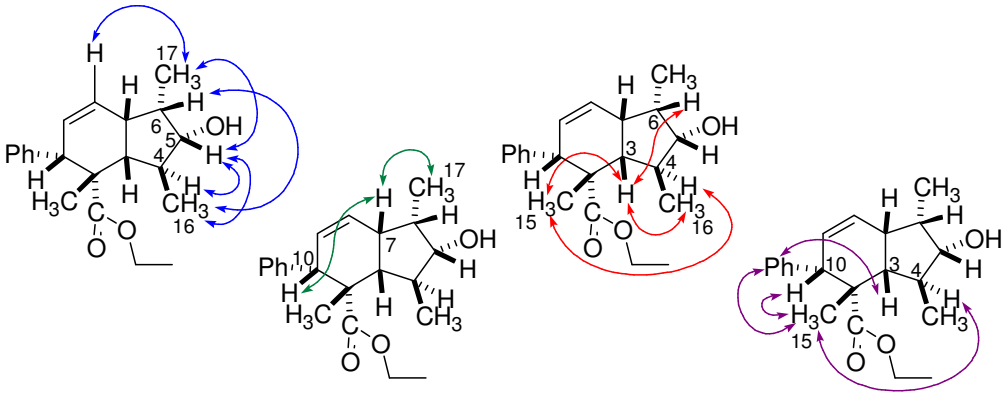


Figure 4.18 Stereochemical assignment of alcohol 242 was achieved by stepwise analysis of the ^{1}H-^{1}H NOESY correlations.

The correlations in red, between the centres of known orientation and the C3 and C15 protons, enabled the stereochemistry at C2 and C3 to be determined. Correlations between the C3 protons and the protons on C6 and C16 indicated, once again, that these groups exist on the same face of the bicyclic core. Assignment of the C2 stereocentre was complicated by the apparently contradictory correlations, in red, between the C4 and C15 protons and between the C3 and C15 protons. Similar, apparently contradictory correlations were observed in cycloadduct **233**, which had a *cis*-ring fusion. This may suggest that alcohol **342** has a *cis*-ring fusion and the slight concave nature of the bicyclic core in this orientation is responsible for placing the

C4 and C15 protons within close proximity. The weak correlation between C4 and C15 was not considered to be highly significant in the stereochemical assignment in light of the strength of the correlation between the C3 and C15 protons which were thus assigned to the same face of the bicyclic core. The relative orientation of the C2 and C3 centres, as shown, satisfies the geometric constraints imparted by the *Z*-dienophile; the C2 ethyl ester and the C3 hydrogen in a *trans*-relationship, suggesting that this assignment of C2 is correct.

Travelling around the ring system, ^{1}H-^{1}H NOESY correlations involving the C7 and C10 centres were examined. The stereochemical restraints imparted by the *E*,*E*-diene are obvious by the correlation, in green, between the C7 and C10 protons, which reveals that these groups are on the same face. Unfortunately the correlation between the C7 and C17 protons, in green, is not a useful indicator of the absolute stereochemistry at C7 because this correlation has been observed when these groups are on the same and opposite faces of the ring. The correlations in purple were examined in an attempt to determine the relative stereochemical arrangement between the C2 and C3 stereocentres and the C7-C10 fragment. Once again, apparently conflicting correlations complicated the analysis. Correlations of the C15 protons to both the C10 and aromatic protons, as well as a correlation between the C3 and aromatic protons were unexpected. However, by considering the magnitude of the coupling constant between the C3 and C7 protons, ^{3}J = 9.3 Hz, a *cis*-relationship (or *syn*coplanar orbital overlap) was predicted, indicating the absolute stereochemistry is as represented in Figure 4.18.

In an effort to explain the seemingly conflicting correlations, in Figure 4.18 in purple, an examination of the predicted conformations of alcohol **242** was performed. Analysis reveals two distinctly different groups of conformers arising from the two ring flipped versions of the *pseudo* chair conformation. The lowest energy conformers from each group reveal that the structure is lower in energy when the ethyl ester occupies the *pseudo* axial position, (Figure 4.19a, -122.2 kcal/mol), compared to the *pseudo* equatorial position (Figure 4.19b, -117.6 kcal/mol). With the ester group in the *pseudo* axial position (Figure 4.19a) the C15 methyl occupies a *pseudo* equatorial position and is thus in close proximity (2.6 Å) to the aromatic ring which adopts a rotamer where it lies perpendicular to the 6-membered ring, accounting for the unexpected correlation between the C15 and aromatic protons (in

purple). Similarly, the perpendicular orientation of the aromatic protons explains why a weak correlation over a distance of 4.4 Å is observed to the C3 protons. Finally, the unexpected correlation between the C4 and C15 protons (in red) which are on opposite faces of the bicycle, can also be explained by examining the low energy conformer (Figure 4.19a). The *cis*-ring fusion produces a concave shape within the bicyclic core, causing the C4 centre to twist slightly bringing the C4 proton to within close proximity (2.2 Å) of the protons on the equatorially oriented C15 methyl. In addition, with the introduction of a bend in the bicyclic core, the C5 centre tucks in slightly enabling both the C16 and C17 protons to correlate to the C5 proton (a correlation represented in blue in Figure 4.18), with interatomic distances of 2.4 Å and 3.1 Å respectively, explaining these observed correlations.

a. *pseudo* axial ethyl ester

b. *pseudo* equatorial ethyl ester

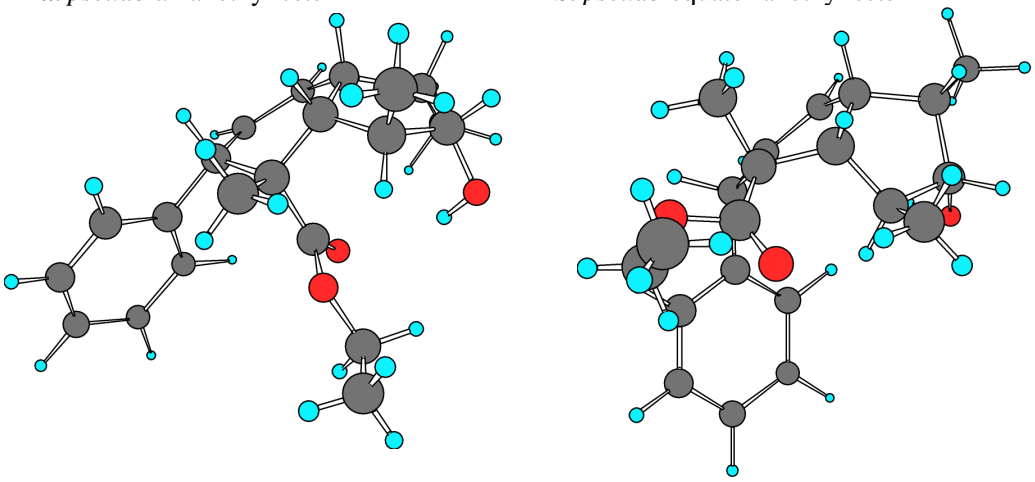


Figure 4.19 The predicted low energy conformers, in both ring flipped orientations, for alcohol 242.

Comparison of the assigned stereochemistry of alcohol **242** with the possible IMDA reaction cycloadducts in Figure 4.14 indicates that the endo product formed through reaction of the bottom face of the diene with the bottom face of the dienophile. Just as for the major adducts, the minor adducts from both the **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114** linear precursors are formed by reaction of the same two faces of the addends, producing stereoisomers differing only at the C2 stereocentre due to the geometry of the dienophile. This difference in the geometry of the dienophile means that the minor isomer **233**, from linear precursor **(2*E*,5*S*)-114**, is generated through an exo transition state while the minor isomer **235**, from linear precursor **(2*Z*,5*S*)-114**, is formed through an endo transition state. This again reinforces the conclusion that any endo/exo selectivity inherent in the system is dominated by the stereochemistry of

the C4-C6 stereotriad, which appears to control the stereochemical outcome regardless of the dienophile geometry.

Confirmation of the stereochemical assignment of alcohol **242**, was achieved by oxidation of the C5 alcohol and re-examination of the stereochemistry. The table of NMR data for ketone **245** is available in Appendix 11. The ^{1}H-^{1}H NOESY correlations confirming the stereochemical assignment of alcohol **242** are shown in red in Figure 4.20. A weak correlation shown in blue, between the C3 and C17 protons, was not seen in alcohol **242** and appears to be quite unexpected. Examination of the predicted low energy conformers again reveals two distinctly different ring flipped conformers, analogous to those in Figure 4.19. These conformers have not been represented due to their conformational similarities with the alcohol **242**. With the ethyl ester in the *pseudo* axial position the conformer is once again slightly lower in energy, -101.9 kcal/mol, than with the ethyl ester in the *pseudo* equatorial orientation, -99.2 kcal/mol. The interatomic distance between the C3 and C17 protons for the more stable conformer, is 4.5 Å, and for the ring flipped counterpart, is 4.8 Å. Thus a weak correlation between the C3 and C17 protons may be predicted based on these interatomic distances.

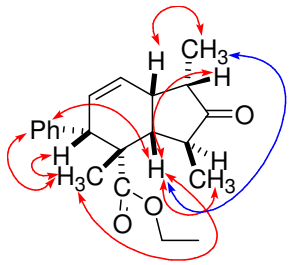


Figure 4.20 The ^{1}H-^{1}H NOESY correlations identified for ketone 245 are consistent with the stereochemical assignment of alcohol 242.

4.3.3 The Affect of the Dienophile Geometry on the Stereochemical Outcome of the IMDA Reaction

The IMDA cycloaddition reaction was performed on two different linear precursors, **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114**, in order to examine the affect of the dienophile geometry on the stereochemical outcome. Figure 4.21 represents a summary of the stereochemical outcome of the IMDA from each of the precursors with the 5*S* stereochemistry, indicating which faces of the diene and dienophiles reacted and the transition state geometry (endo or exo). The major adducts from both linear precursors formed through reaction of the top face of the diene with the bottom face

of the dienophile. However, due to the difference in dienophile geometry, *E* Vs *Z*, the cycloaddition reactions proceeded through different transition states, endo and exo respectively, to form the major cycloadducts, **232** and **234**, which differ only at the C2 stereocentre. Similarly both of the minor adducts, **233** and **235**, formed through reaction of the bottom face of the diene with the bottom face of the dienophile. The transition states through which the cycloaddition reaction proceeded to form the minor adducts from the *E* and *Z* stereoisomers were exo and endo respectively. This implies that the inherent endo/exo selectivity has little control over the transition state geometry and thus the stereochemical outcome of the IMDA. It appears that the C4-C6 stereotriad dictates the stereoselectivity of the IMDA reaction.

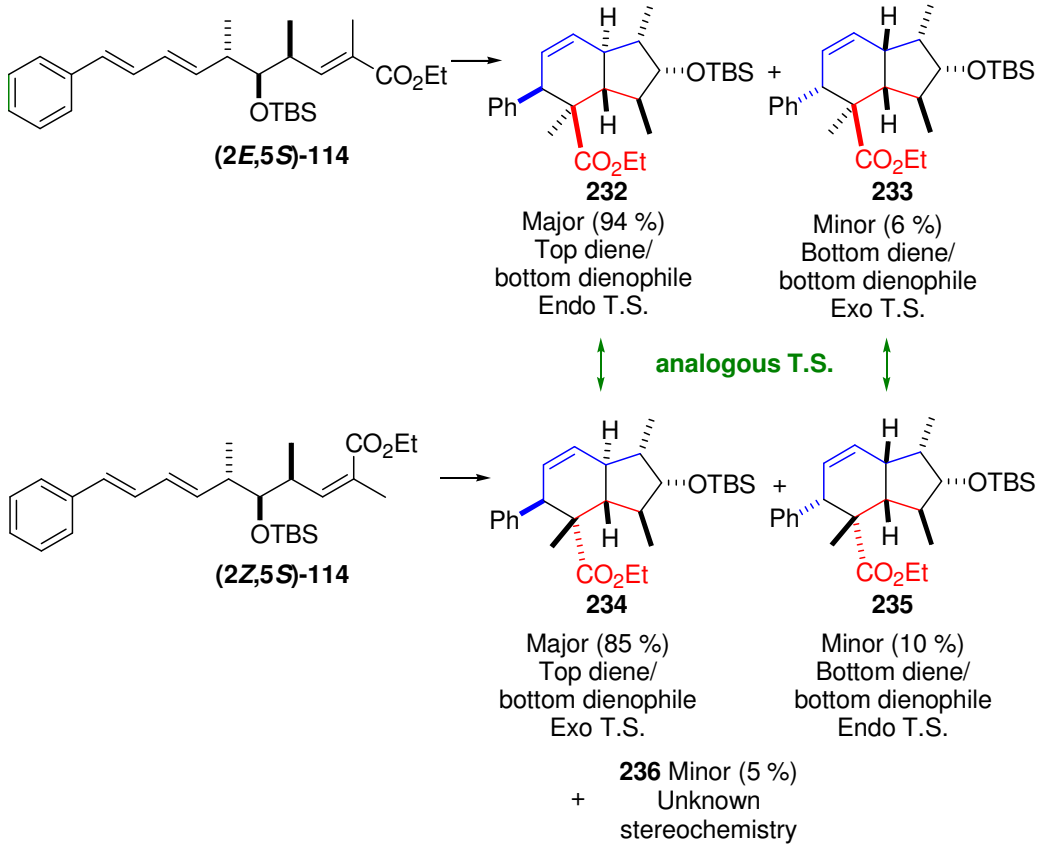


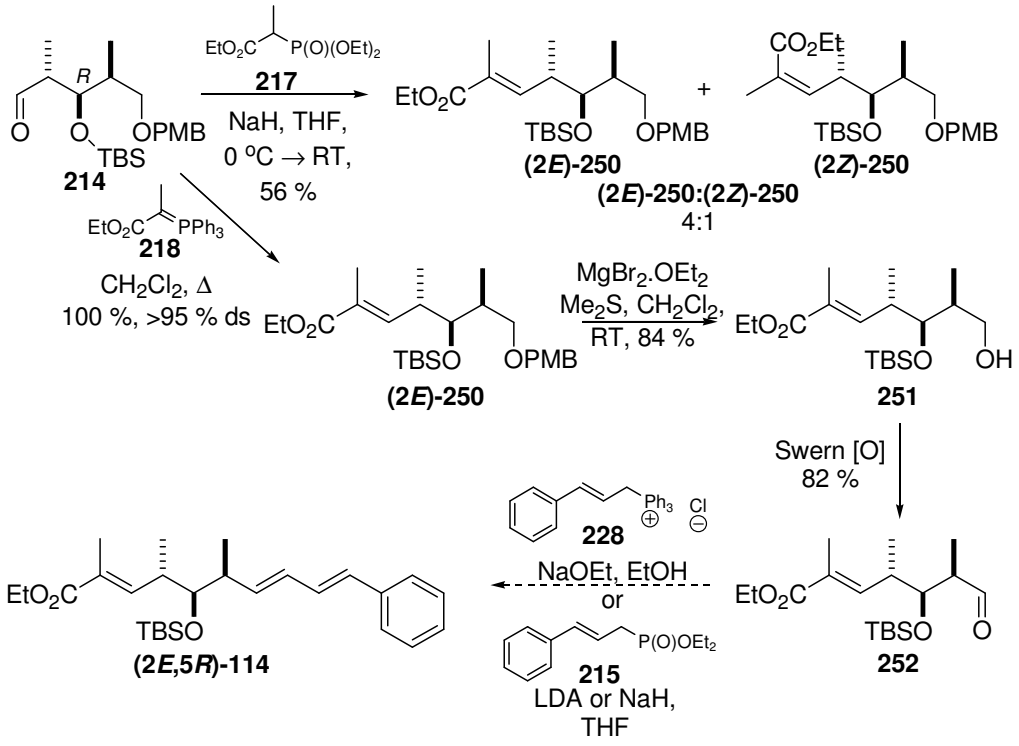
Figure 4.21 Comparison of the stereochemical outcome of the IMDA reaction of linear precursors (2*E*,5*S*)-114 and (2*Z*,5*S*)-114.

4.4 Synthesis of Model System Two

4.4.1 Synthesis of Aldehyde 253

As mentioned in Section 4.1, it was envisaged that linear triene **114** could be synthesised with the opposite stereochemistry at C5 by first installing the dienophile component *via* a Wittig[31] or H.W.E.[237] olefination with aldehyde **214** and then

installing the diene component. Scheme 4.10 outlines the synthetic steps towards this goal, beginning with a Wittig coupling[31] of ylide **218** with aldehyde **214** producing ester **(2*E*)-250** in high yield (100 %) with high stereoselectivity (> 95 %, no detectable *Z*-isomer). The ^{1}H NMR spectrum of ester **(2*E*)-250** indicated the desired product had been formed due to the presence of a downfield doublet of doublets at 6.78 ppm assigned to the vinyl proton. This vinyl resonance is expected to be downfield due to the deshielding effects of being in conjugation with the ester functionality.[245] The equivalent H.W.E. reaction[237] was less selective (4:1, *E*:*Z*) and lower yielding (56 %). Separation of the **(2*E*)-250** and **(2*Z*)-250** isomers by column chromatography enabled characterisation of the minor **(2*Z*)-250** isomer. The most significant difference between the ^{1}H NMR spectra of the **(2*E*)-250** and **(2*Z*)-250** isomers was the chemical shift of the vinyl protons, 6.78 ppm and 5.94 ppm respectively. This is consistent with predictions based on calculated chemical shift values.[245] The vinyl proton in **(2*E*)-250** is therefore much more deshielded than the vinyl proton in **(2*Z*)-250**. This is possibly due to more significant conjugation to the ester carbonyl in **(2*E*)-250** resulting in the vinyl proton experiencing a substantial withdrawal of electron density.



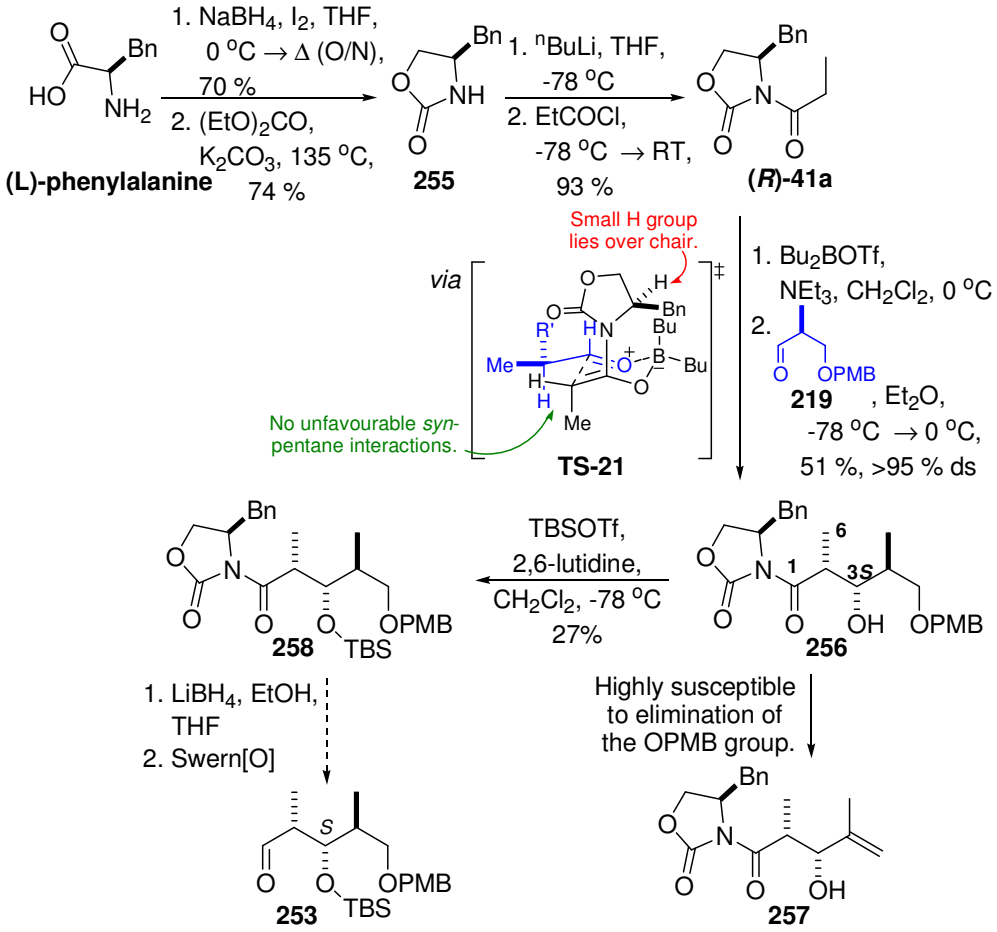
Scheme 4.10 Attempted extension of the methodology of Model System One to the synthesis of linear precursor (2*E*,5*R*)-114.

Liberation of the primary hydroxyl group using DDQ[246] did provide some product

(44 %) in this instance, however the yield was unsatisfactory. The method of Iwasaki and co-workers (Me_2S, $MgBr_2.OEt_2$, CH_2Cl_2) was more successful producing the primary alcohol **251** in 76 % yield.[248] Reproducibility was an issue that was not thoroughly investigated, due to complications in the installation of the diene which saw abandonment of this approach. Subsequent oxidation of primary alcohol **251** under Swern conditions gave aldehyde **252** in good yield (82 %).[205] Several attempts to generate triene **(2*E*,5*R*)-114** *via* Wittig olefinations failed.[236] Either no reaction occurred, even after several days under mild conditions at room temperature, or decomposition of aldehyde **252** occurred if heat was applied to promote the reaction. Modifications to the conditions such as pre-formation of the ylide before addition of the aldehyde were to no avail. Employing phosphonate **215** in a H.W.E. reaction resulted in decomposition of aldehyde **252** immediately with the major decomposition product resulting from cleavage of the silyl ether. A variety of modifications to the procedure such as pre-formation of the anion, using both NaH[237] and LDA,[238] before addition of the aldehyde and employing a variety of reaction temperatures, such as -78 ^{o}C, 0 ^{o}C and room temperature, failed to promote the reaction.

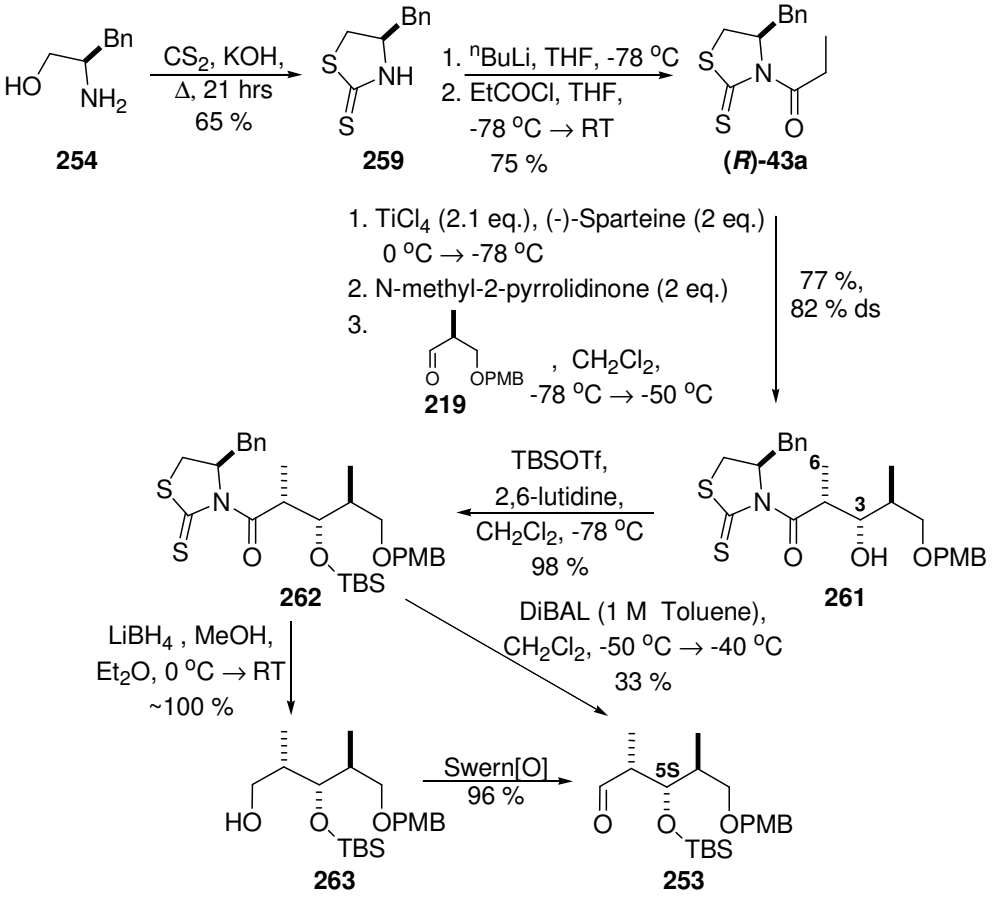
Still striving to achieve the alternative stereochemistry at C5, synthetic efforts shifted to synthesis of an alternative aldehyde **253**. This aldehyde possesses the opposite stereochemistry at C5 to aldehyde **214** and is represented in Scheme 4.11. Evans and co-workers have extensively employed chiral N-acyloxazolidinone derivatives, such as **(*R*)-41a**, in stereoselective *syn*-aldol couplings, introduced in Section 1.3.1.3.2.[83] N-acylated oxazolidinone **(*R*)-41a** was synthesised following literature procedures in a 3 step sequence from (L)-phenylalanine; reduction to alcohol **254** with $NaBH_4$ and I_2,[254] conversion to the oxazolidinone **255**[81] and N-acylation.[83] The *Z*-(O)-enolate of N-acylated oxazolidinone **(*R*)-41a** was generated from Bu_2BOTf and NEt_3 and subsequently coupled to aldehyde **219** to give alcohol **256** (51 %, >95 % ds).[83] The stereochemical assignment of alcohol **256** was based on literature precedent.[83] Excellent diastereoselectivity was achieved for the double stereodifferentiating aldol reaction because both the facial preferences of the enolate and the aldehyde were satisfied in the transition state (**TS-21**). Anti-Felkin[57] addition to aldehyde **219** is favoured from a Z-(O)-enolate due to unfavourable *syn*-pentane interactions experienced in the alternative transition state arising from Felkin addition, as discussed in Section 1.3.1.1. The enolate from ketone **(*R*)-41a** preferentially reacts

from the opposite face to the Bn group placing the smallest H group over the chair in **TS-21**. The low yield for the aldol reaction can be attributed to elimination of the PMB ether, producing alkene **257**, which can be suppressed by maintaining the temperature between -78 ^{o}C and -50 ^{o}C. Unfortunately the susceptibility of the PMB ether to elimination proved to be a significant issue, inhibiting attempts to protect the secondary alcohol as the TBS ether **258**.[208] In fact, alcohol **256** was so sensitive to elimination that even when stored in the refrigerator it survives for only a couple of days. Synthesis of alcohol **256** was confirmed by analysis of the ^{1}H NMR spectrum which revealed a doublet of doublets at 3.9 ppm due to the C3 C*H*OH and a doublet at 1.29 ppm due to the C6 CH_3. Analysis of the ^{13}C NMR spectrum provided further confirmation as six resonances due to carbons attached to electronegative atoms (eg. oxygen or nitrogen) were evident as expected for alcohol **256**. Elimination of the PMB ether was immediately evident in the ^{1}H NMR spectrum. Aside from the obvious absence of the aromatic, benzylic and methoxy resonances, the vinyl proton signals, broad singlets at 4.9 and 4.8 ppm, were indicative of a terminal alkene. In addition, a singlet resonance due to the vinyl methyl C6 was observed at 1.75 ppm. Comparison of these results with previous work within the group[255] indicated that the *syn*, *anti*-adduct **256** was significantly more susceptible to elimination than the corresponding *syn*, *syn*-adduct. The *syn*, *syn*-adduct can be achieved in high yields (83 %) by simply controlling the temperature of the aldol reaction between -78 ^{o}C and -50 ^{o}C and the generated alcohol can be converted to the silyl ether in excellent yields (97 %).[255] An alternative aldol strategy was therefore sought to combat the problems encountered by the elimination of the OPMB ether of alcohol **256**.



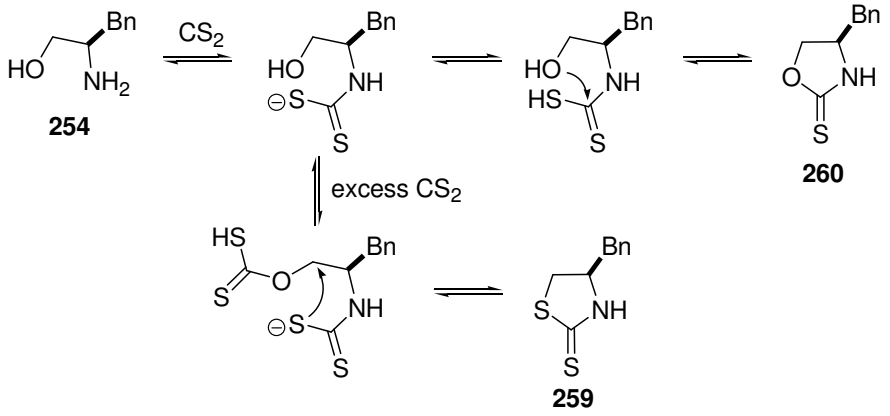
Scheme 4.11 Attempted synthesis of aldehyde 253 using an oxazolidinone aldol strategy.

An obvious alternative to N-acyloxazolidinone **(*R*)-41a** are the structurally related N-acyloxazolidinethiones or the N-acylthiazolidinethiones.[86] These reagents were only discovered in the last 20-25 years and have been employed less exhaustively in the literature, however they offer several benefits over the N-acyloxazolidinones. Preparation of N-acyloxazolidinethione and N-acylthiazolidinethione is synthetically much simpler than synthesis of the N-acyloxazolidinones.[81,256] Both *syn*- (Evans and non-Evans)[257] and *anti*-aldol products are available by simply employing different conditions for the enolisation. The N-acylthiazolidinethione **(*R*)-43a**, Scheme 4.12, was selected for this synthesis as it offered flexibility due to the ability to manipulate the stereochemistry of the aldol adduct through control of reaction conditions. In addition, cleavage of the auxiliary to produce the aldehyde directly, rather than going *via* the alcohol, can be achieved through controlled DiBAL reduction.[258]



Scheme 4.12 Synthesis of aldehyde 253 using a thiazolidinethione aldol strategy.

Scheme 4.12 shows the revised strategy to generate aldehyde **253** with the *S* configuration at C5. Synthesis of the N-acylthiazolidinethione **(*R*)-43a** begins with reduction of (L)-phenylalanine with $NaBH_4$ and I_2,[254] in an identical manner to the oxazolidinone synthesis, (Scheme 4.11, 77 %) and the resulting β-aminoalcohol **254** is converted into the thiazolidinethione **259** under forcing conditions (CS_2 (5 eq.), KOH, Δ, 21 hrs, 65 %).[256] If only one equivalent of CS_2 is used, preferential reaction with the NH_2 group occurs and the free hydroxyl nucleophile is available to undergo a ring closing reaction to give oxazolidinethione **260**, as described in Scheme 4.13. However if an excess of CS_2 is employed, both the NH_2 and OH groups react with CS_2 and ring closure occurs to give thiazolidinethione **259**.



Scheme 4.13 Mechanism of formation of the N-acyloxazolidinethiones (260) and N-acylthiazolidinethiones (259).

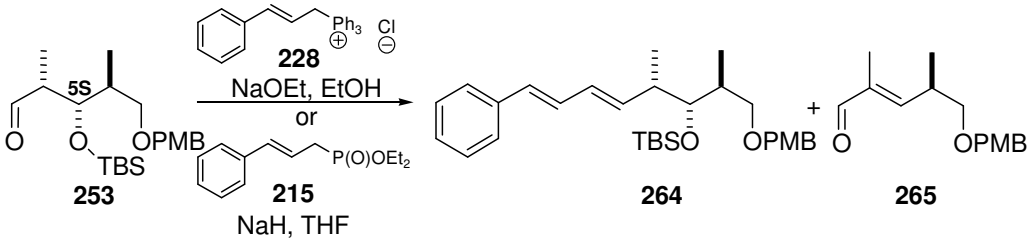
The thiazolidinethione is then N-acylated under standard conditions with propionyl chloride to give N-acylthiazolidinethione **(*R*)-43a** (75 %).[257] Generation of the titanium *Z*-(O)-enolate of N-acylthiazolidinethione using (-)-sparteine (2 eq.) or TMEDA (2 eq.) and subsequent reaction with aldehyde **219** gives the aldol product **261** in moderate yield (40 %) and stereoselectivity.[259] However, if N-methyl-2-pyrrolidinone (2 eq.) is used in conjunction with (-)-sparteine (2 eq.) less base is required (although in an effort to improve the yield further excess equivalents of all reagents were employed) and yields (77 %) and diastereoselectivity (82 %) are greatly improved.[257] The major, "Evans" *syn*-isomer **261** (assigned based on literature precedent)[86] was able to be separated from the two minor isomers (stereochemistry not assigned). The *syn*, *anti*-adduct **261** was formed in good diastereoselectivity because the facial preferences of both the enolate and the aldehyde components are satisfied, as described for the oxazolidinone strategy (**TS-21** in Scheme 4.11). The ^{1}H NMR spectrum of the major isomer confirmed that the alcohol **261** had been synthesised based on the doublet of doublets at 3.97 ppm due to the C3 C*H*OH proton and the doublet at 1.00 ppm due to the C6 CH_3.

TBS protection of alcohol **261** gave silyl ether **262** in an effectively quantitative yield without elimination of the PMB ether.[208] Reductive removal of the auxiliary with DiBAL gave aldehyde **253**, however the yield was low (33 %) due to the affinity of the product to be reduced further to the alcohol **263**.[258] It was ultimately decided that to improve efficiency the auxiliary would be cleaved directly to the alcohol **263** using $LiBH_4$[260] and subsequently oxidised to aldehyde **253** under Swern conditions (96 %, over 2 steps).[205] With the aldehyde **253**, possessing 5*S* stereochemistry, in

hand the next step was to install the diene and dienophile components *via* the two directional Wittig/H.W.E. approach employed in Model System One.

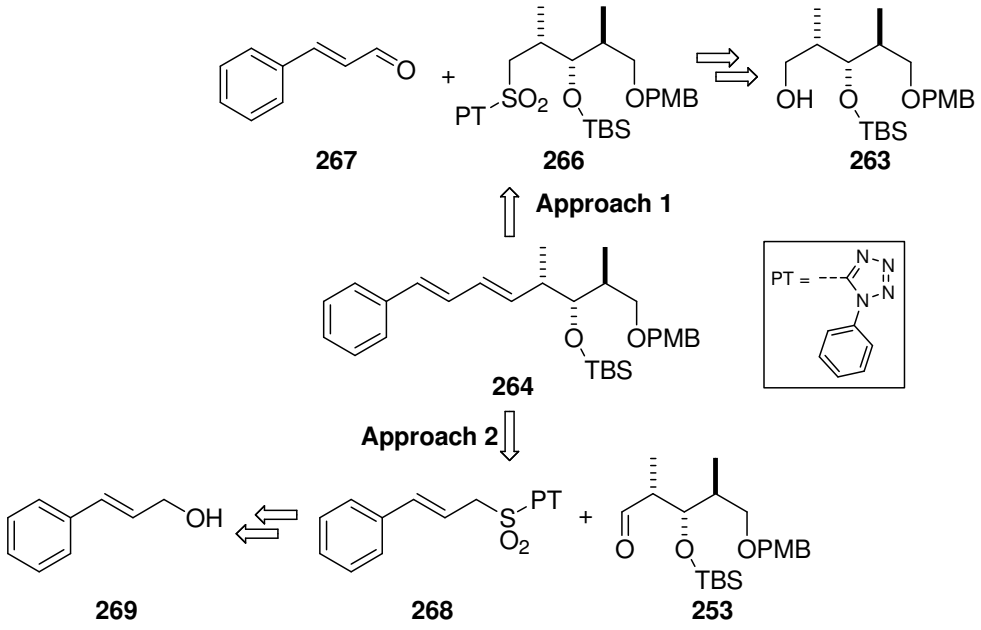
4.4.2 Synthesis of the Linear Precursor (3*E*,5*R*)-114 and Subsequent Cyclisation

Installation of the diene and dienophile functionalities within the linear precursor possessing the 5*R* stereochemistry was proposed in a method analogous to that employed in Model System One. Unfortunately both Wittig[236] and H.W.E.[133] couplings of the ylide derived from salt **228** or phosphonate **215** with aldehyde **253**, to give diene **264,** were unacceptably low yielding, due to the susceptibility of the aldehyde to undergo elimination of the TBS ether, to give conjugated aldehyde **265**. (Scheme 4.14)



Scheme 4.14 Attempted construction of diene 264 *via* Wittig and H.W.E. olefination reactions.

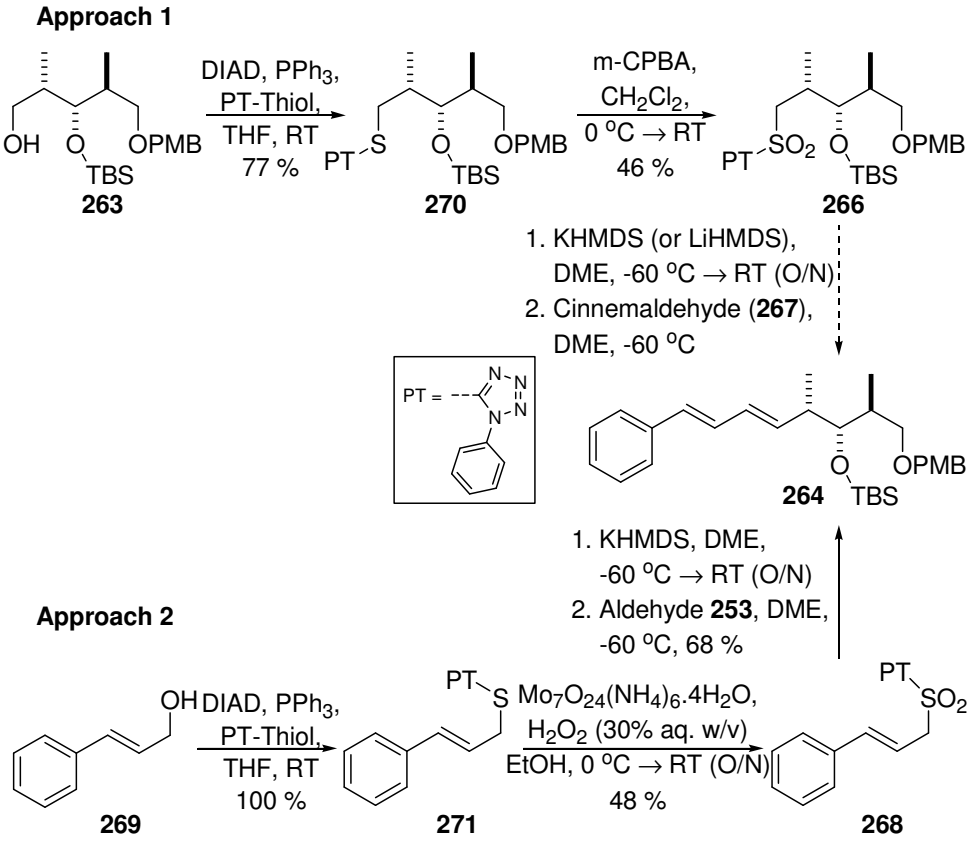
Due to the sensitivity of the TBS ether to elimination, an alternative approach to installing the diene fragment was sought. The "modified" Julia olefination reaction was an obvious option as minimal changes to the designed strategy were necessary and two different approaches were possible, outlined in Scheme 4.15. The primary alcohol of the central chiral fragment, alcohol **263**, could be converted in a 2 step sequence to the sulfone **266** and coupled to commercially available *E*-cinnamaldehyde (**267**). Alternatively aldehyde **253** could be coupled to the sufone **268,** achieved in two steps from *E*-cinnamylalcohol (**269**). Initially 1-phenyl-1H-tetrazol-5-yl (PT) sulfones were considered as they exhibit high *E*-selectivity and stability and are less susceptible to self-condensation eliminating the need for Barbier conditions (refer to Section 1.3.4) which can be problematic with sensitive aldehydes.



Scheme 4.15 Retrosynthetic approaches to the installing the diene component *via* a "modified" Julia olefination reaction.

Considering the first approach, outlined in Scheme 4.16, alcohol **263** was converted in good yield (77 %) to the PT sulfide **270** *via* a Mitsunobu reaction under standard conditions; addition of 1-phenyl-1H-tetrazole-5-thiol (2 eq.), PPh_3 (1.5 eq.) and DIAD (1.8 eq.) to a solution of the alcohol **263** in THF at RT and stirring for 5 minutes.[261,116] Oxidation of sulfide **270** to sulfone **266** was achieved by stirring with *m*-CPBA for 2 days producing sulfone **266** in an unsatisfactory yield (46 %). It was unclear from the ^{1}H and ^{13}C NMR spectra whether the sulfone **266** had formed as no significant changes in chemical shift were noted. The most obvious difference was a shift in a CH multiplet from 2.1 ppm to 2.6 ppm. Due to the potential sensitivity of the sulfone the "modified" Julia olefination between sulfone **266** and cinnamaldehyde (**267**) was immediately attempted rather than waiting for confirmation of sulfone synthesis by mass spectral analysis. The standard conditions for the "modified" Julia olefination were employed, which involved pre-formation of the deep red anion of sulfone **266** by addition of KHMDS to a solution of the sulfone in DME at -60 ^{o}C and stirring for 1 hr.[116] Addition of the aldehyde is performed at -60 ^{o}C and the resulting solution stirred for 30 minutes before warming to room temperature and stirring overnight. The reaction progress could be monitored by TLC to determine the reaction endpoint. In all three attempts, using various equivalents of the reagents and LiHMDS as an alternative base, either no reaction was observed or the yield was extremely poor. While formation of some product

suggests that the sulfone **266** was the product of the oxidation of sulfide **270**, the low yield achieved for both the sulfide oxidation and the subsequent "modified" Julia olefination reaction lead to abandonment of this approach in favour of Approach Two. While using an excess of chiral sulfone **266** may have improved yields the expense associated with its production made this option unattractive.

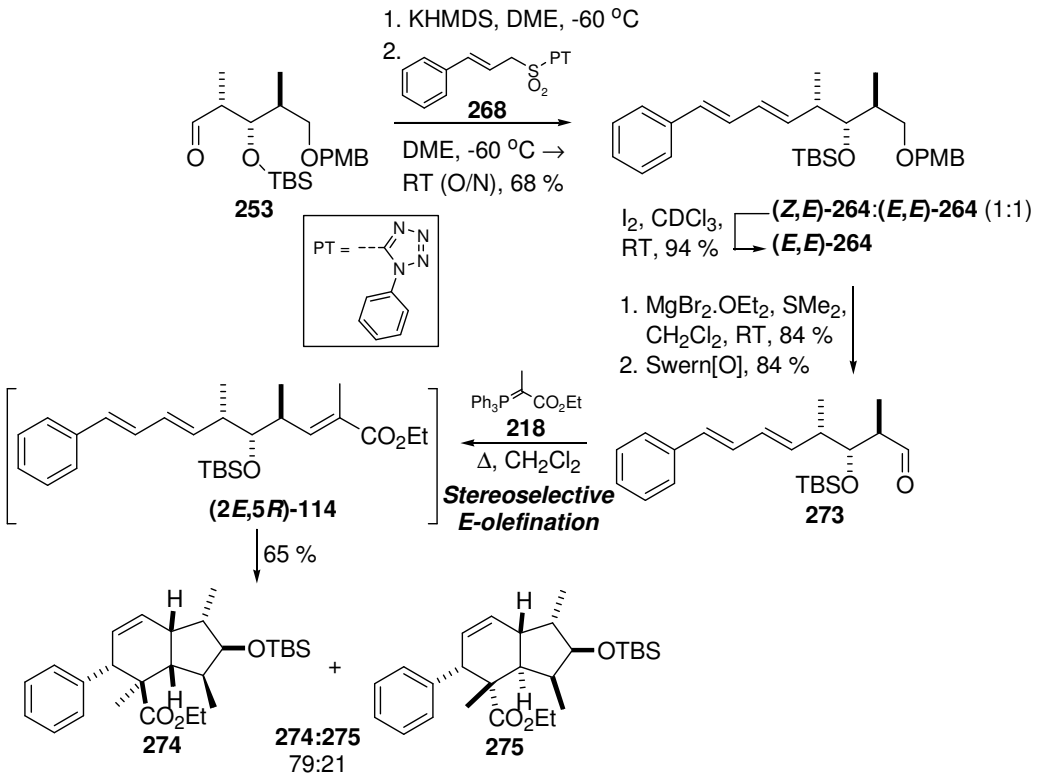


Scheme 4.16 Synthetic attempts towards the two "modified" Julia olefination approaches.

The second approach was considered to be more advantageous for two reasons. The conversion of *E*-cinnamylalcohol (**269**) (derived from reduction of commercially available *E*-cinnamaldehyde (**267**)) to the sulfone **268** could be performed on large scale at relatively low cost when compared to the expense of synthesis of the chiral sulfone **266**. Also, the relatively inexpensive sulfone **268** could be used in excess in an attempt to achieve higher yields for the "modified" Julia olefination reaction. Conversion of the cinnamylalcohol (**269**) to the sulfide **371** *via* the Mitsunobu[116,261] conditions was achieved in quantitative yield and was subsequently oxidised to the sulfone **268** using H_2O_2 (30 % aq. w/v) and catalytic $Mo_7O_{24}(NH_4)_6.4H_2O$.[262,263] Upon oxidation, a shift in the ^{13}C resonance of the CH_2-S carbon from 36 ppm to 61 ppm indicated that the carbon was more de-shielded as expected due to the electron withdrawing effect of oxygen. In addition, a shift in the ^{1}H resonance of the CH_2S

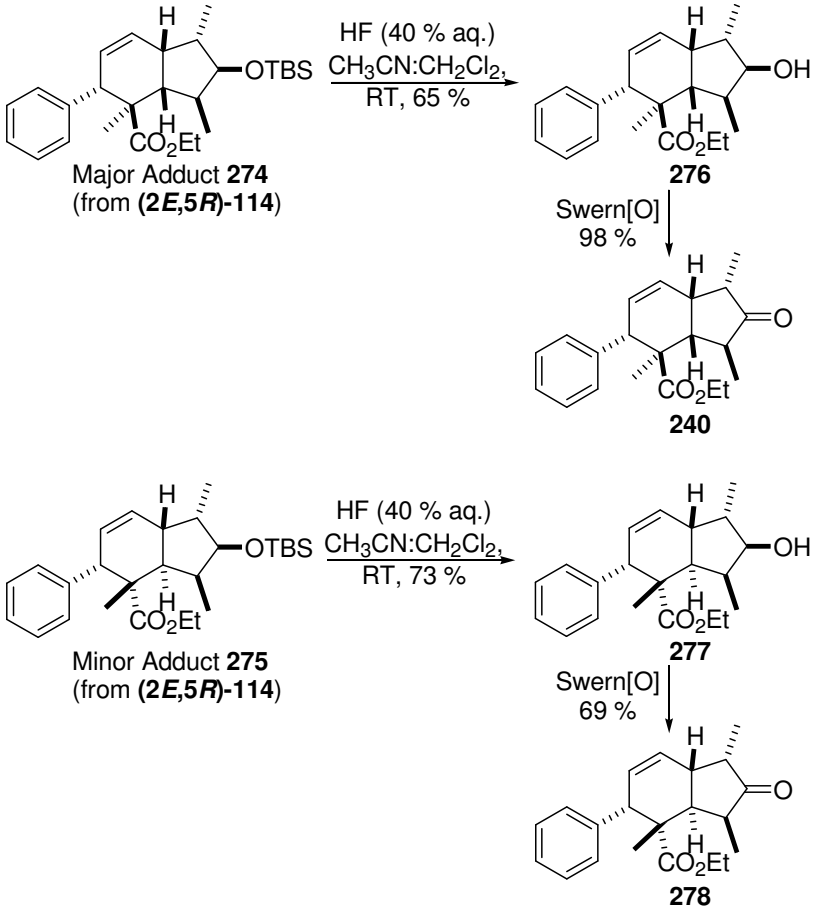
from 4.2 ppm to 4.6 ppm supported this. HRMS (ESI) analysis confirmed formation of the sulfone **268** with a peak for the M + Na^+ ion at 349.0729 m/z, which was in close agreement with the calculated value of 349.0730 m/z.

While initial attempts at coupling sulfone **268** to aldehyde **253** using sulfone **268** (2 eq.) and KHMDS (2.5 eq.) were successful in achieving the olefination, elimination of the OTBS ether also occurred.[116] Using an excess of sulfone **268** (2 eq.) with respect to the KHMDS (1.8 eq.) this elimination could be suppressed and the desired diene **264** was achieved in an acceptable yield (68 %) as a mixture of **(*Z*,*E*)-264** and **(*E*,*E*)-264** isomers (1:1). Proceeding *via* the same reaction sequence used for Model System One, and described in Scheme 4.17, isomerisation of the **(*Z*,*E*)-264** to the **(*E*,*E*)-264** diene was achieved using catalytic I_2.[242-244] The PMB ether was cleaved ($MgBr_2.OEt_2$, Me_2S, CH_2Cl_2, 84 %)[248] to give the primary alcohol **272** which was subsequently oxidised to the aldehyde **273** under Swern conditions (84 %).[205] In contrast to Model System One, attempts to couple the aldehyde **273** to phosphonate **217** *via* a H.W.E. coupling (under the same conditions; pre-formation of the anion and addition of the aldehyde **273** at 0 ^oC before warming to room temperature for 1 hour) gave no reaction with recovery of starting material.[237] However, the Wittig olefination proceeded in 65 % yield, as per the conditions reported for Model System One; aldehyde **273** and ylide **218** in CH_2Cl_2 were heated under reflux for 5 days until the colour change indicated reaction completion, producing two isomeric IMDA cycloadducts **274** and **275** (79:21).[31] Separation of the two cycloadducts, **274** and **275**, was readily achieved by column chromatography and the NMR spectra were analogous to the spectra described in Section 4.2.2, in Model System One, confirming that IMDA cycloaddition had taken place. Tables of NMR data containing the ^1H and ^{13}C assignments are available in Appendix 12 and Appendix 14. The stereoselectivity of the Wittig olefination could be inferred retrospectively from the stereochemistry of the cycloadducts and was found to be highly *E*-selective, with no cycloadducts resulting from the *Z*-dienophile detected. (refer to section 4.4.3 for the stereochemical assignment)



Scheme 4.17 "Modified" Julia olefination of linear precursor (2*E*,5*S*)-114 and subsequent IMDA cyclisation.

The two isomeric cycloadducts **274** and **275** were taken through identical TBS deprotection (HF (40 % aq.), CH_3CN:CH_2Cl_2, 1:1)[197,249] and Swern oxidation[205] steps to those reported for Model System One, as described in Scheme 4.18. Cycloadducts **274** and **275** were subjected to silyl ether cleavage yielding alcohols **276** (65 %) and **277** (73 %). Following Swern oxidation of the alcohols **276** and **277**, ketones **240** and **278** were both achieved in 65 % and 69 % yields respectively.



Scheme 4.18 Deprotection and oxidation of the cycloadducts 274 and 275.

4.4.3 Model System Two – Stereochemical Assignment of Cycloadducts 344 and 345

The investigation of the stereochemical outcome of the IMDA cycloaddition reaction of linear precursor **(2*E*,5*R*)-114**, was carried out in a method analogous to that described in Section 4.3. Molecular modelling studies of the assigned cycloadducts were also performed in order to confirm the stereochemical assignments. The linear precursor with *R* stereochemistry at the C5 centre was synthesised stereoselectively with an *E*,*E*-diene and an *E*-dienophile (assigned retrospectively). Two cycloadducts, **274** and **275** (ratio 79:21), were produced which were separable by column

chromatography and subjected to full stereochemical analysis, described in this section. As a result of the spontaneity of the cycloaddition reaction under the Wittig olefination conditions, the dienophile geometry was not confirmed prior to cyclisation. Therefore both the *E*- and *Z*-dienophile geometries were considered when identifying the possible stereoisomeric cycloadducts, which are depicted in Figure 4.22. A *Z*-dienophile results in a *trans*-relationship between the C3 hydrogen and the C2 ethyl ester while an *E*-dienophile gives a *cis*-relationship between these groups. Due to the stereocontrolled synthesis of the *E,E*-diene, by thermodynamic isomerisation with catalytic I_2, each of the eight possible cycloadducts has a *cis*-relationship between the C7 and C10 protons.

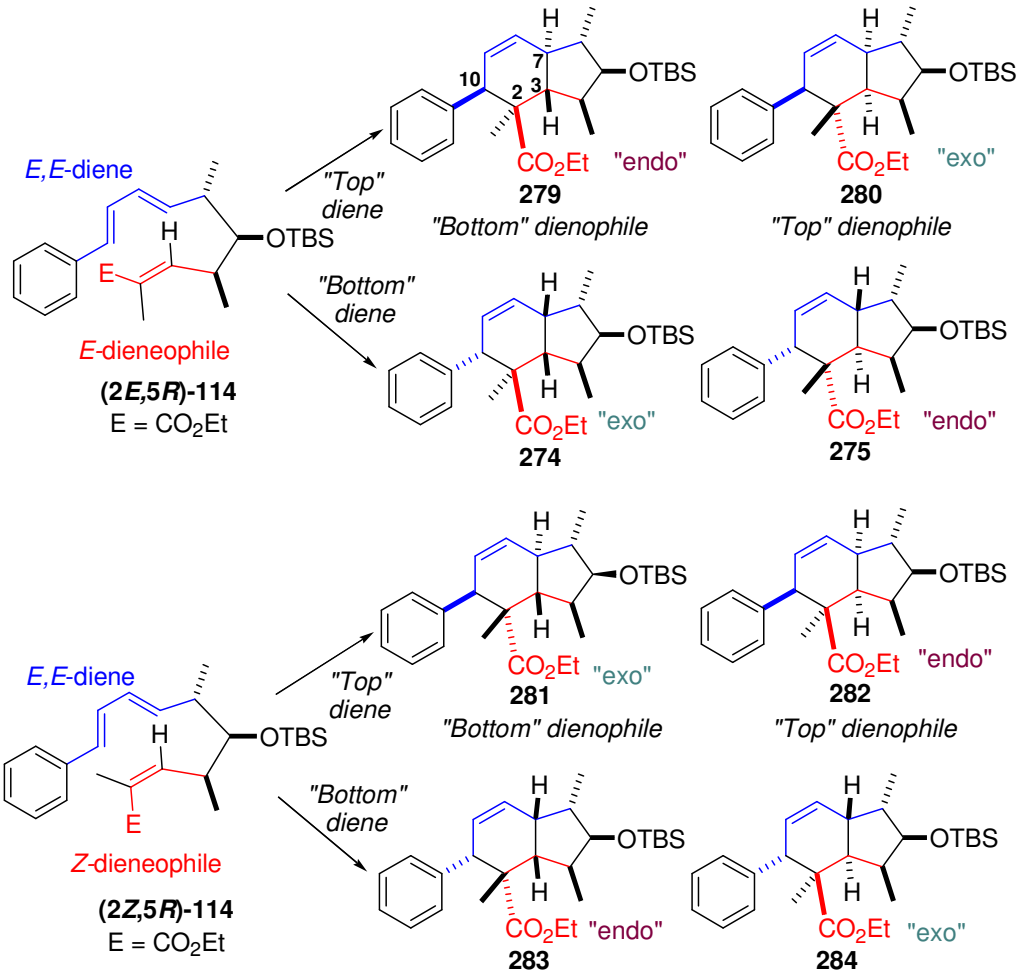


Figure 4.22 The eight possible stereoisomers arising from linear precursors (2*E*,5*R*)-114 and (2*Z*,5*R*)-114.

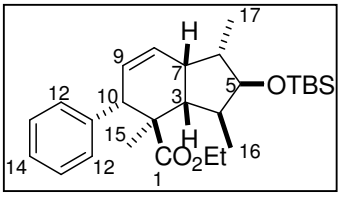
4.4.3.1 Assignment of the Major D.-A. Adduct 274

Employing the same strategy as that described for the stereochemical assignment of the cycloadducts in Model System One, the stereochemistry of cycloadduct **274** was

defined by considering the ^{1}H-^{1}H ROESY correlations in Table 4.5.

Table 4.5 ^{1}H-^{1}H ROESY correlations and stereochemical assignment of cycloadduct 274.

^{1}H No.	^{1}H-^{1}H ROESY [a]
3	H7*, H10, H16
4	H15, H16*
5	H16 (wk), H17
6	H7*, H15, H16, H17
7	H3*, H6*, H8/9*, H17
8	H7*, H10, H17, ArH
9	H7, H10*, H17, ArH
10	H3, H8/9*, ArH(12)
15	H4, H6, ArH(12)
16	H3, H4*, H5 (wk), H6
17	H5, H6*, H7, H8/H9
Ar	H8/9, H10, H15, ArH



[a] NMR spectrometer (600 MHz, C_6D_6).
* Indicates ^{1}H-^{1}H COSY correlations.

The complete stereochemical assignment shown above was achieved by stepwise analysis of the ^{1}H-^{1}H ROESY correlations as described in Figure 4.23. Just as in Model System One, the assignment begins by considering the correlations involving the centres of known stereochemical orientation, shown in blue. A weak correlation is observed between the C5 and C16 protons which is not expected however stronger correlations between the C5 and C17 protons as well as the C16 and C6 protons confirms that the stereochemical relationship between these centres is as depicted.

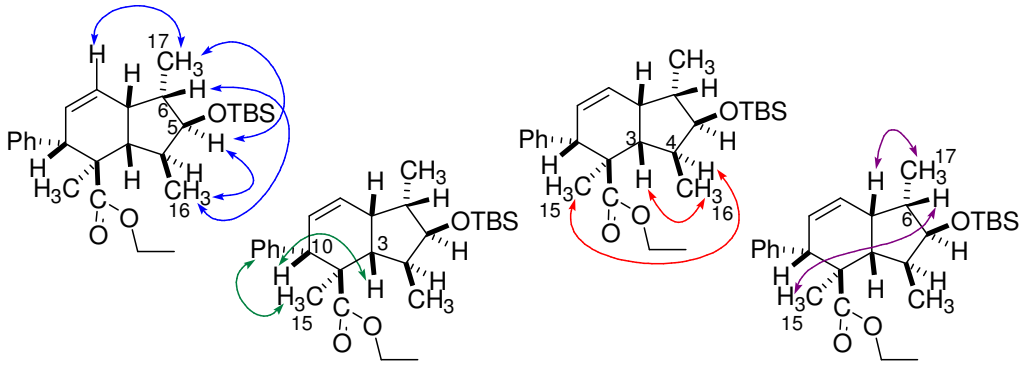


Figure 4.23 Stepwise stereochemical assignment of cycloadduct 274 based on the indicated ^{1}H-^{1}H ROESY correlations.

Determining the relative relationship between the C2 and C3 stereocentres will identify whether this cycloadduct was formed from the *E*- or *Z*-dienophile. Moving around the ring from the centres of known orientation, the correlations in red provide this information. A correlation between the C3 and C16 protons as well as a correlation between the C4 and C15 protons suggests the absolute stereochemistry at these centres is as indicated in Figure 4.23. The absence of a correlation between the C3 and C15 protons confirms the *trans*-relationship between the C3 hydrogen and

the C15 methyl. As a result it is evident that cycloadduct **274** is formed from cyclisation of **(3*E*,5*R*)-114** and that the Wittig olefination reaction produced the *E*-dienophile.

The C10 stereocentre was assigned based on the correlations shown in green. Reinforcing correlations between the C3 and C10 protons and between the C15 and aromatic protons confirmed the assignment of the C10 stereocentre as represented. The C7 proton correlates only to the C17 protons (in purple), a correlation which had proven to be of little value in defining the orientation of the C7 stereocentre in Model System One. However, if the orientation of the *E*,*E*-diene is conserved in the cycloadduct the C7 proton must be on the same face as the C10 proton. This assignment of C7 is supported by the magnitude of the coupling constant between the C3 and C7 protons, of 10.2 Hz, which suggests a *cis*-ring fusion. It was noted in Model System One, that isomers with the *cis*-fused bicycle often demonstrate correlations between the C5 proton and both the C16 and C17 protons due to the concave nature of the bicycle. It is of interest that in this system, with the opposite configuration at C5, correlations to both C16 and C17 protons are again observed for the C5 proton. Attempts to rationalise this with respect to the low energy conformers will be discussed. In general the stereochemical assignment represented in Figure 4.23, appears to account for all of the observed correlations, with one exception, the correlation between the C6 and C15 protons (in purple), as these centres are on opposite faces and are expected to be quite remote.

Examination of the predicted conformers reveals that in each case the phenyl and ethyl ester groups lie in a *pseudo* equatorial orientation with no ring-flipped counterparts which would place these groups in a more sterically demanding *pseudo* axial orientation. Despite the ring-flipped counterpart being higher in energy and thus less favourable, the absence of any predicted conformers with this orientation is thought to be due to the bulky OTBS group anchoring the bicycle in this conformation. The bicyclic core is concave in shape due to the *cis*-fusion of the rings and the major conformational flexibility arises through bond rotations of the appendages. The low energy conformer, in Figure 4.24, was examined to search for evidence to explain the unexpected correlation between the C15 and C6 protons. The concave orientation of the bicyclic core results in the C15 methyl being tucked underneath bringing the C15 and C6 protons within close proximity (4.2 Å)

accounting for the observed correlation.

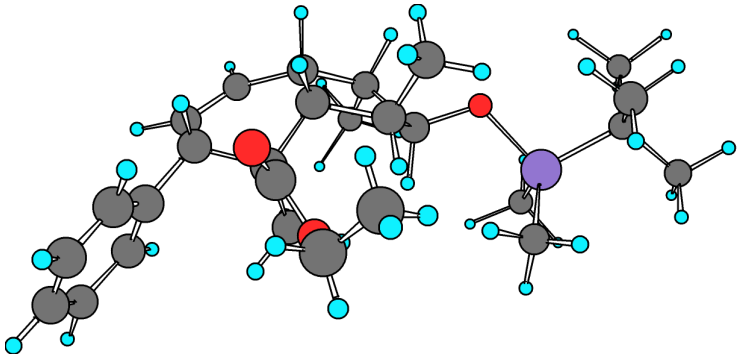


Figure 4.24 The low energy conformer for cycloadduct 274.

As previously mentioned the C5 proton correlates to both the C16 and C17 protons. Examination of the interatomic distances between the C5 proton and the C16 and C17 protons, 3.6 Å and 2.6 Å, respectively accounts for both of these correlations. As for the cycloadducts with the 5*S* stereochemistry, concave nature of the bicyclic core twists the 5-membered ring flattening the C4-C6 stereotriad allowing these protons to interact through space.

Comparison of the assigned stereochemistry, in Figure 4.23, with the four possible isomers arising from the linear precursor **(2*E*,5*R*)-114**, represented in Figure 4.22, indicates that the exo adduct has formed through reaction of the bottom face of the diene with the bottom face of the dienophile. A comparison of the cycloadducts **232** and **233**, from the IMDA reaction of linear precursor **(2*E*,5*S*)-114**, and the cycloadduct **274**, from linear precursor **(2*E*,5*R*)-114**, linear precursors which differ only in the orientation of the C5 stereocentre, is shown in Figure 4.25. Interestingly, cycloadduct **274**, has reacted *via* an analogous transition state (i.e. reaction has occurred between the same faces of the diene and dienophile) to the minor cycloadduct **233,** from the **(2*E*,5*S*)-114** linear precursor, represented in Figure 4.25. The major cycloadduct from the two linear precursors arise from cycloaddition occurring at opposite faces of the diene, suggesting that the orientation of the C5 stereocentre may impart some control over the stereochemical outcome of the IMDA.

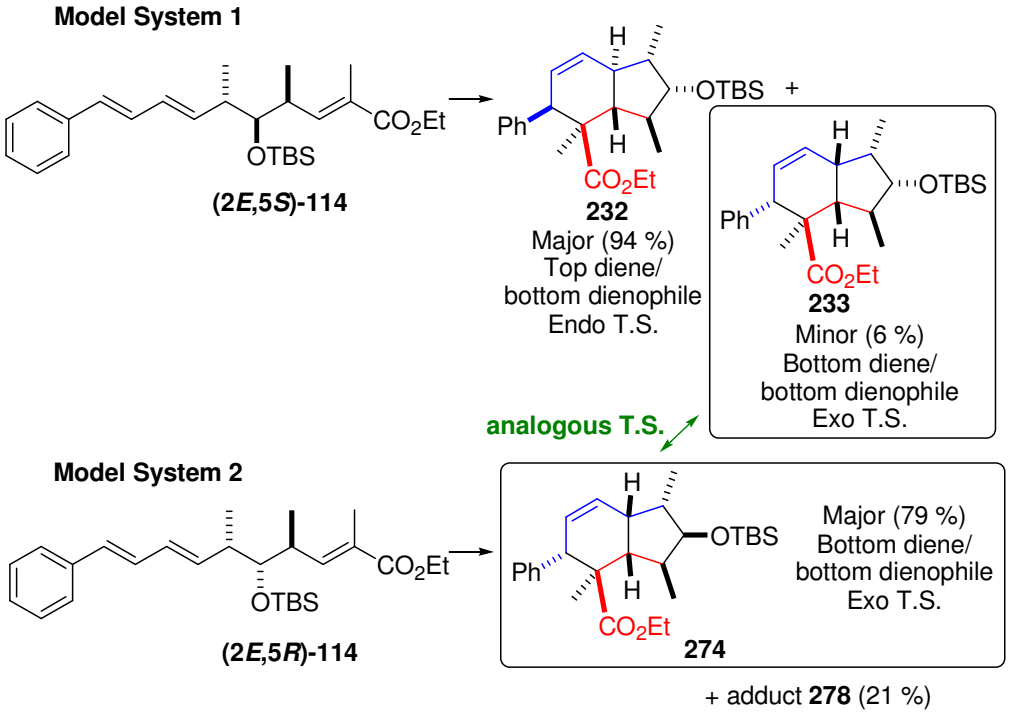


Figure 4.25 Comparison of cycloadduct 274, from (2*E*,5*R*)-114, to the cycloadducts 232 and 233, from (2*E*,5*S*)-114.

Following cleavage of the silyl ether, NMR analysis of the alcohol **276**, was undertaken to confirm the stereochemical assignment. The ^{1}H-^{1}H ROESY correlations for the alcohol **276**, represented in Figure 4.26, were identical to those for the protected precursor **274** reinforcing the stereochemical assignment. The complete set of NMR data for alcohol **276** can be found in Appendix 13.

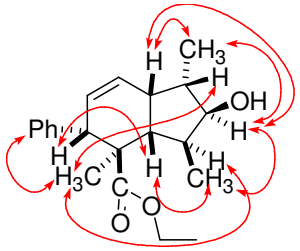


Figure 4.26 The ^{1}H-^{1}H ROESY correlations of alcohol 276 confirm the stereochemical assignment of cycloadduct 274.

In this instance examination of the low energy conformers predicted for this stereoisomer revealed two distinctly different groups of conformers resulting from a ring-flip of the cyclohexene ring. The lowest energy conformers of each ring-flipped version are shown in Figure 4.27. This supports the proposal that the TBS group was responsible for anchoring the conformation of the cycloadduct in one orientation because in the absence of the TBS group the cycloadduct **276** is free to ring-flip. As

expected the low energy conformer with the phenyl and ethyl ester groups in the *pseudo* equatorial orientation (Figure 4.27a) is lower in energy, -123.1 kcal/mol, than the conformer with the phenyl and ethyl ester groups in the *pseudo* axial orientation, -121.7 kcal/mol (Figure 4.27b). As the low energy conformation is structurally analogous to that for the protected cycloadduct and all of the ^{1}H-^{1}H ROESY correlations are identical a full description of the stereochemical assignment of alcohol **276** will not be repeated.

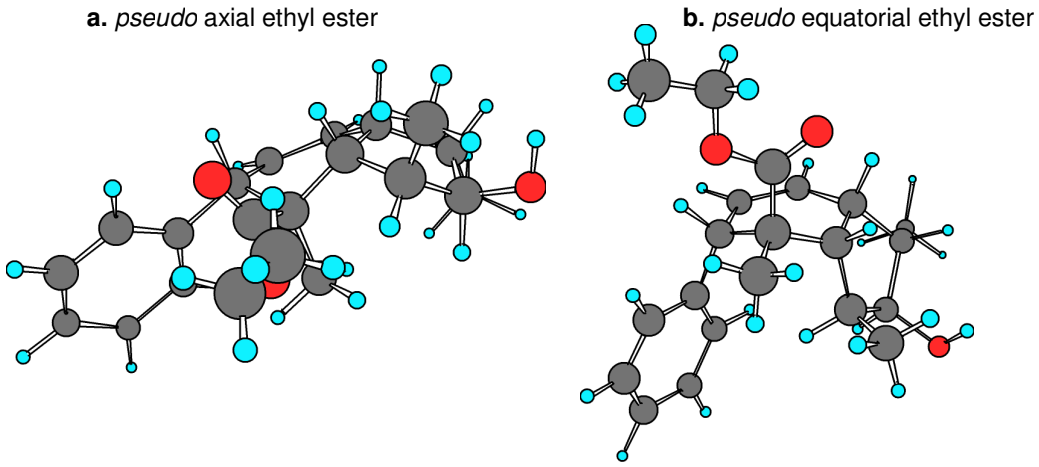


Figure 4.27 The low energy conformers of each of the ring-flipped counterparts of alcohol 276.

As previously mentioned, the cycloadduct **274** forms *via* an analogous transition state to the minor cycloadduct **233** from linear precursor **(2*E*,5*S*)-114** in Model System One. The only difference between these diastereomeric cycloadducts is the orientation of the C5 stereocentre. Upon oxidation of the C5 alcohol in each cycloadduct, this stereocentre is eliminated and thus the ketone products should be identical, as depicted in Figure 4.28. This will provide further evidence to support the stereochemical assignment of these cycloadducts. Following oxidation of alcohol **276**, NMR analysis of the ketone product revealed that it is indeed identical to the ketone **240**, derived from the oxidation of alcohol **238**, supporting the stereochemical assignment of the cycloadducts. As this ketone is identical to that discussed in Section 4.3.2.1.2 a thorough stereochemical analysis of ketone **240** will not be undertaken here.

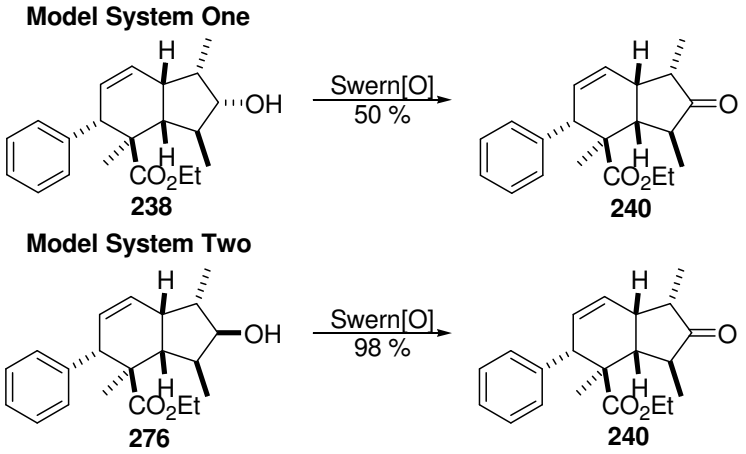


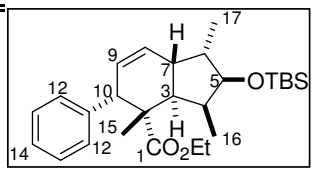
Figure 4.28 Oxidation of alcohols 238 and 276, produces identical ketones 240.

4.4.3.2 Assignment of the Minor D.-A. Adduct 275

Examination of the ^{1}H-^{1}H ROESY correlations listed in Table 4.6 enabled the stereochemical assignment of the minor IMDA adduct **275** as shown.

Table 4.6 ^{1}H-^{1}H ROESY correlations and stereochemical assignment of cycloadduct 275.

^{1}H No.	^{1}H-^{1}H ROESY [a]
3	H5 (wk), H7*, H16(v. wk), H17, ArH(12)(wk)
4	H15, H16*
5	H3 (wk), H6*, H16 (wk), H17(wk)
6	H4 (wk), H5*, H15(wk), H17*
7	H3*, H15
8	H9*
9	H8*, H10*
10	H9*, H15, ArH(12)
15	H4, H7, H6 (wk) H10
16	H3 (v. wk), H4*, H5
17	H3, H5, H6*
Ar	H3(wk), H10, ArH



[a] NMR spectrometer (600 MHz, $CDCl_3$).
* Indicates ^{1}H-^{1}H COSY correlations.

Employing the stepwise strategy, depicted in Figure 4.29, the ^{1}H-^{1}H ROESY correlations were used to identify the stereochemistry at each centre of cycloadduct **275**. The correlations in blue are between stereocentres of known orientation. While the C5 proton correlates weakly to both the C16 and C17 protons this can generally be explained due to the slightly buckled 5-membered ring and will be discussed with respect to the low energy conformation. In addition, an unexpected, weak correlation between the C4 and C6 protons is also observed.

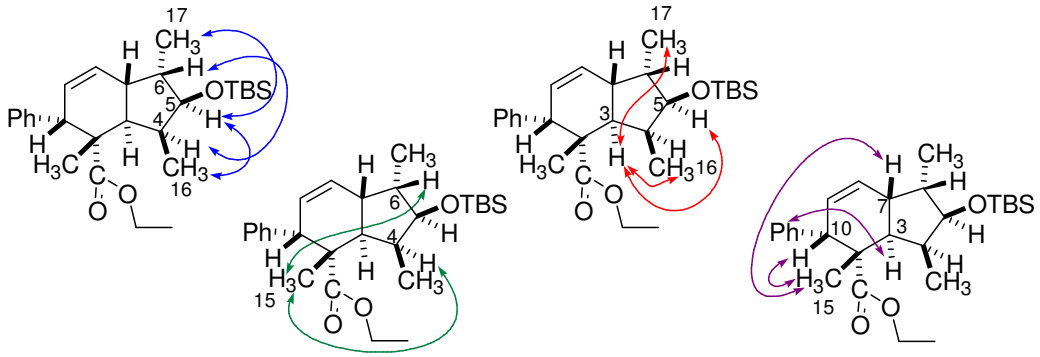


Figure 4.29 Assignment of cycloadduct 275 by stepwise analysis of the ^{1}H-^{1}H *ROESY* correlations.

Examining the correlations, in red, between the stereocentres of known orientation and the C3 proton, allows the absolute stereochemistry at C3 to be defined. In contrast to all of the other cycloadducts the correlation between the C16 protons and the C3 proton in this isomer is quite weak. Instead correlations of the C3 proton to both the C5 and C17 protons are observed, indicating the stereochemistry at C3 is as shown. Correlations of the C15 protons to both the C4 and C6 protons, in green, appear to be contradictory. However, the absence of a C3 to C15 correlation suggests that the absolute stereochemistry of the C2 centre is as shown. Having identified a *cis*-relationship between the C2 ester and the C3 hydrogen this suggests that this cycloadduct was also achieved by IMDA cyclisation of linear precursor **(2*E*,5*R*)-114**. Therefore the Wittig olefination reaction with stabilised ylide **218** was highly *E*-selective as expected based on literature precedent[31] as well as previous experience in Model System One (Section 4.2.2).

The absolute stereochemistry of the C10 and C7 stereocentres was defined considering the correlations in purple. Correlations between the C3 and aromatic protons and the C10 and C15 protons confirm the absolute stereochemistry at C10. Correlations between the C7 and C15 protons suggested the stereochemistry of the C7 stereocentre as shown. Thus, C10 and C7 are on the same face as predicted based on conservation of the geometry of the *E*,*E*-diene in the cycloadduct. The assigned stereochemistry indicates that the ring fusion protons have a *trans*-relationship which is supported by the magnitude of the coupling constant between the C3 and C7 protons, ^{3}J = 12.0 Hz, confirming that these protons are in a *trans*, diaxial arrangement.

Examination of the predicted low energy conformation, illustrated in Figure 4.30, reveals that the bicyclic core is indeed relatively planar due to the *trans*-ring fusion and the ethyl ester adopts a *pseudo* equatorial orientation. All of the discussed correlations can be reasonably expected considering this conformation. A number of unexpected, albeit weak, correlations were also observed. Correlations between the C5 and both the C16 and C17 protons were unexpected as the C16 and C17 groups lie on opposite faces. Examination of the low energy conformation reveals that the interatomic distances between C5 and C16 and C17 are 3.5 Å and 2.4 Å respectively due to the slight twist in the 5-membered ring. In addition, the correlation between the C4 and C6 protons is also unexpected, however the small twist in the 5-membered ring results in an interatomic distance between these protons of 4.2 Å explaining the observed weak correlation.

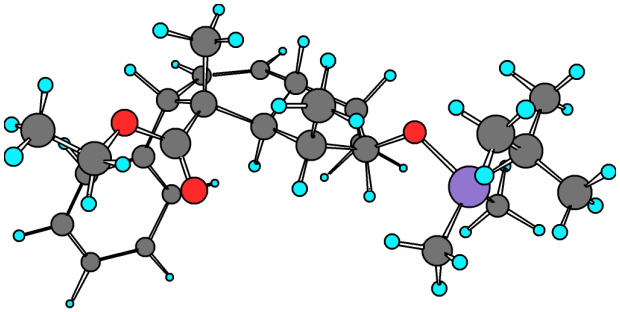


Figure 4.30 The low energy conformation of cycloadduct 275.

Comparison of the assigned stereochemistry of the minor cycloadduct **275** from **(2*E*,5*R*)-114** (Figure 4.29), to the possible stereoisomers, in Figure 4.22, indicates that this adduct is the product of an endo transition state in which the top face of the dienophile reacts with the bottom face of the diene. Comparison of cycloadduct **275**, from the linear precursor **(2*E*,5*R*)-114**, with cycloadducts **232** and **233**, from the linear precursor (**2*E*,5*S*)-114**, is shown in Figure 4.31. Cycloadduct **275** forms through a different transition state to both cycloadducts **232** and **233** suggesting that the orientation of the C5 stereocentre may play an instrumental role in influencing the stereochemical outcome of the IMDA.

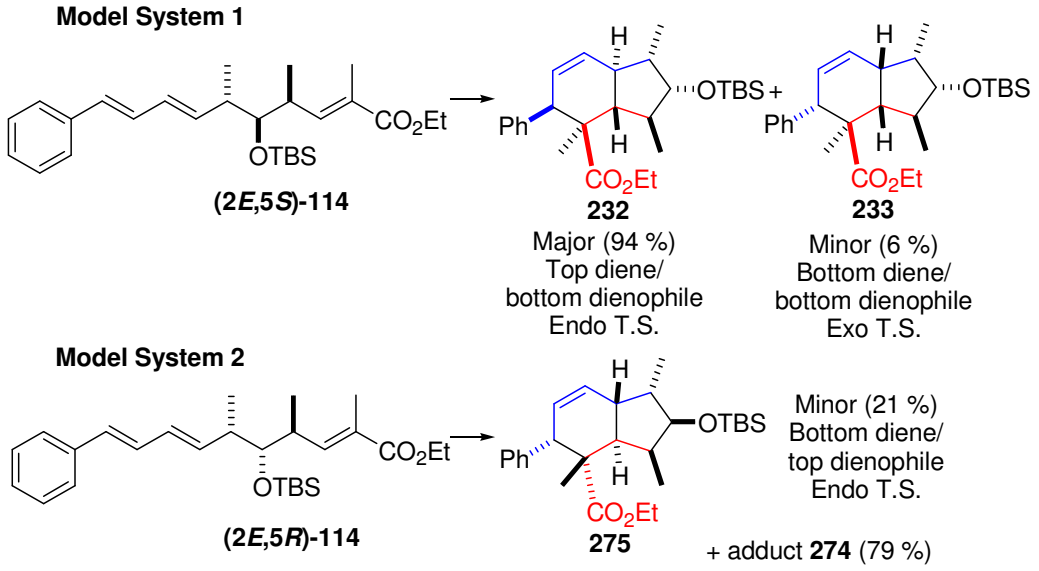


Figure 4.31 Comparison of cycloadduct 275, from (2*E*,5*R*)-114, and cycloadducts 232 and 233, from (2*E*,5*S*)-114.

After cleavage of the silyl ether, alcohol **277**, was subjected to full stereochemical and computational analysis, similarly after oxidation of the secondary alcohol, ketone **278** was also analysed. Tables of NMR data for alcohol **277** and ketone **278** are available in Appendix 15 and Appendix 16 respectively. Figure 4.32 illustrates the observed ^{1}H-^{1}H ROESY correlations all of which supported the stereochemical assignment of cycloadduct **275**. Examination of the low energy conformers of both the alcohol **277** and ketone **278**, indicate they are structurally very similar to the TBS protected analogue **275** previously discussed and thus the ^{1}H-^{1}H ROESY correlations won't be discussed further.

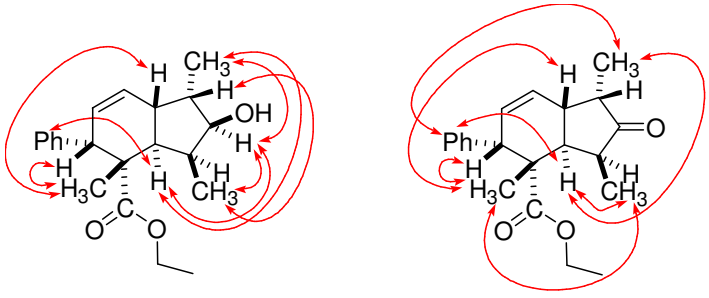


Figure 4.32 ^{1}H-^{1}H ROESY correlations of alcohol 277 and ketone 278 confirm the stereochemical assignment of cycloadduct 275.

4.4.4 The Affect of the Configuration of the C5 Stereocentre on the Stereochemical Outcome of the IMDA Reaction

The IMDA cycloaddition reaction was performed on three linear precursors, differing in the geometry of the dienophile and the orientation of the C5 stereocentre, in an effort to gain an insight into the factors influencing the stereochemical outcome. The affect of the orientation of the C5 stereocentre on the stereochemical outcome of the IMDA is revealed by comparing the cycloadducts from the two linear precursors, **(2*E*,5*S*)-114** and **(2*E*,5*R*)-114**, depicted in Figure 4.33. These precursors both possess an *E*-dienophile, but have opposite stereochemistry at C5. The major IMDA adduct **274** (79 % ds) from the precursor with 5*R* stereochemistry was formed through reaction of the bottom of the diene with the bottom of the dienophile. Interestingly, this cycloadduct forms through the same transition state as the minor adduct **233** (6 % ds) from the precursor with 5*S* stereochemistry. The other two cycloadducts **232** (from **(2*E*,5*S*)-114**) and **275** (from **(2*E*,5*R*)-114**) both formed through an endo transition state, however the opposite faces of both the diene and dienophile components were involved in the reaction. The cycloadduct **275** formed by cycloaddition to the top face of the dienophile, a face that had not previously been seen to react in any of the other cycloadducts.

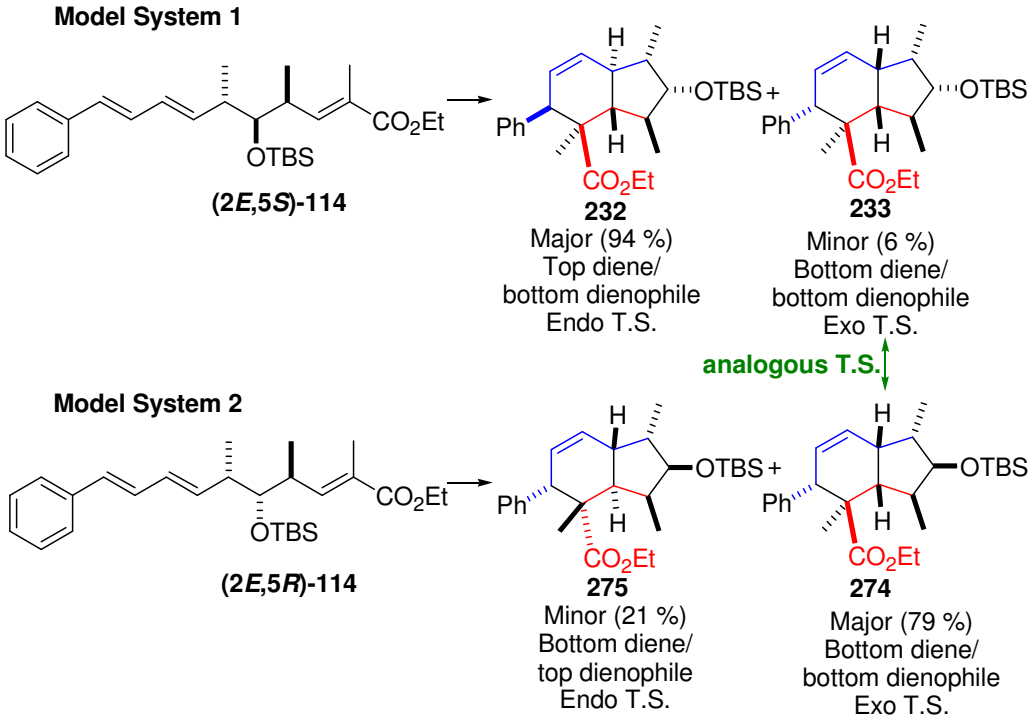


Figure 4.33 Comparison of the stereochemical outcome of the IMDA reaction of (2*E*,5*S*)-114 and (2*E*,5*R*)-114.

The stereochemical outcome of the IMDA cycloaddition of linear precursors **(2*E*,5*S*)-114** and **(2*E*,5*R*)-114**, which differ only in the orientation of the C5 stereocentre, are significantly different indicating that the orientation of the C5 stereocentres is of fundamental importance in controlling the stereochemical outcome of the IMDA. This stereocentre is able to dominate the inherent endo/exo selectivity of the IMDA reaction, with cycloaddition of **(2*E*,5*S*)-114** proceeding via an endo transition state to give major adduct **232** while cycloaddition of **(2*E*,5*R*)-114** proceeds via an exo transition state to give major adduct **274**.

4.5 Conclusions - Extension to the Spiculoic Acids and the Plakotenins

The biosynthesis of both the spiculoic acid and the plakotenin families of natural products are remarkably similar suggesting involvement of related enzymes. They both involve synthesis of structurally similar, linear polyene precursors which undergo an IMDA cycloaddition reaction that may or may not be facilitated by an enzyme. The IMDA cycloaddition reaction for each group of natural products proceeds through different endo transition states producing cycloadducts with different stereochemical features. The model system was designed, incorporating functionalities identified in both groups of natural products, with the view of investigating possible synthetic routes to both the spiculoic acids and the plakotenins. Synthetic methodologies towards different stereo/geometric isomers of the linear polyene precursors have been developed using highly stereoselective substrate-controlled aldol reactions and a variety of olefination reactions. The factors affecting the stereochemical outcome of the subsequent thermally induced IMDA have been explored and some general observations made. Using this information the linear precursors to both families of natural products may potentially be manipulated to give the desired stereochemistry of the cycloadduct.

Comparisons were made between the stereochemical orientation of each of the cycloadducts from the model systems with the stereochemical orientation of the spiculoic acid natural products. Cycloaddition of the linear precursor **(2*E*,5*S*)-114**, in Model System One, gave cycloadduct **232** in 94 % ds. This cycloadduct exhibits the same stereochemical features as the spiculoic acid natural products, which can be seen in Figure 4.34. These results suggest that linear precursors to the spiculoic acids, possessing an *E*-dienophile, an *E*,*E*-diene and the C5 carbonyl group masked as the TBS ether in an *S* orientation, may produce a cycloadduct with the desired stereochemistry.

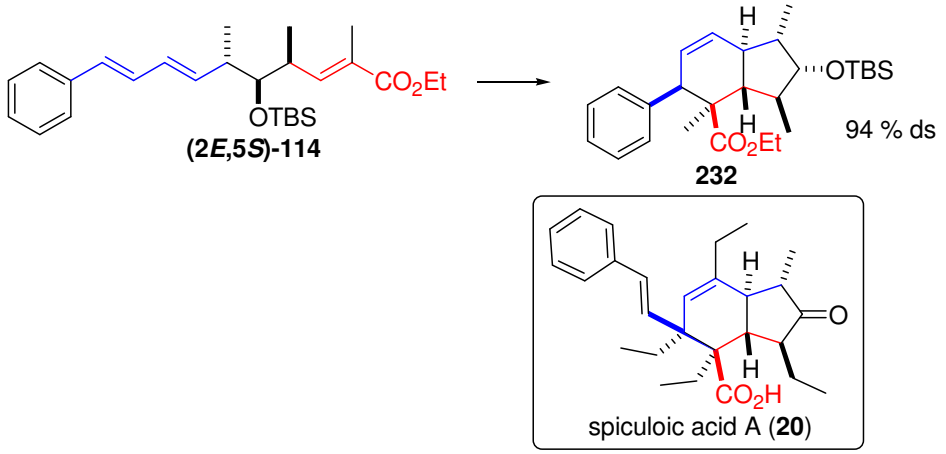
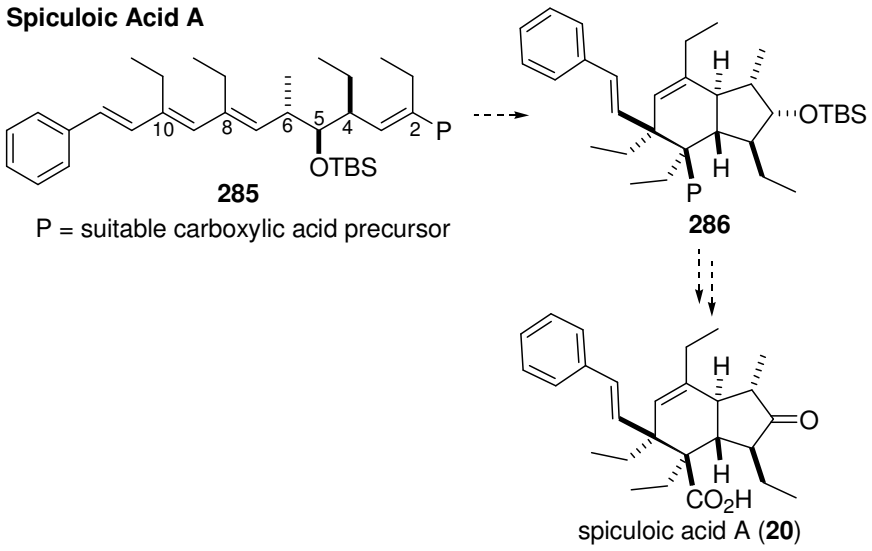


Figure 4.34 Comparison of cycloadduct 232 to the spiculoic acid family of natural products.

When designing the synthetic approach to the linear precursors consideration must be a given to the stereoselective installation of the *E*-dienophile in order to minimise potential isomers and maximise the efficiency of the synthesis. In addition, an alternative method of accessing the carboxylic acid must be considered due to the difficulties encountered in cleaving the ethyl ester. Different methods which could be considered include protection of the acid as an allylic ester, which may be cleaved by a mild palladium-catalysed allyl transfer to morpholine,[264] or conversion to the acid from an alternative functionality such as the aldehyde. Scheme 4.19 depicts the proposed linear precursor **285** to spiculoic acid A (**20**) which has an *E*,*E*-diene, an *E*-dienophile and a 5*S* TBS ether. Cycloaddition of **285** is hoped to produce cycloadduct **286**, which has the stereochemistry required for the natural product, in high diastereoselectivity.



Scheme 4.19 Proposed extension of the model systems to the synthesis of spiculoic acid A (20).

Comparisons were also made between the plakotenins and the stereochemical orientation of each of the model IMDA cycloadducts. Unfortunately none of the cycloadducts possessed stereochemical features identical to the natural products. However, cyclisation of the **(2*E*,5*R*)-114** linear precursor gave minor adduct **275** (21 % ds) which possesses stereochemistry that matches the plakotenins at all centres except the C2 centre, which is derived from the dieneophile, as depicted in Figure 4.35. In the linear precursor **(2*E*,5*R*)-114**, the dienophile had an *E*-geometry but in the plakotenin natural products a *Z*-geometry of the dienophile is required. (Figure 4.35) Thus, it is reasonable to think that if the geometry of the dienophile in the linear precursor was *Z* (i.e. linear precursor **(2*Z*,5*R*)-114**), then the stereochemistry of the cycloadduct may match the stereochemistry of the natural products. This is supported by evidence from Model System One where the two linear precursors, **(2*E*,5*S*)-114** and **(2*Z*,5*S*)-114**, differing only in the dienophile geometry, undergo cycloaddition through analogous transition states (i.e. by reaction at the same faces of addends). Further investigations of the stereochemical outcome of related model systems are required in order to develop a strategy to achieve the desired stereochemistry of the plakotenins with high levels of diastereoselectivity. Potential avenues to pursue, could include exploring the stereochemical outcome of an IMDA of linear precursor **(2*Z*,5*R*)-114** or the equivalent linear precursor with no substituent at C5 (i.e. a methylene group).

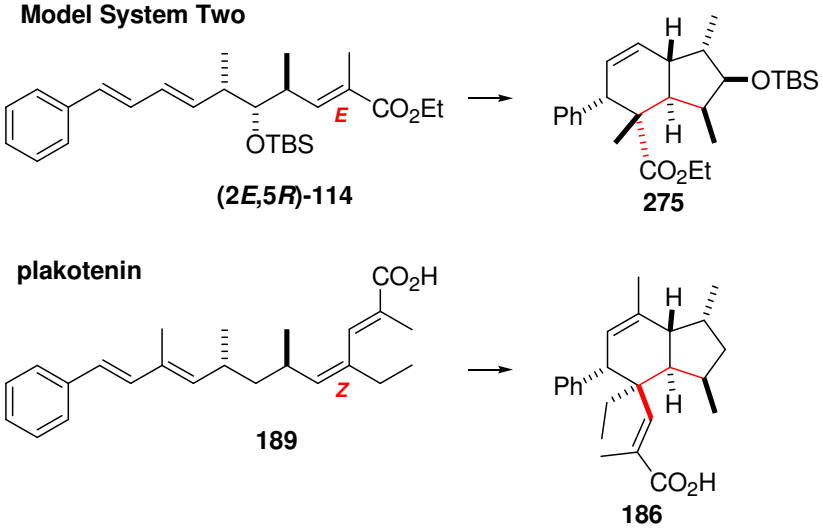


Figure 4.35 Comparison of the stereochemistry of the plakotenins with cycloadduct 275, from cycloaddition of (2*E*,5*R*)-114.

CHAPTER 5 EXTENSION OF THE MODEL SYNTHESIS TO THE SPICULOIC ACIDS

The synthetic methodology employed in the synthesis of Model Systems One and Two described in Chapter Four has been extended to develop a proposed synthetic approach to the spiculoic acid family of natural products. Synthetic efforts towards the linear polyene precursors *via* Wittig, H.W.E. and "modified" Julia olefination reactions as employed in the Model Systems are described. Unfortunately problems were encountered in the construction of the required tri-substituted olefins *via* olefination reactions, due to steric issues involving synthesis and coupling of hindered coupling partners. An alternative synthetic strategy, employing a palladium-catalysed Suzuki cross-coupling reaction to install σ-bonds between vinyl coupling partners, was also investigated. However, synthesis and coupling of hindered coupling partners again proved to be a significant obstacle. As a result of the difficulties encountered in the formation of tri-substituted alkenes, the total synthesis of the spiculoic acid family of natural products was not ultimately achieved.

5.1 Extension of the Model Systems to the Natural Products

In Chapter Three, model systems designed to explore the synthesis of linear polyene precursors and to investigate the stereochemical outcome of the subsequent IMDA cycloaddition reactions were developed, as represented in Figure 5.1. The synthesis of these linear precursors (**114**) and the thorough stereochemical evaluation of the IMDA cycloadducts (**113**) employing 2D NMR spectroscopy, is described in Chapter Four. The linear precursors were synthesised with both *R* and *S* orientations of the C5 OTBS ether and with *E* and *Z* geometries of the dienophile component in order to examine what affect this may have on the stereochemical outcome of the IMDA reaction. The results of this investigation have provided some understanding of the factors influencing the stereochemical outcome of the IMDA reaction. Armed with this knowledge an approach to the spiculoic acid family of natural products was devised.

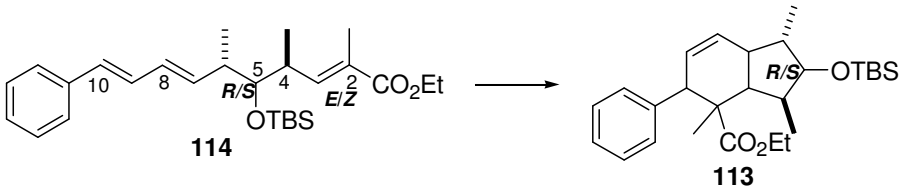
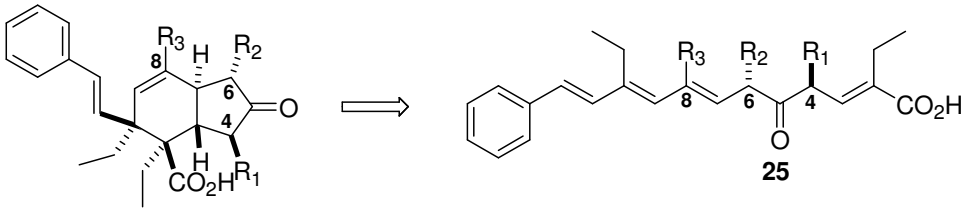


Figure 5.1 The IMDA cycloaddition reaction of linear precursors 114 were investigated in the model systems.

Each of the members of the spiculoic acid A family of natural products differ only in the substitution of methyl or ethyl groups around the spiculane skeleton. Figure 5.2 reveals the structures of each of the members of the spiculoic acid A family of natural products proposed to be formed by an IMDA cycloaddition reaction of the corresponding linear precursor (**25**).



spiculoic acid A (**20**) R_1 = Et, R_2 = Me, R_3 = Et
isospiculoic acid A (**22**) R_1 = Me, R_2 = Et, R_3 = Et
nor-spiculoic acid A (**23**) R_1 = Me, R_2 = Et, R_3 = Me
dinor-spiculoic acid A (**24**) R_1 = Me, R_2 = Me, R_3 = Me

Figure 5.2 The spiculoic acid A family of natural products are proposed to be synthesised *via* an IMDA cycloaddition reaction of linear precursor 25.

The thermally induced IMDA reaction of each of the linear precursors of the model systems, proceeded in generally high yield, with moderate to good diastereoselectivity (>70 % yield, >79 % ds). Investigation of the stereochemical outcome of the IMDA reaction of each of the three linear precursors revealed that linear precursor **(2*E*,5*S*)-114** produced a cycloadduct **232** (94 % ds) with analogous stereochemistry to that of the spiculoic acids. The stereochemical consistencies between the spiculoic acids and the dominant cycloadduct **232** from **(2*E*,5*S*)-114**, are highlighted in Figure 5.3. This suggested that synthesis of the linear precursors **285**, with the C5 carbonyl group protected as the TBS ether in the *S* configuration, may induce the desired stereochemistry in the cycloadduct. However the natural product is significantly more complex than the model system and therefore simply replicating the stereochemical orientation of the C5 stereocentres and the geometry of the diene and dienophile components will not guarantee the stereochemistry of the cycloadduct.

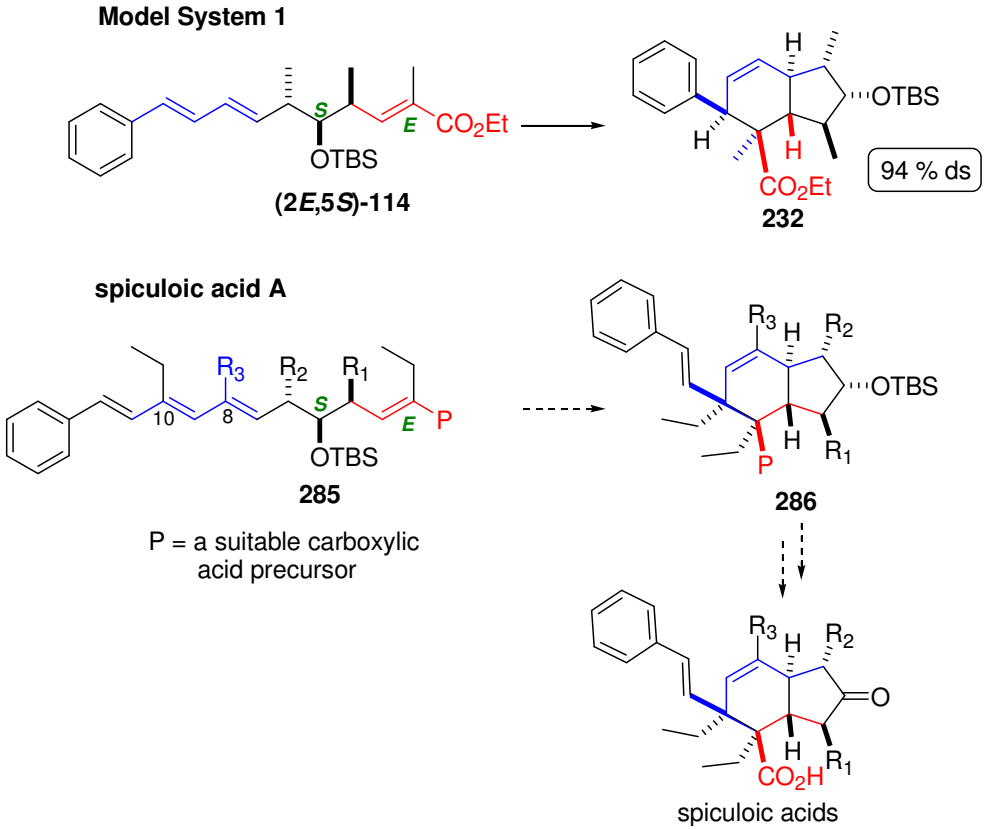


Figure 5.3 Spiculoic acid A has analogous stereochemistry of that of cycloadduct 232.

Before embarking on the total synthesis, the differences between the natural products and the model systems, revealed in Figure 5.3, need to be considered. The exo-cyclic double bond present in the spiculoic acids was omitted from the model system. As a result the linear precursor **(2*E*,5*S*)-114** simply possesses a diene in conjugation with the phenyl group, while the linear precursors to the natural products (**285**) have the phenyl group in conjugation with a triene. The most significant difference between the natural products and the developed model systems, likely to complicate synthesis of the spiculoic acids, is the substitution of ethyl and methyl groups (at C8 and C10) on the diene moiety. The model system lacks these tri-substituted double bonds and was designed this way in order to simplify the synthesis of the linear precursors enabling a more time and cost efficient synthesis. Synthesis of tri-substituted double bonds *via* olefination reactions can pose a two-fold synthetic challenge; getting the reactants to couple and installing the double bonds in a stereocontrolled fashion. The increased steric bulk of the reagents inhibits coupling to form the tri-substituted double bonds compared to the 1,2-di-substituted counterparts. Increased substitution adds further complications to the stereoselective formation of olefins because selective formation of *E*-olefins is often under thermodynamic control and additional

substituents on the alkene may result in the alternative geometries having similar energies. Therefore thermodynamic control of the olefination reaction may not be achievable. Despite the synthetic challenges involved in the synthesis of conjugated, tri-substituted alkenes it was hoped that with the range of different options available to achieve olefin synthesis (Wittig, H.W.E. and Julia) already investigated in Chapter Four, stereoselective synthesis of this target would be achievable.

5.1.1 Retrosynthetic Analysis

In order to extend the approach used for the model systems to the natural products an additional olefin must be inserted in conjugation with both the diene and the phenyl group. Examination of the desired linear precursors **285** indicated that the conjugated triene could be broken at any of the three double bonds, represented in Figure 5.4, enabling construction *via* Wittig or H.W.E. olefination reactions, as employed in Model System One. This "extra" olefin can be added to the ylide/phosphonate **287** to be coupled to the chiral fragment **288** installing the triene in one step (in blue). Alternatively the central chiral fragment can be extended to incorporate one (**290**, in red) or two (**292**, in green) double bonds to then be coupled to an ylide/phosphonate **289** or **291** producing the conjugated triene. A stepwise approach of sequential olefination reactions, installing each of the double bonds in the conjugated triene **285** was avoided as a convergent synthesis was considered a better option. In retrospect, a sequential approach may have been more successful, such as that employed by Baldwin and co-workers in their total synthesis of *ent*-spiculoic acid A which is described in Section 3.2.1.2.[234]

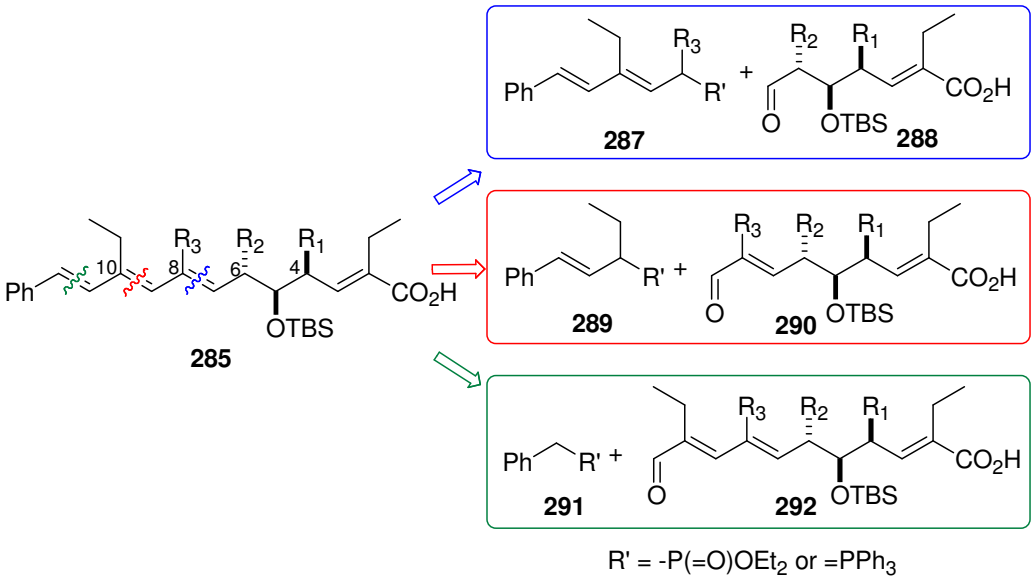


Figure 5.4 Possible disconnections at each of the olefins of the triene moiety of the linear precursors (285) to the spiculoic acids.

In search of a convergent approach by which synthesis of each of the members of the spiculoic acid family of natural products could be achieved with only minor modifications, it was decided that disconnection of the central olefin (in red) was the preferred alternative. This would enable ylide/phosphonate **289** to be employed in the synthesis of each of the natural products which all possess the ethyl substitution at the C10 olefin. It was envisaged that a synthetic strategy could be developed that would ultimately provide access to the entire family of spiculoic acids with simple modifications to the R_1-R_3 groups of chiral aldehyde **290**.

dinor-Spiculoic acid A (**24**) has methyl substitution at C4 and C6 and thus the stereotriad of the linear precursor (**293**) could be achieved from the same central chiral fragment **214** developed for Model System One, as depicted in Figure 5.5. In addition, *dinor*-spiculoic acid A has a methyl substituent at C8 (R_3 = Me) rather than ethyl, potentially simplifying the synthesis with decreased steric bulk around the diene. Thus, *dinor*-spiculoic acid A was selected to investigate a synthetic approach which may be extended to all of the natural products.

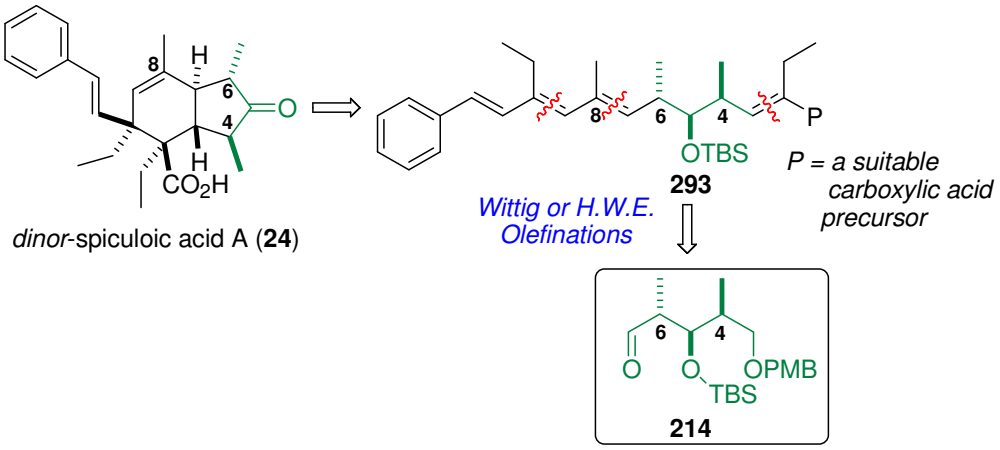
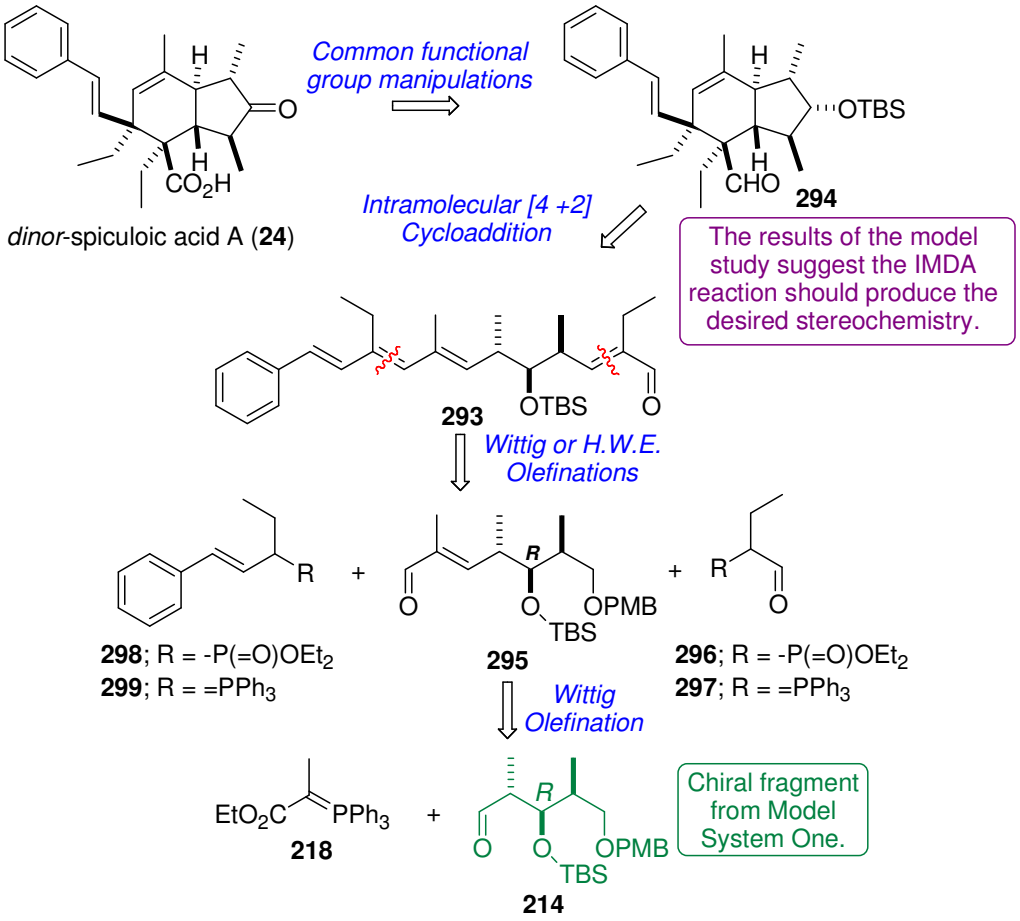


Figure 5.5 A retrosynthesis of *dinor*-spiculoic acid A reveals chiral aldehyde 214 may be employed as a starting material.

Following the success achieved in Model System One it was hoped that a similar synthetic approach, employing Wittig and H.W.E. olefinations to extend a central chiral fragment in two directions, could be employed to achieve the linear triene **293**. A retrosynthetic analysis of *dinor*-spiculoic acid A, described in Scheme 5.1 shows formation of the cycloadduct **294** from the IMDA reaction of linear precursor **293**. Subsequent functional group manipulation, such as silyl ether cleavage and oxidations, of the cycloadduct **294** was expected to give the natural product (**24**).



Scheme 5.1 Retrosynthetic analysis of *dinor*-spiculoic acid A (24).

During the investigation of Model System Two, described in Section 4.4, problems encountered with the sensitivity of the dieneophile functionality suggested that the diene moiety should be installed before generation of the potentially sensitive dienophile functionality in this system. Thus the dienophile moiety is proposed to be incorporated into the linear precursor **293** immediately prior to cyclisation. Due to the difficulties encountered in hydrolysing the ethyl ester to reveal the desired acid functionality in the ultimate step of the model system synthesis, (described in Section 4.2.2), an alternative method of generating the acid functionality was proposed. Rather than masking the acid as the ethyl ester it was decided an aldehyde precursor may be a better option. The aldehyde could be readily oxidised to the corresponding acid, following the IMDA cycloaddition reaction, and would still facilitate a normal electron demand IMDA reaction with the aldehyde group withdrawing electron density from the dienophile. Therefore the dienophile moiety, is available from either a H.W.E. olefination using known phosphonate **296** (which can be synthesised on a large scale in one step[265]) or a Wittig olefination employing commercially available

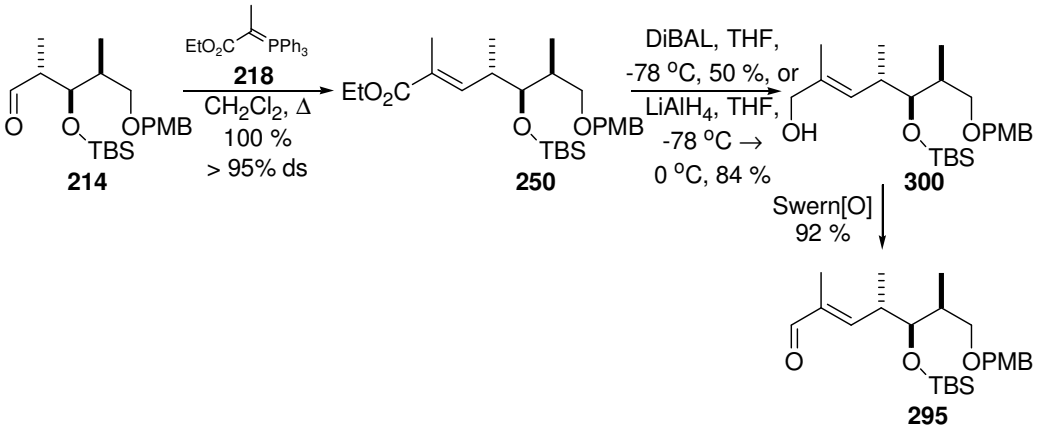
stabilised ylide **297**. In addition to being available commercially, ylide **297** has been reported to be highly *E*-selective and is thus the favoured option.[266]

Linear precursor **293** can be disconnected at the double bonds shown, to be constructed *via* a two-directional Wittig/H.W.E. approach. The conjugated triene moiety may be generated through a Wittig or H.W.E. coupling of ylide **299** or phosphonate **298** with aldehyde **295**. As previously discussed this would provide a convergent approach to all of the natural products as ylide **299** or phosphonate **298** can be employed towards synthesis of each of the spiculoic acid family of natural products. However, ylide **299** and phosphonate **298** are much more hindered than ylide **261**, used in Model System One, possessing an extra ethyl group adjacent to the phosphorus atom which may inhibit the olefination reaction. In addition, while the Wittig olefination installing the conjugated diene in Model System One, proceeded with poor stereoselectivity (*E*:*Z* 1:1), the *Z*-isomer was readily isomerised to the thermodynamically favoured *E*-isomer using I_2 catalytically. Assuming the reaction can be promoted in this more hindered system, the stereoselectivity of the olefination reaction is likely to be poor and thermodynamic isomerisation may not be as effective due to similar thermodynamic requirements of the alternative double bond geometries. Thus, there remain a number of potential difficulties with this proposed methodology that may need to be addressed as they arise.

Chiral aldehyde **295** can be readily achieved though an *E*-selective Wittig olefination of commercially available stabilised ylide **218** and the chiral aldehyde **214,** developed for Model System One. (Scheme 5.1) Chiral aldehyde **214**, has the desired stereochemistry within the C4-C6 stereotriad and methyl substitution at C4 and C6 making it an ideal starting unit to begin construction of the linear precursor. In the attempted synthesis of the linear precursor **(2*E*,5*R*)-114**, in Model System Two, the proposed Wittig olefination was performed in quantitative yield in greater than 95 % diastereoselectivity, refer to Section 4.4, Scheme 4.10. A simple sequence of reduction of the ester to the alcohol and subsequent oxidation will provide aldehyde **295**.

5.1.2 Synthesis of Aldehyde 295

The proposed synthetic strategy to *dinor*-spiculoic acid A (**24**), involves a two directional Wittig/H.W.E. approach to the linear precursor **293** starting with chiral aldehyde **295**. (Scheme 5.1). The synthesis of aldehyde **295** was readily achieved in three steps, outlined in Scheme 5.2, from central chiral fragment **214** which was prepared in Section 4.2.1, Scheme 4.3. As reported in Section 4.4, Scheme 4.10, the Wittig olefination between central chiral aldehyde **214** and stabilised ylide **218** occurs in a highly *E*-selective manner (> 95 % ds) in quantitative yield, to give ester **250** by simply heating the reagents under reflux in CH_2Cl_2 for 5 days.[31] The presence of a single olefinic resonance, a doublet of doublets at 6.78 ppm, and a singlet resonance at 1.79 ppm due to the vinyl methyl group indicated that the reaction had occurred with high diastereoselectivity. Attempts at reduction of the ester **250** using DiBAL in THF at -78 ^{o}C proceeded only halfway after several hours and efforts to push the reaction to completion by warming to -50 ^{o}C and then to room temperature were to no avail.[267] Fortunately, $LiAlH_4$, was found to be a much more suitable reducing agent yielding alcohol **300** in good yield (84 %).[268] Upon addition of $LiAlH_4$, to a solution of the ester in THF at -78 ^{o}C and subsequently warming to 0 ^{o}C, the reaction was complete by TLC analysis after only 10 minutes. Subsequent oxidation to aldehyde **295** was achieved in high yield (92 %) under Swern conditions.[205]

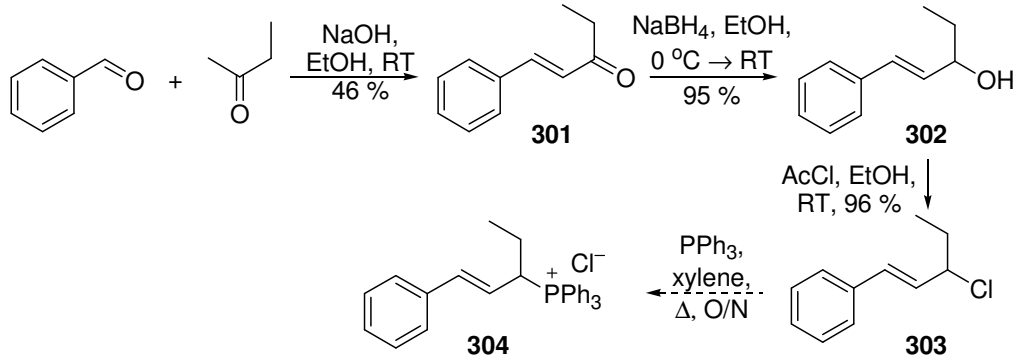


Scheme 5.2 Synthesis of aldehyde 295, *via* a Wittig olefination approach.

5.1.3 The Wittig/H.W.E. Olefination Approach to the Triene.

Due to the success achieved in installing the diene component *via* a Wittig olefination in the model system, and the ease of isomerisation of the diene to the

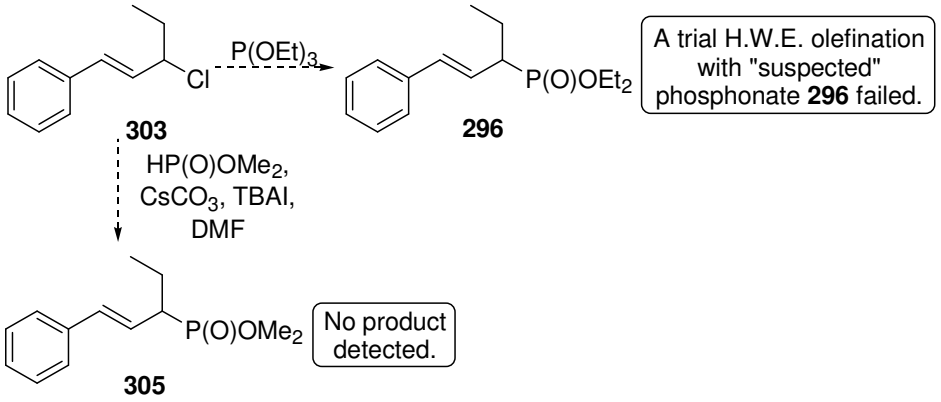
thermodynamically favoured *E*,*E*-diene, with catalytic I_2, this approach was considered a viable option towards the natural product. Synthesis of the desired triphenylphosphine salt **304**, outlined in Scheme 5.3, began with a simple aldol coupling between benzaldehyde and methyl, ethyl ketone. Although the yield was quite low (46 %), the reaction could be performed on multi-gram scale due to the ready availability and low cost of reagents. The least hindered proton on the methyl group is removed in preference to the methylene proton by the hydroxide base generating the terminal enolate which undergoes aldol condensation and spontaneous dehydration under the basic conditions, producing the desired ketone **301**. Reduction of ketone **301**, with $NaBH_4$[240] proceeded in good yield (95 %) to alcohol **302**, which was converted to the chloride **303** using AcCl.[241] Chloride **303** was extracted into EtOAc and could be used without further purification (96 % crude). Unfortunately attempts at generating the triphenylphosphine salt **304** by heating the crude chloride **303** with triphenylphosphine in xylene under reflux overnight were unsuccessful.[236] No triphenylphosphonium salt precipitated out of solution suggesting that the reaction had failed and attempts to extract any product from the crude mixture were unfruitful. Heating under reflux in xylene for several days also failed to generate any product. The steric bulk around the secondary chloride **303** was suspected to be inhibiting reaction at this centre.



Scheme 5.3 Attempted synthesis of triphenylphosphine salt 304.

Focus then shifted to synthesis of the corresponding phosphonate, in the hope that a H.W.E. olefination could be employed to install the triene. Reaction of the chloride **303** with triethylphosphite was suspected to have generated the diethyl phosphonate **296**, however the yield was very low (12 %).[269] It was difficult to confirm the synthesis of the phosphonate due to the low purity and small quantities achieved. The presence of a downfield quartet and an upfield triplet suggested incorporation of the ethoxy groups. The small amount of "potential" phosphonate **296** was used in a trial

H.W.E. olefination reaction however no product was identified from the reaction mixture. Attempts were also made towards the synthesis of the dimethyl phosphonate **305**, employing the milder conditions of Salvatore and co-workers, where dimethylphosphite reacts with primary alkyl halides in the presence of TBAI and Cs_2CO_3 at room temperature.[270] Following separation of the complex reaction mixture, no potential product could be identified which was once again attributed to the steric bulk of the secondary chloride.



Scheme 5.4. Attempted synthesis of phosphonates 296 and 305 to be employed in a H.W.E. approach to the triene.

Due to the difficulties encountered in generating the desired trialkylphosphine salts and phosphonate esters from the secondary chloride **303**, an alternative approach to installation of the double bond was sought. Construction of the conjugated triene could be achieved through the "modified" Julia olefination reaction which was found to be successful in construction of the diene in Model System Two. In this system the "modified" Julia olefination reaction had been successfully employed with a highly sensitive aldehyde **253** and thus it was hoped that these conditions would be sufficiently mild to enable synthesis of the desired triene. The "modified" Julia olefination approach is analogous to the Wittig/H.W.E. methodology in that the installation of the central carbon to carbon double bond of the triene is the objective.

5.1.4 The Julia Olefination Approach to the Triene

The 1-phenyl-1H-tetrazol-5-yl (PT) and benzothiazole-2-yl (BT) sulfones are the most commonly utilised heteroaryl-sulfones used in the "modified" Julia olefination reaction in natural product synthesis.[111] Due to the success of the PT sulfones in the "modified" Julia olefination reaction in Model System Two, the PT sulfones were initially targeted. Two alternative approaches to installation of the triene *via* the

"modified" Julia olefination reaction are described in Figure 5.6. An achiral secondary sulfone **307** can be coupled with chiral aldehyde **295** or a chiral primary sulfone **308** can be coupled with ketone **301**.

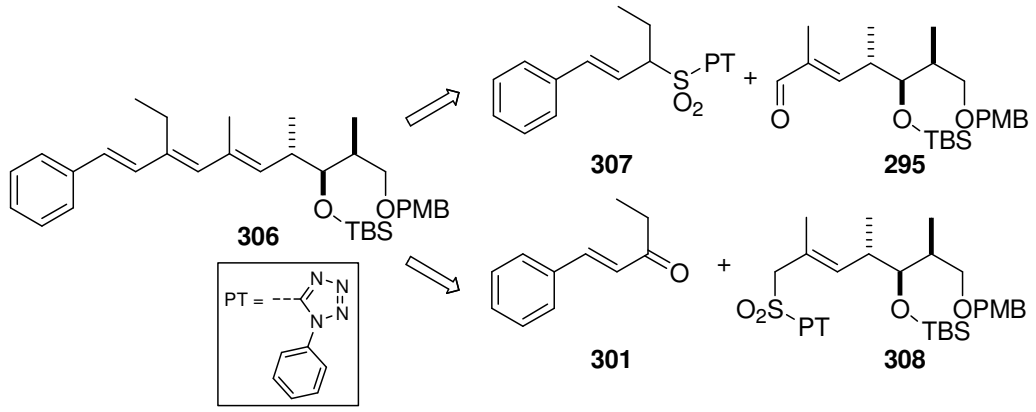
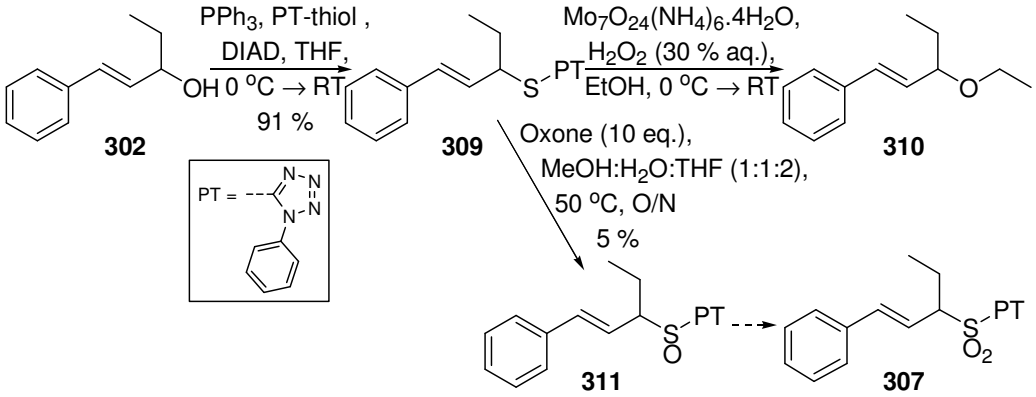


Figure 5.6 Two approaches to the linear triene employing "modified" Julia olefination conditions.

Due to the relatively low cost associated with synthesis of achiral sulfone **307**, compared to chiral sulfone **308**, this approach was considered to be more attractive. Employing the standard Mitsunobu conditions for sulfide synthesis; PPh_3 (1.5 eq.), 1-phenyl-1H-tetrazol-5-yl (PT) thiol (2 eq.) and DIAD (1.8 eq.) were added to a solution of alcohol **302** in THF at room temperature and the solution stirred for 5 minutes. [116,261,271] After this time no product was detected and the starting material had polymerised. As a result the reaction was attempted again, under modified conditions; DIAD (1.1 eq.) was added dropwise to a cooled (0 ^{o}C) solution of alcohol **302**, PT-thiol (1.1 eq.) and PPh_3 (1.1 eq.) in THF. The solution was slowly warmed to room temperature and stirred overnight producing sulfide **309** in 91 % yield (with slight contamination of a by-product after purification).[272] Synthesis of the PT-sulfide **309** was obvious from both the ^{1}H and ^{13}C NMR spectra. In addition to the ten aromatic proton resonances, the proton signal at 4.6 ppm due to the CH_2-S protons had shifted downfield from 4.2 ppm in alcohol **302**. The ^{13}C NMR spectrum showed eight non-equivalent phenyl and two vinyl carbon signals in addition to a resonance at 58 ppm due to the CH_2S carbon and a resonance at 153 ppm due to the carbon within the heterocycle bound to the sulphur atom. Synthesis of the sulfide **309** was affirmed by LCMS analysis which indicated a molecular ion at 345 m/z corresponding to the M + Na^+ ion.



Scheme 5.5 Synthetic efforts towards sulfone 307.

A range of oxidants, solvents, temperatures and solid supports were investigated, however all attempts to oxidise sulfide **309** to the sulfone **307** failed. Table 5.1 summarises the conditions employed in the oxidation attempts and the reaction products isolated.

Table 5.1 Summary of the oxidation conditions employed in the attempted oxidation of sulfide 309 to sulfone 311.

Conditions	**Product**
$Mo_7O_{24}(NH_4)_6.4H_2O$ (0.5 eq.), H_2O_2 (30% w/v, 4.7 eq.), EtOH (0.1 M), 0 °C → RT, O/N[263]	Ether **310**.
Oxone (4 eq.), MeOH:H_2O:THF (1:1:2, 0.1 M), RT, O/N[273]	Recovered SM.
Oxone (10 eq.), MeOH:H_2O:THF (1:1:2, 0.1 M), 50 °C, O/N[273]	Recovered SM/sulfoxide **311** (5%).
Oxone (10 eq.), MeOH:H_2O:THF (1:1:2, 0.05 M), 100 °C, O/N[273]	Oxidative cleavage of double bond.
Oxone (5 eq.), acetone:H_2O (1:1, 0.13 M), 50 °C, O/N[274]	Recovered SM.
Oxone (10 eq.), acetone:H_2O (1:1, 0.05 M), 100 °C, O/N[274]	Oxidative cleavage of double bond.
Oxone (1.5 eq.), silica gel/H_2O, CH_2Cl_2 (0.2 M), RT, O/N[275,276]	Recovered SM.
Oxone (1.5 eq.), alumina/H_2O, CH_2Cl_2 (0.2 M), RT, O/N[275,276]	Recovered SM.

Employing H_2O_2 (30 % w/v aq.) and catalytic $Mo_7O_{24}(NH_4)_6.4H_2O$ in ethanol resulted in substitution of the thioether by the ethanol to give ether **310**.[263] Oxone was investigated as an alternative oxidising agent. Stirring at room temperature, 50 °C or overnight in either MeOH:H_2O:THF[273] or acetone:H_2O[274] with various equivalents of oxone (4-10 eq.) yielded predominantly unreacted starting material. At 50 °C very small quantities of sulfoxide **311** were isolated (5 %). NMR analysis of the small amounts of sulfoxide **311** generated was insufficient to determine whether oxidation had proceeded to the sulfoxide **311** or the sulfone **307**. A large shift in the

^{1}H resonance of the CH_2-S protons to 5.6 ppm (from 4.6 ppm) indicated that this centre was more deshielded due to the electron withdrawing effect of the oxygen however, just how many oxygen atoms were attached to the sulfur was unclear. The ^{13}C NMR spectrum revealed only a small shift of the CH_2-S carbon from 58 ppm to 62 ppm and the aromatic carbons of the heterocycle remained unaffected. LCMS analysis confirmed synthesis of the sulfoxide **311** with a molecular ion of 384 m/z corresponding to the M + K^+ ion. Attempts at driving the oxidation reaction towards the sulfone **307** by heating to 100 ^{o}C in both acetone:H_2O (1:1) and MeOH:H_2O:THF (1:1:2) resulted in oxidative cleavage of the double bond.

In a final attempt at effecting oxidation of the sulfide **309**, a solid support was added to provide a surface for reaction. In two separate attempts silica gel and alumina were activated and stirred with H_2O before addition to solutions of sulfide **309** followed by addition of oxone.[276,275] The resulting slurries were stirred at room temperature overnight after which time no reaction had occurred and starting material was recovered.

An alternative sulfone synthesis was sought due to the difficulties encountered in the oxidation of the PT-sulfide **309** to the PT-sulfone **307**. The BT-heterocyclic activator was considered as an alternative because it is commonly used in natural products synthesis[111] and the starting material benzothiazole was available on site. Several literature examples of β,γ-unsaturated sulfones suggested that the desired sulfone **314** may be achieved employing this approach and successfully coupled *via* a "modified" Julia olefination reaction.[273,277] Two examples of β,γ-unsaturated sulfones (**312** and **313**) which were synthesised by oxidation (oxone-THF:MeOH:H_2O) of the corresponding sulfides are represented in Figure 5.7. Additionally, sulfone **313** is a secondary sulfone as is the desired sulfone **314,** suggesting that secondary BT-sulfones can be synthesised and coupled successfully.

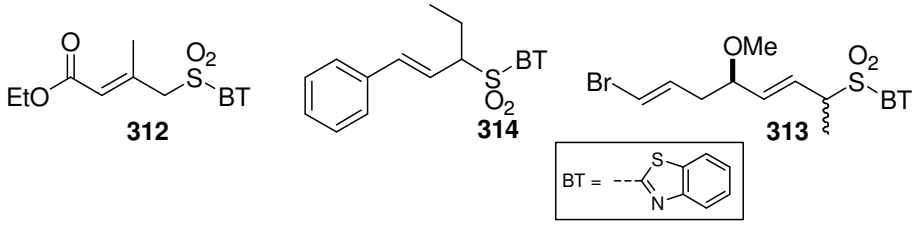
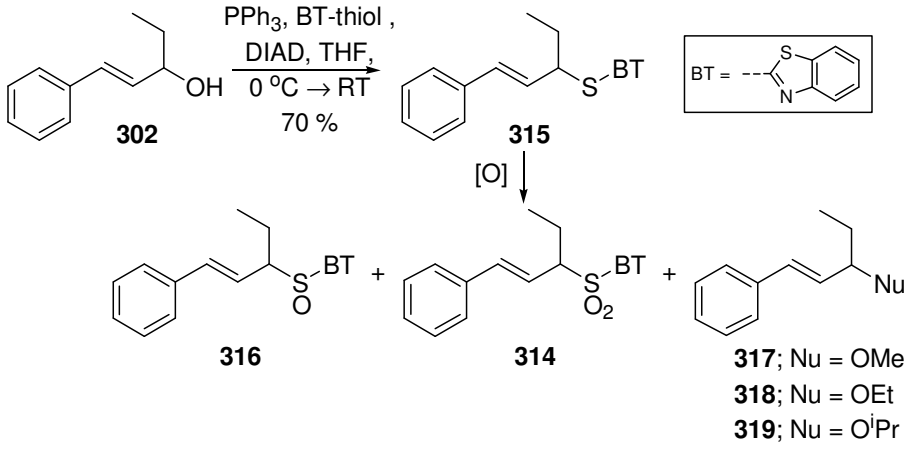


Figure 5.7 Literature examples of BT-sulfones 312 and 313 and the BT-sulfone 314 targeted in this study.

While the BT-sulfones were not considered to be particularly desirable coupling partners due to their propensity for self-condensation, at this point the goal was to generate any sulfone to attempt the "modified" Julia olefination. If self-condensation was found to be an issue, the Barbier conditions described in Section 1.3.4, may be employed to overcome this problem, however sensitive or complex aldehydes are less compatible with this approach.

Synthesis of the desired sulfone **314** and subsequent "modified" Julia olefination attempts are outlined in Scheme 5.6. Employing the modified Mitsunobu conditions used to synthesise PT-sulfide **309**, the corresponding BT-sulfide **315** was achieved in 70 % yield.[272] Synthesis of the BT-sulfide **315** was confirmed by LCMS analysis with a molecular ion at 334 m/z corresponding to the M + Na^+ ion. NMR analysis revealed a resonance at 4.2 ppm in the ^1H spectrum due to the CH_2-S protons and a peak at 53 ppm in the ^{13}C spectrum, due to the CH_2-S carbon.



Scheme 5.6 Synthesis of BT sulfone 314.

Unfortunately attempts to oxidise sulfide **315** to the sulfone **314** were again problematic. A variety of oxidising agents were investigated and are summarised in Table 5.2. Employing H_2O_2 (30% w/v aq.) and catalytic $Mo_7O_{24}(NH_4)_6.4H_2O$ in both ethanol and isopropanol and at different reaction temperatures (0 $^oC \rightarrow$ -20 ^oC or 0 $^oC \rightarrow$ RT) produced predominantly the nucleophilic displacement products (**318** and **319**).[263,278] However small amounts of sulfoxide **316** (5%) were isolated from the reaction at room temperature. Maintaining the reaction at 0 ^oC all day and then storing in the freezer (-20 ^oC) overnight allowed formation of some sulfone **314**, albeit a very small amount (11 %).[278] Similarly, with oxone (4-10 eq.) the major product **317** arose from displacement of the heterocycle with MeOH.[273] A small

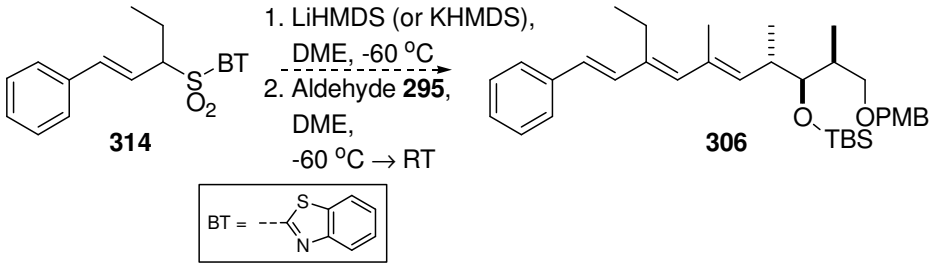
amount of sulfone **314** (12 %) was achieved when fewer equivalents of oxone were used. Not surprisingly, $NaIO_4$ in H_2O:MeOH:THF (1:1:2) also resulted in the methanol displacing the heterocycle, producing **317**.[279] $NaBO_3$ in both acetic acid and MeOH:NaOH yielded the nucleophilic displacement product and starting material respectively.[280] Finally, oxidation using NMO/TPAP was attempted however no reaction occurred after stirring at 40 ^oC, O/N.[281]

Table 5.2 Summary of the oxidation conditions employed in the attempted oxidation of sufide 315 to sulfone 314.

Conditions	**Product**
$Mo_7O_{24}(NH_4)_6.4H_2O$ (0.04 eq.), H_2O_2 (30% w/v, 2.9 eq.), EtOH (0.2 M), 0 $^oC \rightarrow$ RT, O/N[263]	Ether **318**/sulfoxide **316** (5 %).
$Mo_7O_{24}(NH_4)_6.4H_2O$ (0.04 eq.), H_2O_2 (30% w/v, 2.9 eq.), EtOH (0.2 M), 0 $^oC \rightarrow$ -20 ^oC, O/N[278]	Ether **318**/sulfone **314** (11 %).
$Mo_7O_{24}(NH_4)_6.4H_2O$ (0.1 eq.), H_2O_2 (30% w/v, 4.7 eq.), ^{i}PrOH (0.01 M), 0 $^oC \rightarrow$ RT, O/N	Ether **319**/oxidative cleavage of double bond.
Oxone (10 eq.), MeOH:H_2O:THF (1:1:2, 0.05 M), RT, O/N[273]	Ether **317**/sulfoxide **316** (23 %).
Oxone (4 eq.), MeOH:H_2O:THF (1:1:2, 0.1 M), RT, O/N[273]	Ether **317**/sulfone **314** (12 %).
$NaIO_4$ (2.5 eq.), H_2O:MeOH:THF (1:1:2), 0 $^oC \rightarrow$ RT, O/N[279]	Ether **317**.
$NaBO_3.4H_2O$ (5 eq.), acetic acid (0.14 M), 50 ^oC, 2hrs[280]	BT cleaved.
$NaBO_3.4H_2O$ (5 eq.), MeOH:NaOH (1 M), 50 ^oC, 2 days[280]	Recovered SM.
Molec. Sieves 4 Å, NMO, CH_3CN, TPAP, RT $\rightarrow$ 40 ^oC, O/N[281]	Recovered SM.

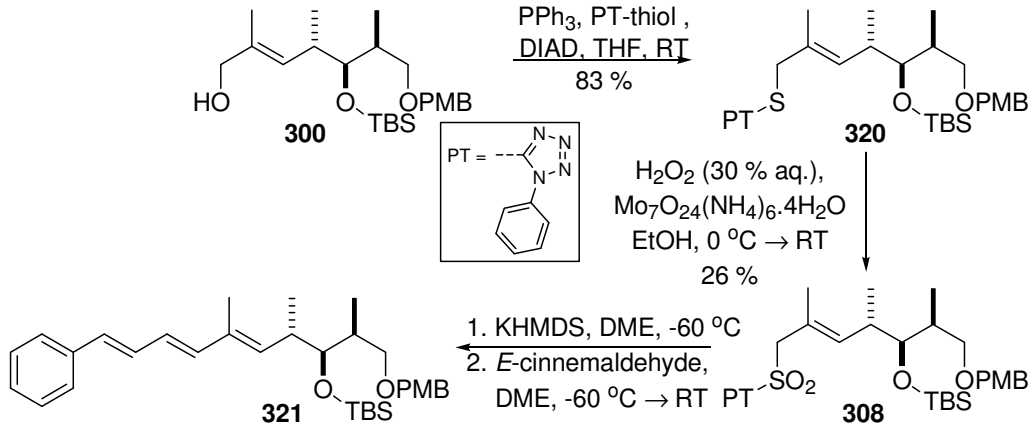
In the two instances where a very small amount of the desired sulfone **314** was formed confirmation of synthesis was again achieved by LCMS analysis which revealed a molecular ion at 366 m/z, corresponding the M + Na^+ ion for sulfone **314**. The ^1H NMR spectrum revealed a peak at 4.2 ppm due to the CH_2-SO_2 protons and the ^{13}C spectrum revealed a peak at 70 ppm, due to the CH_2-SO_2 carbon.

Having affirmed that the desired sulfone **314**, has been synthesised, although in very small quantities, attempts were made at coupling BT-sulfone **314** (2.9 eq.) and aldehyde **295**, in a "modified" Julia olefination reaction as described in Scheme 5.7.[116] Both KHMDS (2.6 eq.) and LiHMDS (2.6 eq.) in DME were employed in separate attempts however both yielded only recovered starting materials.[272] This was thought to be due to the increased steric bulk around the secondary sulfone **314** inhibiting reaction.



Scheme 5.7 Attempted "modified" Julia olefination coupling of sulfone 314 and aldehyde 295.

Due to the difficulties in generating the desired achiral sulfones **307** and **314**, in addition to the apparent steric issues inhibiting the coupling reaction, the alternative "modified" Julia olefination approach to the desired product, proposed in Figure 5.6, was investigated. Reaction between chiral sulfone **308** and ketone **301** was hoped to occur more readily due to primary sulfone **308** having less steric bulk around the sulphur atom. The PT-sulfide **320** was synthesised from alcohol **300**, employing the general Mitsunobu conditions described above in 83 % yield (Scheme 5.8).[116,261] Subsequent oxidation with H_2O_2 (30 % w/v, aq.) and catalytic $Mo_7O_{24}(NH_4)_6.4H_2O$ provided sulfone **308**, albeit in a poor yield of 26 %.[272] The low yield can be attributed to decomposition of the starting material with evidence of cleavage of the PMB ether. A single, small scale attempt at coupling sulfone **308** to commercially available *E*-cinnamaldehyde (3 eq.) was performed under the standard "modified" Julia olefination conditions employed in Model System Two.[272] *E*-Cinnamaldehyde was selected as a less hindered alternative to ketone **301** and was hoped to couple more readily. A small amount of the desired triene was believed to have formed due to the presence of multiple vinyl signals in the ^{1}H NMR spectrum of one of the fractions from the column, however characterisation of the potential product could not be achieved due to the very small quantity produced. In order to further investigate the viability of the "modified" Julia olefination reaction in the synthesis of the triene **306**, optimisation of the conditions for the synthesis of sulfone **308** was required. The expense involved in further investigating the oxidation of expensive chiral sulfide **320**, lead to abandonment of this approach. A more economically favourable approach was to search for an alternative to the achiral PT-sulfone **307** and BT-sulfone **314**.



Scheme 5.8 Synthesis and attempted "modified" Julia olefination reaction of chiral sulfone 308.

5.1.4.1 Future Directions: Alternative "Modified" Julia Olefination Reactions

It was suspected that the steric bulk of the secondary sulfones **307** and **314** was inhibiting the reaction with aldehyde **295**. A return to the literature revealed a number of potential alternative sulphur containing coupling partners for the Julia olefination reactions that have been employed to generate tri-substituted alkenes. A more recently discovered aromatic activator is the 3,5-bis(trifluoromethyl)phenyl (BTFP) group which has proven to be successful in the generation of both tri- and tetra-substituted alkenes.[282,283] Relatively hindered secondary BTFP sulfones, such as **322** and **323** in Figure 5.8, have been coupled to aldehydes in good to moderate yields however with ketones the yields are generally poor.[282,283] A general observation is that as the steric bulk around the carbonyl and the sulfone increases, the yield decreases. Unfortunately this approach is unlikely to be successful in generation of the desired triene because the reaction selectivity is only moderate and is favoured towards the *Z*-alkene not the *E*-alkene which is desired for the spiculoic acid synthesis.

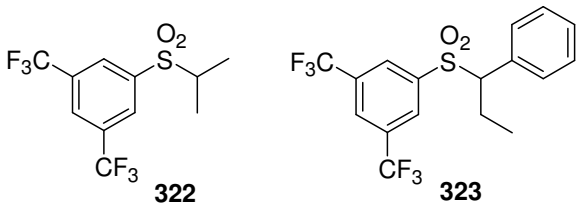
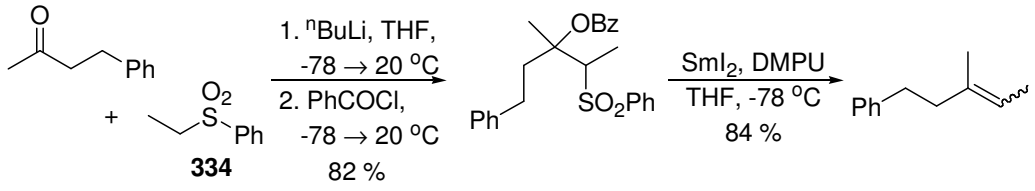


Figure 5.8 3,5-Bis(trifluoromethyl)phenyl (BTFP) sulfones used in synthesis of tri- and tetra-substituted alkenes.

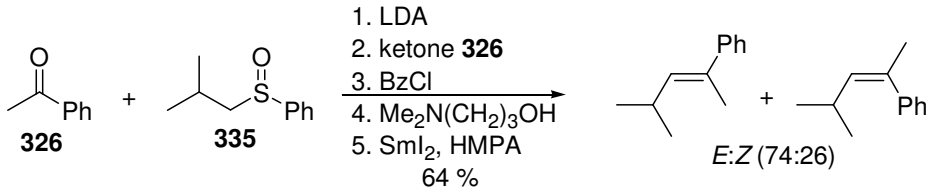
An alternative approach, reported by Marko and co-workers, involves coupling the anion of primary phenyl sulfone **334** to a ketone to generate the tri-substituted

alkene.[284,285] Both cyclic and acyclic ketones were successfully employed with yields ranging from 69 to 93 % with *E*:*Z* product ratios of ~2:1. Scheme 5.9 shows an example of this approach in generating a tri-substituted alkene.



Scheme 5.9 Synthesis of a tri-substituted alkene using phenyl sulfone 334 in a Julia olefination reaction.[284,285]

A slight modification to this approach, reported by Marko and co-workers, involves the direct coupling of primary or secondary phenyl sulfoxides **335** to an aldehyde or ketone to generate di-, tri- or tetra-substituted alkenes.[286] Moderate to high yields and high levels of *E*-selectivity were achieved even for tri- and tetra-substituted alkenes, an example of which is shown in Scheme 5.10. This approach appears to be the most attractive option due to the prevalence for formation of the *E*-alkene which is desired in the spiculoic acid linear precursors. Unfortunately the olefination reactions studied to date have involved relatively simple aldehydes, ketones and sulfoxides, so extension of this approach to the spiculoic acids may reveal further challenges. Due to time limitations, these two approaches reported by Marko and co-workers have not yet been explored towards the total synthesis of the spiculoic acids.[284,285,286] As these methods are reported to generate tri-substituted alkenes with moderate to good *E*-selectivity it is hoped that by employing these conditions access to the linear triene will be achieved.



Scheme 5.10 Synthesis of tri-substituted alkenes *via* a "modified" Julia olefination employing sulfoxide 335.[286]

5.1.5 The Palladium-Catalysed Cross-Coupling Approach to the Triene

It was becoming apparent, following the failed attempts at employing the Wittig, H.W.E. and "modified" Julia olefination reactions, that installation of a tri-substituted double bond may not be a viable approach to achieving the linear triene.

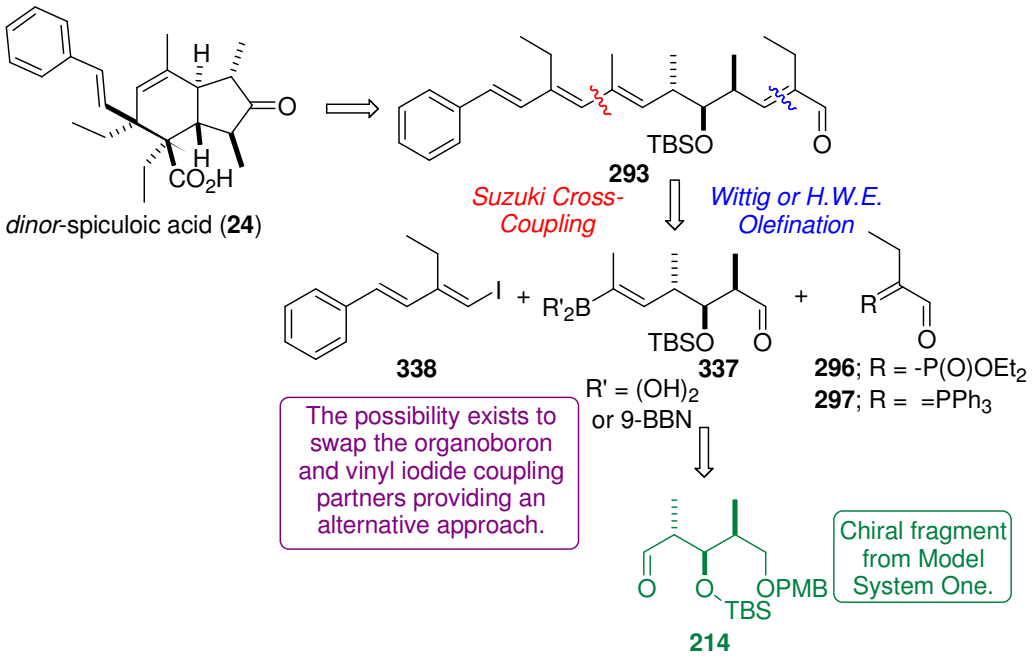
In addition to the difficulties in synthesising the hindered phosphorus containing reagents for the Wittig/H.W.E. olefinations and sulfones for the "modified" Julia olefinations, the limited reactivity of the bulky, cross-coupling partners appeared to be a problem, An alternative approach, pursued in parallel to investigations of the "modified" Julia olefination reaction, were the various palladium-catalysed cross-coupling reactions using organometallic reagents.

Palladium-catalysed cross-coupling reactions were explored in the hope that construction of the carbon to carbon single bonds between the olefinic bonds would be a more viable approach to the linear triene. Rather than forming the tri-substituted, central double bond of the triene in a stereoselective olefination reaction, a single bond could be constructed between vinyl coupling partners. For a detailed review of palladium-catalysed cross-coupling reactions refer to Section 1.3.6.

The Stille cross-coupling reaction of organohalides and organotin reagents is a popular tool in natural products synthesis.[51,50] The mild reaction conditions, functional group tolerance and high selectivity make this an attractive approach. The organotin reagents are quite stable and easily handled however the tin-containing reagents and by-products are highly toxic. Another popular cross-coupling approach used extensively in total synthesis is the Suzuki reaction, whereby an organoborane is coupled to an organohalide.[52,53] Just like the organotin reagents, organoboranes are quite stable and easily handled making them a synthetically attractive option. The Suzuki cross-coupling reaction is effective in the stereoselective synthesis of conjugated polyenes, occurs under moderate conditions and has relatively benign reagents and by-products. As a result the Suzuki cross-coupling reaction was considered the most attractive of the palladium-catalysed cross-coupling reactions available. A discussion of the features of both the Suzuki and Stille cross-coupling reactions can be found in Sections 1.3.6.2.3 and 1.3.6.2.2 respectively.

Retrosynthetic analysis revealed that a convergent approach to the synthesis of all of the spiculoic acids could still be achieved by breaking the carbon to carbon single bond indicated in Scheme 5.11. Construction of the carbon to carbon σ bond can be achieved through a Suzuki cross-coupling reaction between vinyl iodide **338** and vinyl organoborane **337**. Just as in the olefination approach, vinyl iodide **338** is common to all of the members of the spiculoic acid family of natural products, and

could thus be utilised in the synthesis of each. Flexibility exists within this strategy because the vinyl iodide or vinyl organoborane coupling partners can be switched enabling two alternative routes to the conjugated triene. Installation of the dienophile moiety is again proposed *via* a Wittig or H.W.E. olefination reaction using ylide **297** or phosphonate **296**. Chiral aldehyde **214**, developed for Model System One, is once again an appropriate precursor compound providing access to halide or alkyne derivatives which may be used to synthesise various organoboron reagents.

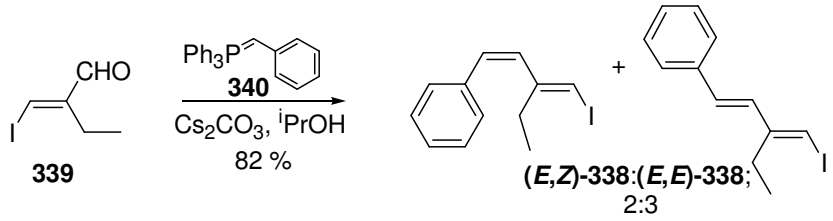


Scheme 5.11 Retrosynthetic analysis of a palladium-catalysed cross-coupling approach to the linear precursor 293.

5.1.5.1 Synthesis of Vinyl Iodide 338

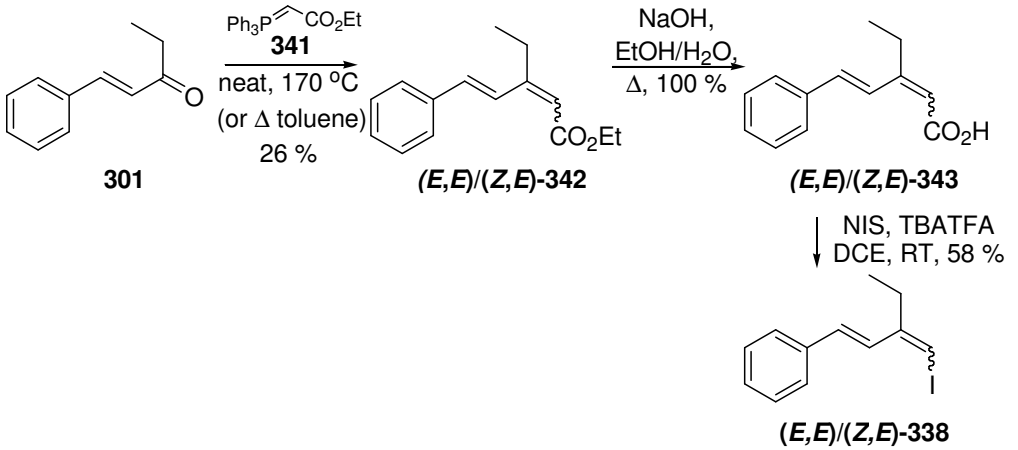
Vinyl iodide **(*E*,*E*)-338**, had previously been reported by Mehta and Kunda[232] in their synthetic efforts towards a model of spiculoic acid A. They employed a six step sequence ending in a Wittig olefination reaction, shown in Scheme 5.12, between the ylide **340** and aldehyde **339**, producing the **(*E*,*Z*)-338** and **(*E*,*E*)-338** iodo-alkenes in a 2:3 ratio in 82 % yield. While separation of the isomers was readily achieved by column chromatography, the reagents are relatively low cost and the synthesis straight-forward, the poor *E*-selectivity of the Wittig olefination instigated the pursuit of an alternative synthetic route to **(*E*,*E*)-338**. An extensive search of the literature revealed that synthesis of the desired fragment in a stereoselective manner was not a trivial task. Indeed a number of options were investigated, and are discussed herein.

However difficulties in achieving iodo-alkene **(*E*,*E*)-338**, with stereochemical purity ultimately led to the synthesis reported by Mehta and Kunda being employed.[232]



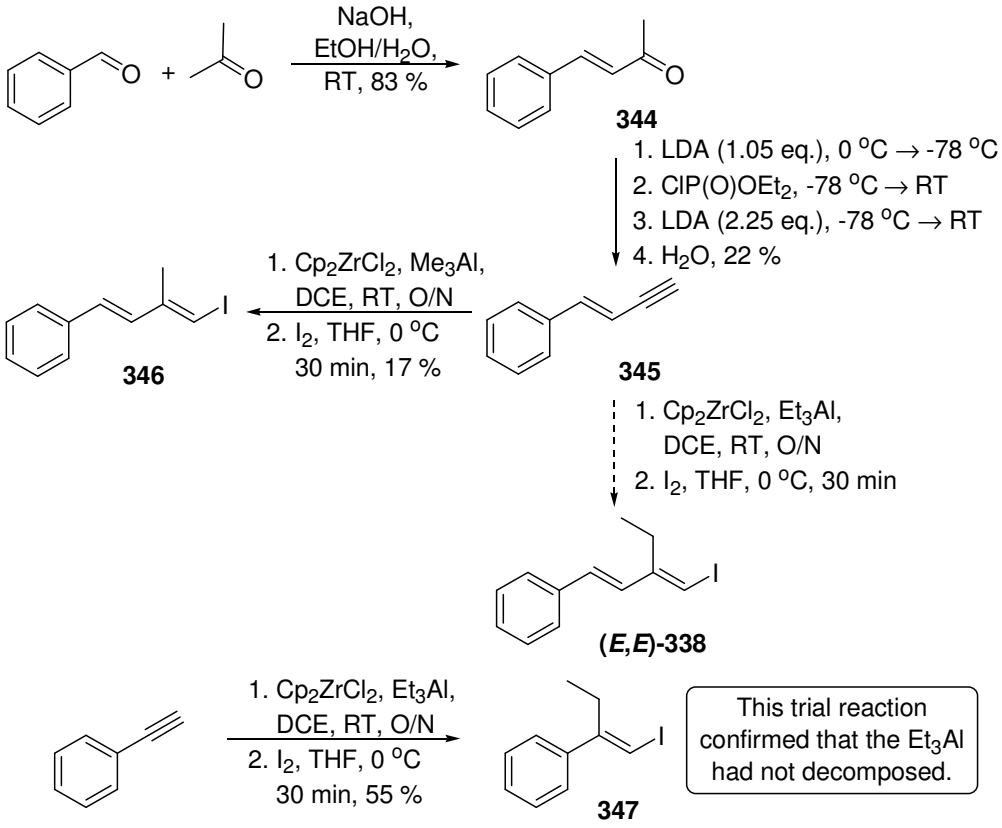
Scheme 5.12 Synthesis of vinyl iodide (*E*,*E*)-338 *via* a Wittig olefination, reported by Mehta and Kunda.[232]

A variety of alternative strategies to stereoselectively synthesise vinyl iodide **(*E*,*E*)-339** were investigated. A Wittig olefination approach, outlined in Scheme 5.13, involves reaction of ketone **301** (synthesis described in Section 5.1.3) and commercially available ylide **341**. In general ylide **341** will couple to aldehydes with high levels of *E*-selectivity, in good yield and at relatively mild temperatures (40 ^{o}C).[287] However in this case the ylide must react with ethyl ketone **301**, which is much more hindered than simple aldehydes. General strategies to encourage more unreactive species to undergo Wittig olefination reactions include employing higher temperatures and more concentrated reaction conditions.[100] As such, the neat reagents were heated to 170 ^{o}C for several days, producing mixtures of **(*E*,*E*)-342** and **(*Z*,*E*)-342** in poor yield (26 %) due to incomplete conversion of the starting materials. These isomers were partially separated by column chromatography however attempted isomerisation of the **(*Z*,*E*)-342**, adduct to the **(*E*,*E*)-342** adduct, using catalytic I_2 was unacceptably slow. Attempts at improving the yield by heating the reagents under reflux in toluene for several weeks yielded mostly recovered starting materials. Three isomeric vinyl esters were isolated, suggesting isomerisation of the double bond within vinyl ketone **301** was also occurring. The mixture of vinyl esters, **(*E*,*E*)/(*Z*,*E*)-342**, were hydrolysed (NaOH/EtOH) in quantitative yield to acids **(*E*,*E*)/(*Z*,*E*)-343** and were subsequently converted with reasonable efficiency (58 %) to the vinyl iodides **(*E*,*E*)/(*Z*,*E*)-338** with TBATFA and N-iodosuccinimide in a halodecarboxylation reaction.[288] Unfortunately the vinyl iodides, **(*E*,*E*)-338** and **(*Z*,*E*)-338**, were inseparable by column chromatography. Problems in isolating the desired product combined with the poor yield for the Wittig olefination step, even under harsh conditions, lead to abandonment of this approach.



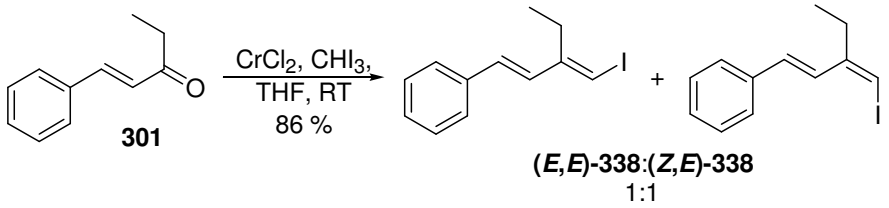
Scheme 5.13 An alternative Wittig approach to the synthesis of vinyl iodide (*E*,*E*)-338.

An alternative approach involved generation of the vinyl iodide **(*E*,*E*)-338** *via* the terminal alkyne **345**, as described in Scheme 5.14. Ketone **344** was generated in good yield (83 %), *via* an aldol coupling between benzaldehyde and acetone and subsequent dehydration of the aldol adduct in situ. The corresponding lithium enolate of ketone **344** was converted to the phosphonate ester using chlorodiethylphosphite which upon addition of LDA (>2 eq.) and quenching with H_2O quench produced terminal alkyne **345** in low yield (22 %).[289] Conversion of alkyne **345** to the vinyl iodide **346** with Cp_2ZrCl_2, Me_3Al and I_2 also occurred in quite a poor yield (17 %).[290] Duplicating these conditions employing Et_3Al, rather than Me_3Al, which was required to achieve the desired ethyl substitution on the diene, yielded no product. It was thought that the reaction may have failed because the Et_3Al, which was quite old, may have decomposed. A trial reaction converting acetylene to the vinyl iodide under the same conditions yielded iodide **347** in 55 % yield suggesting that the problem was not with the quality of the Et_3Al and that perhaps the alkyne **345** was sensitive to decomposition under the reaction conditions. As a result this approach was abandoned and an alternative strategy sought.



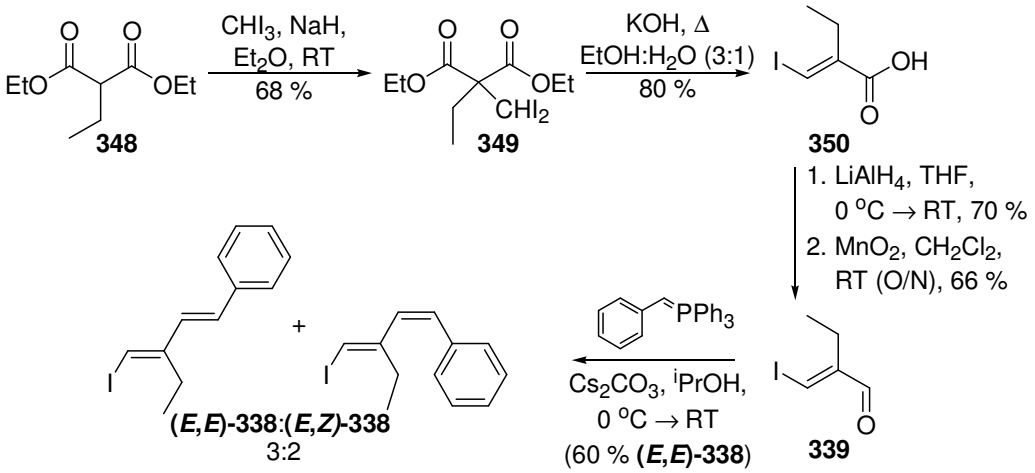
Scheme 5.14 Attempted stereoselective synthesis of vinyl iodide (*E*,*E*)-339 from terminal alkyne 345.

Takai and co-workers reported the direct conversion of ketones to vinyl iodides using $CrCl_2$ and CHI_3 in THF.[291] Scheme 5.15 illustrates the conversion of ketone **301** into vinyl iodides ***(E,E)*-338** and **(*Z*,*E*)-338** which were achieved as a 1:1 mixture of isomers in good yield (86 %) under these conditions. Attempted isomerisation with catalytic I_2 was unreasonably slow and was abandoned. Attempts to separate **(*E*,*E*)-338** and **(*Z*,*E*)-338** by column chromatography were unsuccessful. Evans and Black reported that using dioxane or dioxane/THF as the solvent leads to higher yields of *E*-iodides.[292] Unfortunately the low solubility of the reagents in dioxane resulted in only starting material being recovered.



Scheme 5.15 Synthesis of the desired (*E*,*E*)-338 and the undesired (*Z*,*E*)-338 as a 1:1 inseparable mixture.

Following the unsuccessful attempts towards an alternative, stereoselective synthesis of **(*E*,*E*)-338**, access to the desired iodide was achieved by employing the method reported by Mehta and Kunda, outlined in Scheme 5.16.[232] Alkylation of diethyl α-ethylmalonate (**348**) with tri-iodomethane gave compound **349**. Decarboxylative elimination and ester hydrolysis promoted by KOH gave carboxylic acid **350** in good yield (80 %). Reduction of the carboxylic acid **350** to the alcohol **351** and subsequent oxidation using MnO_2 produced aldehyde **339**. The final step, a Wittig olefination reaction with ylide **340**, produced a separable mixture of the desired iodide **(*E*,*E*)-339** and **(*E*,*Z*)-339**. With the pure **(*E*,*E*)-338**, iodide coupling partner in hand (achieved in 13 % overall yield over five steps from diethyl malonate (**348**)) the organoborane coupling partner **337** was targeted.

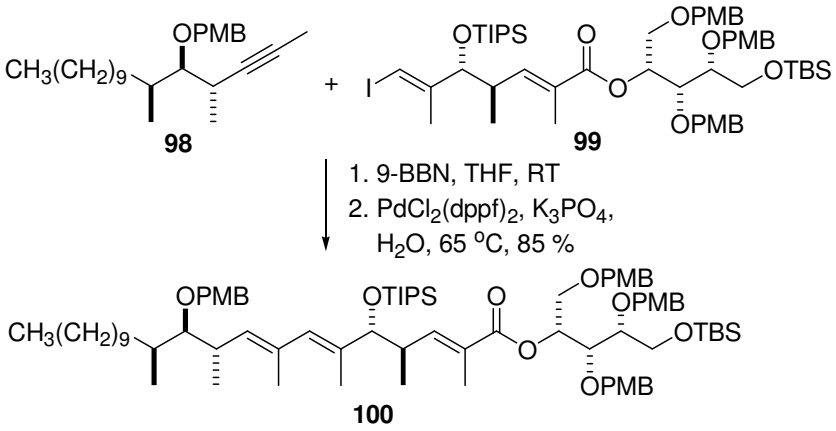


Scheme 5.16 Synthesis of the (*E*,*E*)-338 and (*E*,*Z*)-338 iodides employing the method reported by Mehta and co-workers.

5.1.5.2 The Suzuki Cross-Coupling Approach

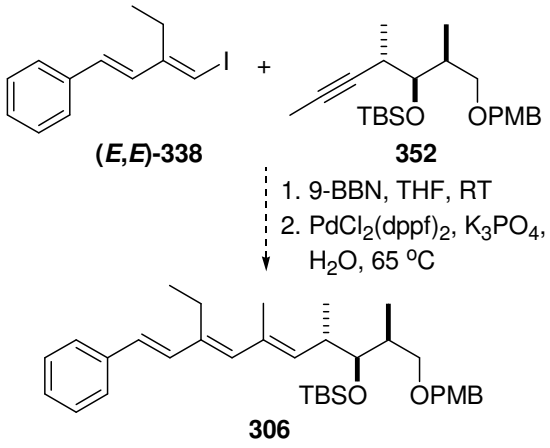
The Suzuki cross-coupling reaction occurs readily between vinyl halides and vinyl organoboranes.[52,53] Kobayashi and co-workers employed a Suzuki cross-coupling reaction in their total synthesis of the polypropionate derived natural product, Khafrefungin, outlined in Scheme 5.17.[189] There are a number of similarities between this system and the devised approach to *dinor*-spiculoic acid A, outlined in Scheme 5.11. In the synthesis of khafrefungin, methyl alkyne **98** is converted to the organoborane using 9-BBN and is subsequently coupled to vinyl iodide **99**. This system exhibits many similarities in structure, stereochemistry and functional groups with the proposed synthetic approach outlined in Scheme 5.11. The vinyl iodide coupling partner **99** is tri-substituted as is **(*E*,*E*)-338**, the vinyl coupling partner for

the proposed synthesis of the spiculoic acids. Both systems possess OPMB and OTBS protecting groups and double bonds suggesting that these functional groups are tolerant to the coupling conditions. Alkyne **98** is remarkably similar to central chiral fragment **214** (Scheme 5.11) with analogous stereochemistry of the stereotriad. Based on the success of the Suzuki cross-coupling reaction (85 % yield) in the total synthesis of Khafrefungin, an extension of this approach was considered to be an attractive option for the synthesis of the spiculoic acids.



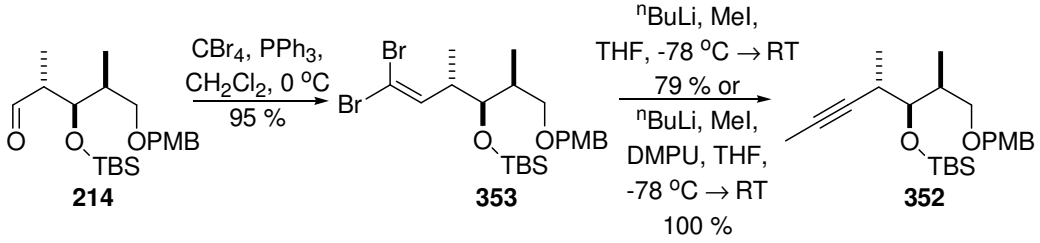
Scheme 5.17 Suzuki cross-coupling reaction employed in the total synthesis of Khafrefungin.[189]

Various vinyl organometallic reagents are available stereoselectively from the corresponding alkyne precursors such as vinyl tin,[293] vinyl boron[189,294,295] or vinyl halides derivatives.[296] This introduces the opportunity to investigate alternative organometallic cross-coupling reactions if required. Thus, in a strategy analogous to that employed by Kobayashi and co-workers in their synthesis, outlined in Scheme 5.17, alkyne **352** was targeted, to be employed in a Suzuki cross-coupling reaction as described in Scheme 5.18.



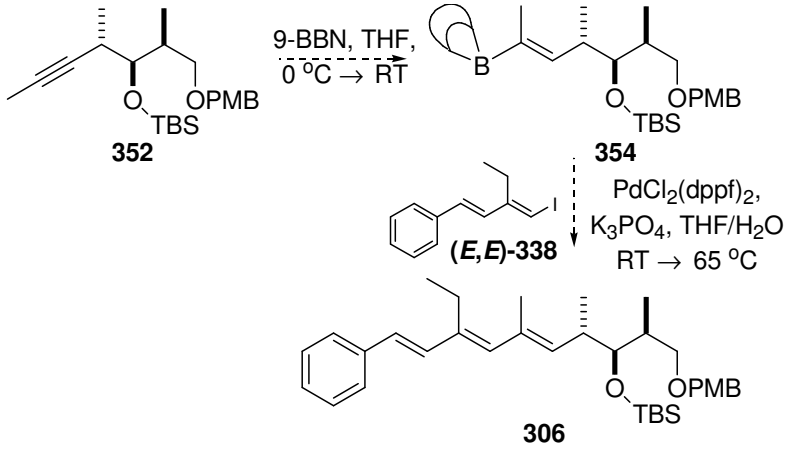
Scheme 5.18 The proposed approach to the spiculoic acids employing a Suzuki cross-coupling reaction similar to that employed by Kobayashi and co-workers.

The central chiral aldehyde **214**, from Model System One, was converted to the dibromoalkene **353**, in good yield (95 %), *via* a Wittig olefination reaction whereby the ylide is generated in situ from CBr_4 and PPh_3, as described in Scheme 5.19.[297] A standard Corey-Fuchs procedure was employed to generate alkyne **352**.[298] The addition of DMPU to the reaction mixture resulted in higher yields of the alkyne being achieved and with higher purity.[299]



Scheme 5.19 Synthesis of chiral alkyne 352.

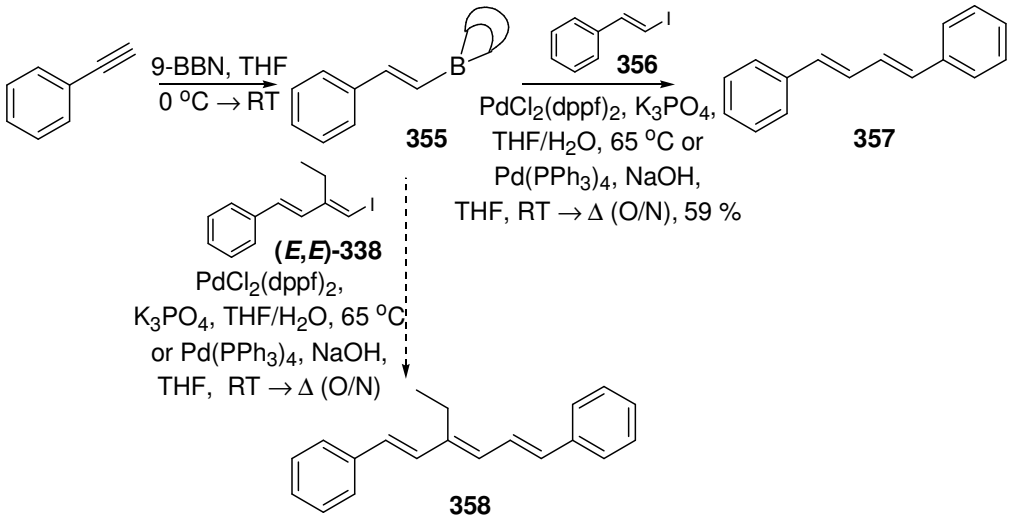
An advantage of this Suzuki cross-coupling approach is that alkyne **352** can be converted to the organoborane using 9-BBN and used directly in the coupling reaction without isolation. The procedure involves addition of 9-BBN to a solution of the alkyne **353** at 0 °C, which is warmed to room temperature and stirred overnight to allow formation of the organoborane **354**. The Suzuki cross-coupling reaction is then performed by addition of vinyl iodide (***E*,*E*)-338**, K_3PO_4 and $PdCl_2(dppf)_2$ and heating to 65 °C for 30 minutes. Unfortunately no product was observed and a very small amount of alkyne **352** was recovered.



Scheme 5.20 Attempted synthesis of organoborane 354 and subsequent palladium-catalysed Suzuki cross-coupling to vinyl iodide (*E*,*E*)-338.

In order to investigate why the reaction failed a trial coupling between acetylene and vinyl iodide **359** (Scheme 5.21) was attempted to identify whether the problem was

lack of, or inefficient formation of the organoborane **354** or whether the steric bulk of the coupling partners was inhibiting the reaction. Coupling between these two relatively unhindered coupling partners, organoborane **355** and iodide **356**, did produce 1,4-diphenylbuta-1,3-diene (**357**) as a mixture of isomers, however there were several other compounds in the reaction mixture as well. Alternative conditions, using $Pd(PPh_3)_4$ and NaOH were also employed and the coupling reaction proceeded as expected, yielding 59 % of the *E*,*E*-diene **357**.[294] This suggested that the problem was not with the quality of the 9-BBN and that the organoborane **355** is forming. It must be considered however that phenyl acetylene is a terminal alkyne whereas alkyne **352**, required for the total synthesis, is a non-terminal alkyne so it is still possible that the more hindered secondary organoborane **354** is not forming from alkyne **352**.

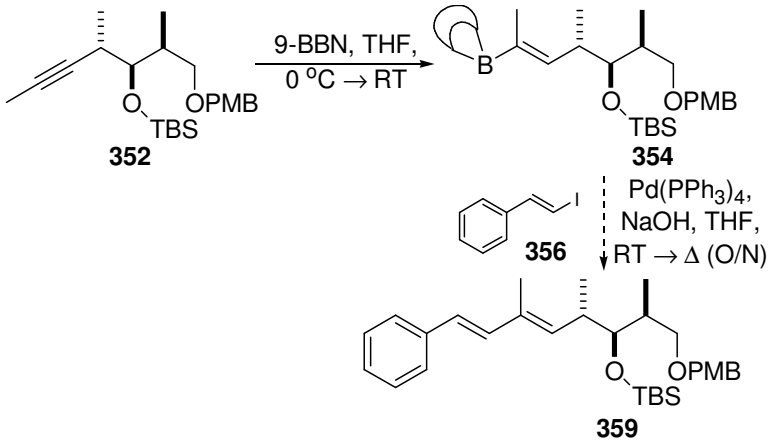


Scheme 5.21 Attempted synthesis and palladium-catalysed Suzuki cross-coupling reactions of the 9-BBN-derived organoborane 355.

A second trial reaction between acetylene and the more hindered vinyl halide **(*E*,*E*)-338** was performed under both sets of conditions, to determine whether the steric bulk of the secondary iodide was inhibiting to reaction or whether the secondary boronic acid **354** was not being formed, perhaps due to the steric issues involved with accessing the internal alkyne functionality. Formation of boronic acid **355** followed by an in situ attempted cross-coupling with iodide **(*E*,*E*)-338** employing $PdCl_2(dppf)_2$ and K_3PO_4, yielded only recovered iodide and decomposition products.[189] Under the alternate reaction conditions ($Pd(PPh_3)_4$ and NaOH) the crude ^1H NMR spectrum, of the product was inconclusive as it was dominated by peaks from 9-BBN derivatives. Following purification by column chromatography no

compounds resembling the product or iodide **(*E*,*E*)-338** were isolated. Under these conditions it was thought that perhaps the iodide **(*E*,*E*)-338** was decomposing.

Having identified that the tri-substituted vinyl iodide **(*E*,*E*)-338** may be sensitive to the conditions of the cross-coupling reaction a final trial reaction between organoborane **354** and less substituted vinyl iodide **356** was attempted, outlined in Scheme 5.22. Following formation of the organoborane **354**, the Suzuki reaction was attempted employing $Pd(PPh_3)_4$ and NaOH.[294] Once again the reaction was unsuccessful and alkyne derived materials were isolated. This suggested that either the organoborane **354** is forming but is failing to couple or the alkyne **352** may be sensitive to the conditions employed to generate the organoborane or perform the Suzuki cross-coupling reaction.

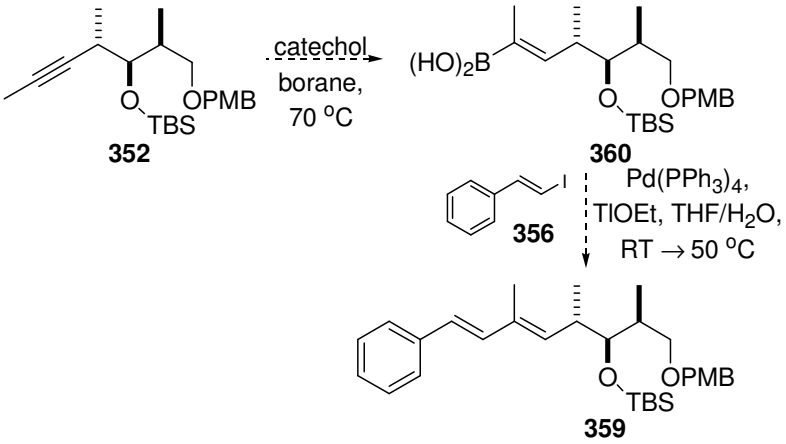


Scheme 5.22 Attempted coupling of 9-BBN-derived organoborane 354 with vinyl iodide 356.

An alternative approach for the Suzuki coupling involves the synthesis of the boronic acid **360**, which can be isolated prior to coupling.[295] Vinyl boronic acids may be generated from the corresponding alkyne or vinyl halide. Alkyne **352** and catechol borane were heated to 70 °C for two hours before diluting with $MeOH/H_2O$. Examination of the ^1H NMR spectrum¬ of the crude product revealed a potential vinyl proton doublet at 5.9 ppm suggesting formation of the vinyl boronic acid. In addition, the other resonances expected from the organic components such as methyl doublets at 1.0 and 1.2 ppm, the multiple CHO proton signals at 3.4 - 4.4 ppm and the aromatic, OTBS and OPMB resonances were present. A vinyl methyl group (generally around 1.5 - 2.5 ppm) was not clearly apparent but it was unclear how the boronic acid functionality would influence the electronic environment of the vinyl

¬ ^{11}B NMR spectra were not able to be acquired on site.

methyl. The coupling reaction was attempted, on very small scale, with iodide **356**; to a solution of the suspected boronic acid **360**, $Pd(PPh_3)_4$ and iodide **356** in THF was added TlOEt in H_2O and the solution warmed to 50 °C for 1 hour.[300] Following purification of the reaction mixture by column chromatography only a very small amount of material was isolated. One fraction may have contained a small amount of product suggested because of the possible presence of multiple vinyl proton signals and starting material related peaks (such as the OPMB and OTBS groups). However it was only a very small amount. Due to the cost associated with investigating the Suzuki coupling using the chiral reagents this avenue was not pursued further and achiral reagents were employed in subsequent investigations.

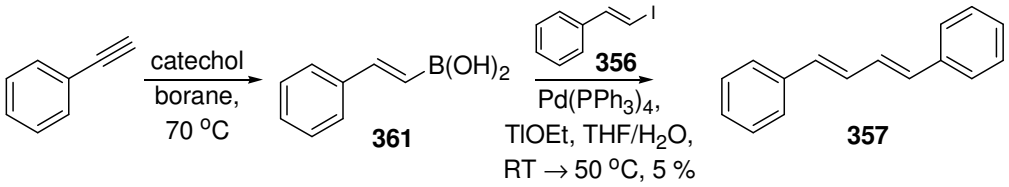


Scheme 5.23 Attempted synthesis and coupling of the boronic acid 360 with vinyl iodide 356.

In order to identify whether synthesis of the boronic acid **360** from catechol borane was achieved, the vinyl boronic acid **361** was generated from reaction of acetylene with catechol borane. ^{1}H NMR analysis¬ of this product indicated the presence of phenyl protons and broad singlet at 5.4 ppm integrating for 2 protons, thought to be due to the $B(OH)_2$ protons. However the presence of ethoxide derived peaks, a quartet at 3.6 ppm and a triplet at 1.2 ppm were unexpected. In addition no vinyl proton signals could be seen, however these signals could be expected to resonate at similar chemical shifts to the aromatic protons so it is possible they were just obscured. A trial coupling between the vinyl iodide **356** and the potential boronic acid **361**, described in Scheme 5.24, yielded a very small amount of diene **357** (~5 %) confirming that the boronic acid **361** had indeed been synthesised. The coupling partners in this reaction are not sterically hindered, and would thus be expected to couple readily. This suggests that the low yield may be due to ineffective formation

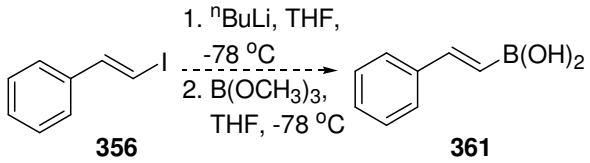
¬ ^{11}B NMR spectra were not able to be acquired on site.

of the boronic acid, indicating that perhaps the quality of the catechol borane is poor, or that the boronic acid is forming but is being quenched prior to coupling.



Scheme 5.24 Synthesis of boronic acid 361 was confirmed by the isolation of a small amount of diene 357.

Due to the difficulties in generating the organoborane **361** from the reaction of acetylene with catechol borane, an alternative approach was considered. Organoboranes may be synthesised from the corresponding halides *via* an intermediate organolithium species which reacts with an appropriate electrophile. The organolithium equivalent of vinyl iodide **356** was generated with ^{n}BuLi and $B(OCH_3)_3$ in THF was added slowly at -78 ^{o}C.[301,302] After warming to room temperature the solution was left to stir overnight. The desired boronic acid **361** was expected to be isolated as a white solid, which could be filtered off and recrystallised from Et_2O, however the small scale reaction attempts made filtration and recrystallisation difficult and thus investigations of this approach were discontinued.



Scheme 5.25 Alternative approach to the boronic acid 361.

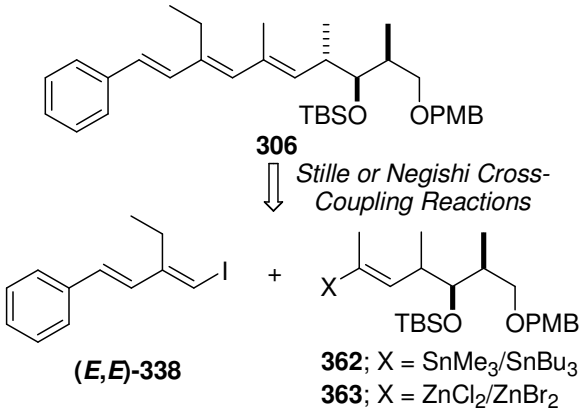
5.1.5.2.1 Summary of the Suzuki Cross-Coupling Attempts

A number of synthetic strategies were employed to generate the organoborane coupling partners for the Suzuki cross-coupling reaction. While the organoboranes derived from the reaction of acetylene with 9-BBN, readily coupled with 1,2-di-substituted alkenes, the more hindered tri-substituted vinyl iodide **(*E*,*E*)-338** failed to couple. This was proposed to be due to the increased steric bulk of the tri-substituted iodide ***(E*,*E*)-338** and its sensitivity to the cross-coupling conditions. While the terminal alkyne of acetylene was readily converted to the organoborane **355**, it was unclear whether the organoborane derivative **354**, of the more hindered internal alkyne **352**, was forming. Attempted generation and Suzuki cross-coupling reactions of the chiral organoborane **354** were all unsuccessful.

The boronic acids are often employed as alternative coupling partners in the Suzuki cross-coupling reactions. A number of approaches towards the synthesis of boronic acids and the subsequent cross-coupling reactions were attempted however in most instances either no reaction occurred or very poor yields were achieved. It was unclear whether the boronic acids were forming and simply failing to couple or whether they weren't forming in the first place. This problem is exacerbated by the difficulties in characterisation of organometallic reagents by techniques such as NMR, IR and GCMS.

5.1.5.3 Future Directions: Alternative Palladium-Catalysed Cross-Coupling Reactions

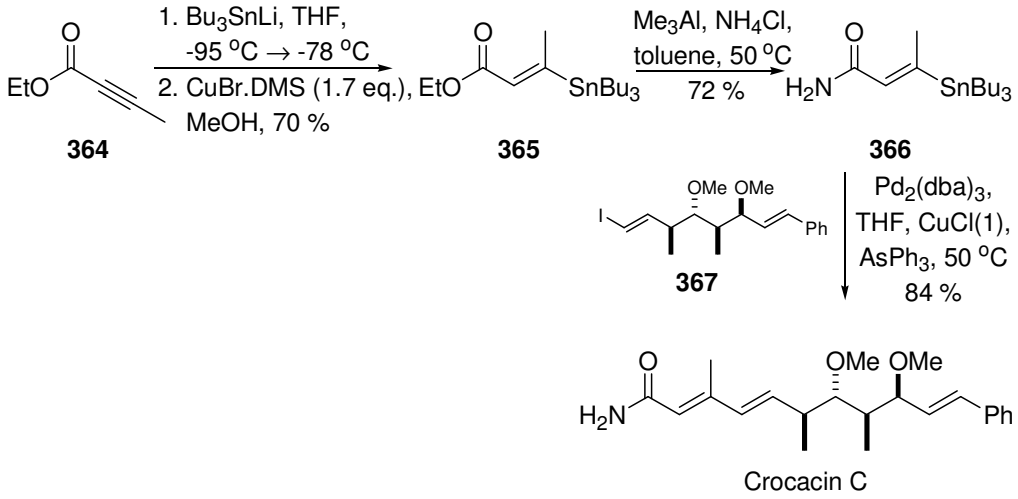
Due to the problems encountered in the synthesis of the boronic acids/organoboranes and subsequent Suzuki cross-coupling reactions alternative palladium-catalysed cross-coupling reactions were considered to offer a more suitable approach to the highly substituted conjugated triene. The flexibility of the designed synthesis allows modifications to the cross-coupling reaction partners to enable examination of alternative palladium-catalysed cross-coupling reactions, such as Stille and Negishi reactions outlined in Scheme 5.26.



Scheme 5.26 Alternative palladium-catalysed cross-coupling reactions to install the triene moiety.

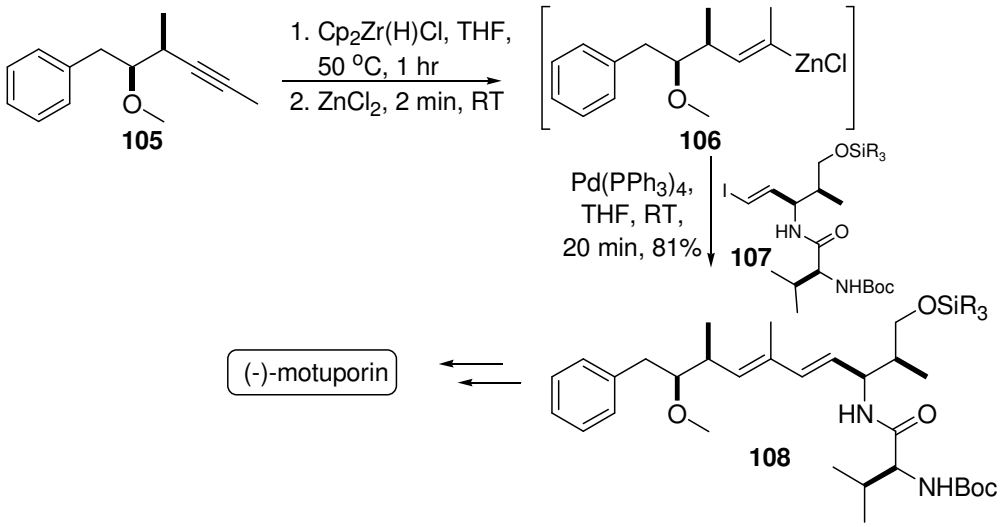
A number of total and partial syntheses employing the Stille cross-coupling reaction to produce highly substituted, conjugated double bonds have been reported in the literature. Dias and co-workers reported a stereoselective Stille cross-coupling reaction between a secondary vinyl stannane and a bulky vinyl iodide in the total synthesis of crocacin C.[293] Their approach, outlined in Scheme 5.27, involves

synthesis of the vinyl stannane **365** from alkyne **364** *via* a conjugate organostannyl cuprate addition. Following conversion of the ester to the amide, stannane **366** was coupled to iodide **367** in a Stille cross-coupling reaction. crocacin C was achieved with high *E*-selectivity in good yield (84 %). Employing this approach towards the spiculoic acids, it may be possible to synthesise vinyl stannnane **362** from alkyne **352** and subsequently couple to ***(E,E)*-338**, producing the desired conjugated triene **306** with high stereoselectivity, as proposed in Scheme 5.26.



Scheme 5.27 Total synthesis of crocacin C, featuring a Stille cross-coupling reaction.[293]

Since its development in 1977, the Negishi cross-coupling reaction has been somewhat overshadowed by the popularity of the Stille and Suzuki cross-coupling reactions in total synthesis. However, the total synthesis of (-)-motuporin reported by Hu and Panek illustrates the success of this reaction in coupling a secondary zinc chloride to a large, stereocomplex iodide.[193,251] Their strategy, described in Scheme 5.28, involves synthesis of zinc chloride **106** from alkyne **105**, and subsequent cross-coupling with iodide **107**, producing *E*-alkene **108** in good yield (81 %). Employing an analogous approach it may be possible to convert alkyne **352** into the zinc chloride **363** which may be coupled to iodide ***(E,E)*-338**, to generate triene **306**, as described in Scheme 5.26.



Scheme 5.28 Total synthesis of (-)-motuporin, featuring a Negishi cross-coupling reaction.[193,251]

A variety of other palladium-catalysed cross-coupling reactions such as Heck, Tsuji-Trost and Sonogashira cross-coupling reactions are also available and may provide an alternative approach to the natural products. These reactions are reviewed in Section 1.3.6.2.

5.2 Conclusion

A number of synthetic approaches to the generation of the conjugated triene moiety required in the linear precursors **285** to the spiculoic acids have been investigated. Installation of the central tri-substituted double bond *via* olefination reactions, such as Wittig, H.W.E. and "modified" Julia, were plagued with difficulties. The dominant issue obstructing these approaches was synthesis of the desired secondary organophosphorus or sulfone reagents for the olefination reaction. In addition, in the case of the "modified" Julia olefination reaction where the desired secondary sulfones **307** and **314** were achieved, steric constraints in getting the hindered reagents to couple was also a significant obstacle.

The alternative approach to installation of the conjugated triene moiety, through construction of a carbon to carbon single bond between two vinyl reagents (organohalides and organoboranes) using a palladium-catalysed Suzuki cross-coupling reaction was also explored. This approach experienced many of the same difficulties as the olefination reaction in that inefficient formation of the organoboranes and steric bulk of the tri-substituted vinyl coupling partners were thought to be the major problems.

In retrospect the decision to target a convergent synthesis by installation of the trisubstituted central double bond of the conjugated triene was quite ambitious. This approach, had it been successful, would have provided an efficient route to all of the members of the spiculoic acid family of natural products. However, difficulties arise because the tri-substituted olefin targeted for construction, is quite hindered and is in fact the most hindered of the three olefins in the linear precursor to *dinor*-spiculoic acid A. An alternative approach could be to construct either of the other two olefins of the linear triene, as discussed in Section 5.1.1, Figure 5.4.

5.3 Future Directions

Despite the difficulties encountered in the synthesis of the tri-substituted olefins by olefination reactions, a number of synthetic options to achieving synthesis of the conjugated triene moiety remain to be investigated. "Modified" Julia olefination reactions employing phenyl sulfones or phenyl sulfoxides to generate tri-substituted olefins have been presented in Section 5.1.4.1. Alternatively, a range of palladium-

catalysed cross-coupling reactions could be employed to generate conjugated alkenes *via* construction of carbon to carbon σ bonds between vinyl coupling partners. Possible approaches utilising Stille and Negishi cross-coupling reactions are introduced in Section 5.1.5.3.

During the course of this investigation Baldwin and co-workers published the total synthesis of *ent*-spiculoic acid A.[234] This approach, described in Section 3.2.1.2, is less convergent than the proposed methodology targeted in this study involving stepwise formation of the three double bonds of the conjugated triene. Baldwin and co-workers failed to comment on the stereospecificity of their IMDA cycloaddition reaction, simply reporting that *ent*-spiculoic acid A was produced in 25 % yield.

A major focus of this study was to further investigate the stereoselectivity of the IMDA cycloaddition reaction, employing a similar approach to that described for the Model Systems. Careful analysis of the IMDA cycloadduct(s) obtained from cycloaddition of a linear precursor was hoped to provide evidence supporting or refuting the involvement of a Diels-Alderase in the formation of the spiculoic acid family of natural products. If the thermodynamic product of cyclisation of the linear precursor produces a cycloadduct in high diastereoselectivity, with stereochemistry matching the natural product this would suggest that enzymatic involvement is not necessary in formation of the natural product. However, it would not rule out enzymatic involvement. Conversely, if the thermodynamic cycloadduct does not match the natural product, or if the diastereoselectivity is significantly different, this may suggest enzymatic involvement in the biosynthesis of the spiculoic acid family of natural products.

Future work could involve synthesis of the linear triene, employing the method reported by Baldwin and co-workers, followed by a thorough stereochemical evaluation of the cycloadduct(s), which Baldwin and co-workers failed to comment on. While this approach does not present a synthetic challenge, it may provide an avenue to explore the potential involvement of a Diels Alderase in the biosynthesis of the spiculoic acid family of natural products.

CHAPTER 6 EXPERIMENTAL PROCEDURES

6.1 General Experimental Procedures

All reactions were carried out under an atmosphere of nitrogen in oven dried glassware. Dichloromethane, triethylamine and dimethylethylamine were distilled over calcium hydride; propionaldehyde was distilled over calcium chloride and tetrahydrofuran and ether were distilled over sodium and benzophenone. Sodium hydride (60 % dispersion in mineral oil) was washed with mixed hexanes and dried under nitrogen before use. Other reagents were used as they came.

Analytical thin layer chromatography was performed on Merck Keiselgel 60 F_{254} silica aluminium backed sheets and were developed in potassium permanganate,[^] anisaldehyde[˅] or monitoring by a U.V. lamp. Column chromatography was performed on Merck Keiselgel (particle size: 0.04-0.063 mm) 230-400 mesh silica.

^{1}H NMR spectra were recorded at either 200 MHz, 300 MHz or 600 MHz on a Varian Mercury, Varian Gemini, Varian Unity Inova or Bruker Avance II 600 Spectrometer. ^{13}C NMR spectra were recorded at either 50 MHz, 75 MHz or 151 MHz on a Varian Mercury, Varian Gemini, Varian Unity Inova or Bruker Avance II 600 Spectrometer. $CDCl_3$ was used as the solvent and internal lock and referenced to $CHCl_3$ (δ 7.26) for ^{1}H NMR and $CDCl_3$ (δ 77) for ^{13}C NMR. Chemical shift vales are reported in ppm, coupling constants are reported in Hz. Abbreviations used; Ar = aromatic, apt = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet.

Structural and stereochemical assignments were made using ^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY, ^{1}H-^{13}C HETCOR, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HMBC, ^{1}H-^{1}H NOESY and ^{1}H-^{1}H ROESY spectra. Spectra were recorded at ambient temperature with normal detection (200 MHz and 300 MHz) or inverse detection (600 MHz) with a 1 sec. relaxation time in all cases. 200 MHz and 300 MHz ^{1}H-^{1}H COSY spectra were collected using a relay-h pulse sequence. Data was collected with 256 increments and transformed with a sine bell function in both dimensions to give a resulting data set

[^] $KMnO_4$ (3 g), K_2CO_3 (20 g), 5 % NaOH (5 mL) and H_2O (300 mL)
[˅] *p*-anisaldehyde (9.2 mL), H_2SO_4 (12.5 mL), AcOH (3.75 mL) and EtOH (338 mL)

of 1024 x 1024 in most cases. 300 MHz ^{1}H/75.5 MHz ^{13}C HETCOR spectra were collected using a hector pulse sequence using WALTZ-16 decoupling. Data was collected with no less than 64 increments and transformed using line broadening in both dimensions to give a resulting data set of no less than 2048 x 256. 600 MHz. ^{1}H-^{1}H COSY spectra were collected using a gCOSY pulse sequence. Data was collected with 2 x 200 increments and transformed with a sq. sine bell function in both dimensions to give a resulting data set of 2048 x 2048. 600 MHz ^{1}H/151 MHz ^{13}C HMQC spectra were collected using a gHMQC pulse sequence. Data was collected with 2 x 128 increments and transformed with a Gauss function in both dimensions to give a resulting data set of 2048 x 2048. 600 MHz ^{1}H/151 MHz ^{13}C HMBC spectra were colleted using a gHMBC pulse sequence. Data was collected with 400 increments and transformed with a sine bell function in both dimensions to give a resulting data set of 2048 x 2048. 600 MHz ^{1}H-^{1}H ROESY spectra were collected using a standard ROESY pulse sequence with a mixing time of 0.3 sec. Data was collected with 2 x 200 increments and transformed with a Gauss function in both dimensions to give a resulting data set of 2048 x 2048. ^{1}H-^{1}H NOESY spectra were collected using a standard pulse sequence with a mixing time of 0.5 sec. Data was collected with F2 4096 and F1 1024 and transformed with a QSINE function in both dimensions to give a resulting data set of 2048 x 4096.

All optical rotations were measured on a PolA AR 21 polarimeter referenced to the sodium D line (589 nm) at 20^{o}C, using the spectroscopic grade solvents specified and at the concentrations (*c*, g/100 mL) indicated. The measurements were carried out in a cell with a 1 dm path length.

Electron Impact (EI) mass spectra and Electrospray Ionisation (ESI) mass spectra were recorded using a Bruker 4.7 T FTMS Ultra High Resolution spectrometer. ESIMS/MS were recorded on a Micromass Quattro micro spectrometer. High resolution mass spectral data are presented as molecular formula, molecular ion (M^{+}, Na^{+} or K^{+}), calculated and measured masses to 4 significant figures. Low resolution mass spectral data are reported as mass-to-charge ratio (m/z) with intensity relative to the base peak indicated. LCMS were recorded on a Micromass Quattro micro, tandem quadrupole mass spectrometer with positive ion electrospray ionisation. Mass spectral data are presented as the molecular formula, molecular ion and calculated and measured masses to 3 significant figures.

Infrared spectra were recorded on a BIO-RAD FTS-40A Fourier Transform spectrophotometer with the absorptions recorded in wavenumbers (cm^{-1}). Samples were analysed as thin films on NaCl discs, with samples being dissolved in CH_2Cl_2 or $CHCl_3$ before being applied to the disc and allowing the solvent to evaporate.

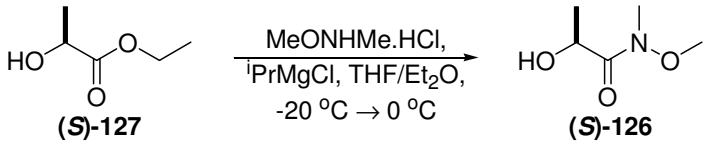
UV/Visible spectra were recorded using a Varian Cary 50 Scan spectrophotometer using the spectroscopic grade solvents specified.

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

6.2 Experimental Procedures for Chapter 2

6.2.1 Synthesis of the lactate derived α-chiral ketones 39 and 40

(*S*)-2-hydroxy-N-methoxy-N-methylpropionamide ((*S*)-126)



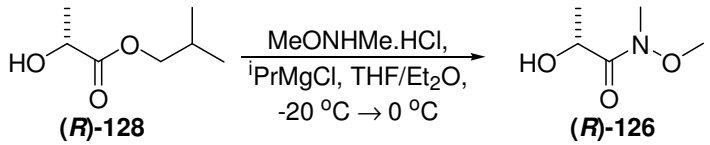
(*S*)-127 **(*S*)-126**

To a solution of ethyl (*S*)-lactate (**(*S*)-127**) (4.0 g, 0.034 mol) and N,O-dimethylhydroxylamine hydrochloride (8.28 g, 0.085 mol) in THF:Et_2O (1:1, 100 mL) at -20 °C was added a solution of ^{i}PrMgCl (2 M in THF, 85 mL) dropwise over 30 min. The resulting solution was stirred for a further 30 min at -20 °C before warming slowly to 0 °C and stirring for another 30 min. After this time the reaction was quenched by the slow addition of NH_4Cl (sat. aq., 80 mL) which formed a white solid that dissolved upon addition of H_2O (50 mL). The product was extracted with Et_2O (4 x 80 mL) and CH_2Cl_2 (4 x 80 mL). The combined Et_2O extracts were washed with brine (80 mL) and the total combined extracts dried ($MgSO_4$) and concentrated in *vacuo*. The resulting yellow oil was purified by Kugelrohr distillation (50 °C at 0.05 mm Hg) to give 4.51 g (99 %) of amide **(*S*)-126** as a clear, colourless oil with spectroscopic data consistent with that reported.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (1H, q, *J* = 6.6 Hz, HOC*H*(CH_3)C(=O)); 3.63 (3H, s, OCH_3); 3.36 (1H, br s, O*H*); 3.15 (3H, s, N(CH_3)); 1.27 (3H, d, *J* = 6.6 Hz, HOCH(CH_3)C(=O)); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 175.5; 64.7; 61.1; 32.2; 20.7;

IR (film, cm^{-1}) 3435; 2982; 2940; 1656; 1458; 1367; 1139; 1085; 1036; 991; 667; $[\alpha]_D^{20}$ = -40.8 (*c*1.0 , $CHCl_3$).

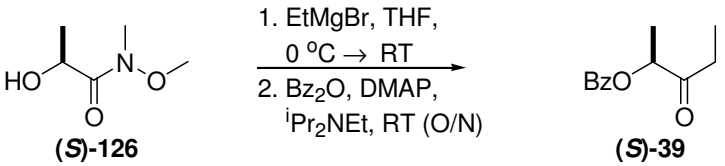
(*R*)-2-hydroxy-N-methoxy-N-methylpropionamide ((*R*)-126)



As per the procedure for **(*S*)-126** using isobutyl (*R*)-lactate (**(*R*)-128**) (4.0 g, 0.027 mol), purification by Kugelrohr distillation (50 °C at 0.5 mm Hg) yielded 3.06 g (84 %) of the amide **(*R*)-126** as a clear, colourless oil with spectroscopic data consistent with that reported.[77]

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = +45.9 (*c* 1.2, $CHCl_3$).

(*S*)-2-benzyloyloxypentan-3-one ((*S*)-39)

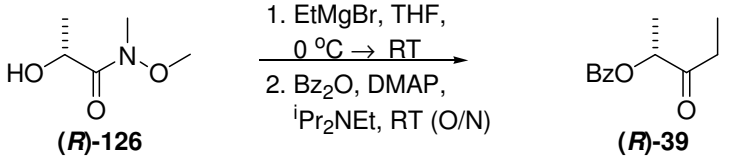


To a solution of the amide **(*S*)-126** (2.60 g, 0.020 mol) in THF (80 mL) at 0 °C was added EtMgBr (1 M in THF, 65 mL) dropwise and the mixture was allowed to warm to room temperature. After 1 hour the reaction was quenched by slow addition of NH_4Cl (sat. aq., 100 mL). The product was extracted with Et_2O (1 x 50 mL) and CH_2Cl_2 (2 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated in *vacuo* to approx. 120 mL. Benzoic anhydride (6.9 g, 0.030 mol), DMAP (0.25 g, 2.03 mmol) and diisopropylethylamine (6.68 mL, 0.038 mol) were added to this solution at room temperature. The resulting clear solution was stirred overnight before quenching with ethylamine diamine (1.31 g, 1.49 mL, 0.023 mol). The solution was diluted with H_2O (100 mL) and extracted with Et_2O (4 x 50 mL). The combined ether extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The resulting oil was purified by column chromatography (80 % CH_2Cl_2/mixed hexanes, R_f = 0.59) to yield 2.13 g (52 %) of ketone **(*S*)-39** a clear, colourless oil with spectroscopic data consistent with that reported.[77]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar*H*); 7.60-7.55 (1H, m, Ar*H*); 7.47-7.42 (2H, m, Ar*H*); 5.34 (1H, q, *J* = 6.9 Hz, BzOC*H*(CH_3)); 2.65 (1H, dq, *J* = 18.3, 7.2 Hz, C(=O)C$H_A$$H_B$); 2.51 (1H, dq, *J* = 18.3, 7.2 Hz, C(=O)C$H_A$$H_B$); 1.52

(3H, d, *J* = 6.9 Hz, BzOCH(C*H*$_3$)); 1.08 (3H, t, *J* = 7.2 Hz, C(=O)CH$_2$C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.4; 165.9; 133.3; 129.7; 129.4; 128.4; 75.1; 31.4; 16.4; 7.2; **IR** (film, cm^{-1}) 2985; 2942; 1720; 1603; 1452; 1316; 1300; 1270; 1178; 1110; 1097; 1072; 1027; 974; 713; 688; $[\alpha]_D^{20}$ = +21.0 (*c* 1.0, $CHCl_3$).

(*R*)-2-benzoyloxypentan-3-one ((*R*)-39)

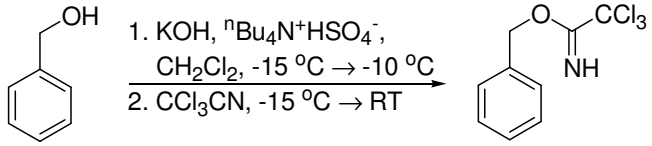


(*R*)-126 **(*R*)-39**

As per the procedure for **(*S*)-39** using amide **(*R*)-126** (2.6 g, 0.020 mol), purification by column chromatography (80 % CH_2Cl_2/mixed hexanes, R_f = 0.40) yielded 2.04 g (43 %) of the ketone **(*R*)-39** as a clear, colourless oil with spectroscopic data consistent with that reported.[77]

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = -23.7 (*c* 1.5, $CHCl_3$).

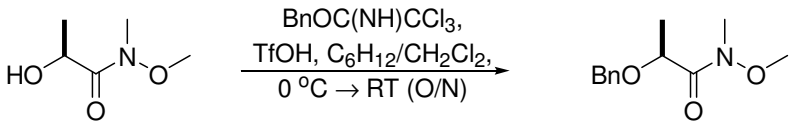
2,2,2-trichloroacetimidic acid benzyl ether



To a solution of benzyl alcohol (4.00 g, 37 mmol, 3.83 mL) in CH_2Cl_2 (40 mL) at -15 → -10 °C was added a solution of potassium hydroxide (50 % aq., 40mL) and tetra-$^{n-}$butylammoniumhydrogen sulfate (0.06 g, 0.18 mmol) and the resulting mixture stirred vigorously for 5 minutes. Trichloroacetonitrile (6.41 g, 44.4 mmol, 4.45 mL) was added dropwise and the mixture stirred at -15 → -10 °C for 30 minutes. The solution was then warmed slowly to room temperature and stirred for an additional 30 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo* to approx. one third of the volume. The solution was filtered through a 2 cm pad of Celite, washed through with CH_2Cl_2 (50 mL) and concentrated in *vacuo* to yield 9.3 g (99 %) of the immidate as a yellow oil.

^{1}H NMR (300MHz, $CDCl_3$) δ 8.40 (1H, br s, N*H*); 7.46-7.35 (5H, m, Ar*H*); 5.35 (2H, s, ArC*H*$_2$O); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.6; 135.5; 128.5; 128.3; 127.7; 127.0; 70.7; **IR** (film, cm^{-1}) 3342; 3036; 2953; 1666; 1499; 1456; 1381; 1303; 1293; 1075; 1030; 995; 828; 796; 736; 712; 696; 648.

(*S*)-2-benzyloxy-N-methoxy-N-methylpropionamide ((*S*)-129)

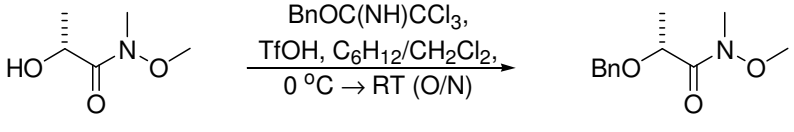


(*S*)-126 **(*S*)-129**

To a solution of the alcohol **(*S*)-126** (0.10g 7.51 mmol) and $BnOC(NH)CCl_3$ (0.23g, 9.01 mmol) in cyclohexane (1 mL) and CH_2Cl_2 (0.5 mL) was added trifluoromethane sulfonic acid (17 mg, 0.11 mmol, 9 μL) dropwise at 0 °C. The solution was then warmed to room temperature and stirred overnight. TLC analysis indicated that the reaction was incomplete, however addition of further trifluoromethane sulfonic acid (0.05 eq.) failed to drive the reaction to completion. The solution was diluted with Et_2O (10 mL), washed with $NaHCO_3$ (sat. aq., 5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was triturated with hexane to remove the trichloroacetamide. Purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.33) yielded 0.135 g (85 %) of benzylether **(*S*)-129** as a clear, colourless oil with spectroscopic data consistent with that reported.[303]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m, Ar*H*); 4.66 (1H, d, *J* = 11.7 Hz, OCH_AH_BPh); 4.403 (1H, d, *J* = 12.0 Hz, OCH_AH_BPh); 4.399 (1H, q, *J* = 6.6Hz, $C(=O)CH(CH_3)$); 3.57 (3H, s, OCH_3); 3.20 (3H, s, $N(CH_3)$); 1.39 (3H, d, *J* = 6.6 Hz, $C(=O)CH(CH_3)$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 137.7; 128.3; 127.9; 127.7; 71.1; 61.2; 53.4; 32.3; 17.9; **IR** (film, cm^{-1}) 2979; 2936; 1731; 1670; 1454; 1367; 1156; 1108; 1061; 990; 910; 827; 738; $[\alpha]_D^{20}$ = -60.3 (*c* 1.1, $CHCl_3$).

(*R*)-2-benzyloxy-N-methoxy-N-methylpropionamide ((*R*)-129)

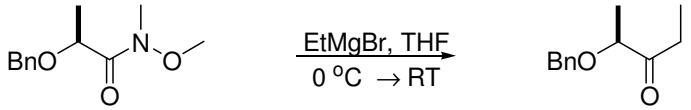


(*R*)-126 **(*R*)-129**

As per the procedure for **(*S*)-129** using alcohol **(*R*)-126** (1.05 g, 7.91 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.28) yielded 1.17 g (70 %) of the benzyl ether **(*R*)-129** as a clear, colourless oil with spectroscopic data consistent with that reported.[303]

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = +61.4 (*c* 1.5 , $CHCl_3$).

(*S*)-2-benzyloxypentan-3-one ((*S*)-40)

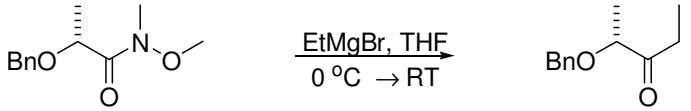


(*S*)-129 **(*S*)-40**

To a solution of the amide **(*S*)-129** (1.17 g, 5.54 mmol) in THF (22.2 mL) at 0 °C was added dropwise a solution of EtMgBr (1 M in THF, 17.8 mmol, 17.8 mL) and the solution allowed to warm to room temperature. After 1 hour NH_4Cl (sat. aq., 30 mL) was added and the organics were extracted with Et_2O (2 x 20 mL) and CH_2Cl_2 (2 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (90 % CH_2Cl_2/ mixed hexanes, R_f = 0.42) yielding 0.73 g (69 %) of the ketone **(*S*)-40** as a clear, colourless oil with spectroscopic data consistent with that reported.[303]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m, Ar*H*); 4.56 (1H, d, *J* = 11.7 Hz, OCH_AH_BPh); 4.50 (1H, d, *J* = 11.7 Hz, OCH_AH_BPh); 3.95 (1H, q, *J* = 6.9 Hz, $C(=O)CH(CH_3)$); 2.65 (1H, dq, *J* = 18.3, 7.2 Hz, $CH_3CH_AH_B$); 2.54 (1H, dq, *J* = 18.3, 7.2 Hz, $CH_3CH_AH_B$); 1.35 (3H, d, *J* = 6.9 Hz, $C(=O)CH(CH_3)$); 1.06 (3H, t, *J* = 7.2 Hz, CH_3CH_2); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 213.5; 137.6; 128.4; 127.8; 127.7; 80.5; 71.8; 30.5; 17.5; 7.3; **IR** (film, cm^{-1}) 2981; 2939; 2879; 1718; 1456; 1370; 1106; 738; 698; $[\alpha]_D^{20}$ = +40.7 (*c* 1.1, $CHCl_3$).

(*R*)-2-benzyloxypentan-3-one ((*R*)-40)



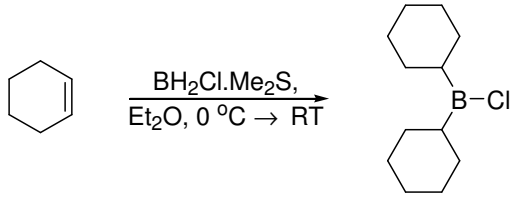
(*R*)-129 **(*R*)-40**

As per the procedure for (***S*)-40**, using amide **(*R*)-129** (1.27 g, 5.54 mmol), purification by column chromatography (90 % CH_2Cl_2/mixed hexanes, R_f = 0.42) yielded 0.89 g (67 %) of the ketone **(*R*)-40** as a clear, colourless oil with spectroscopic data consistent with that reported.[303]

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = -44.7 (*c* 1.5, $CHCl_3$).

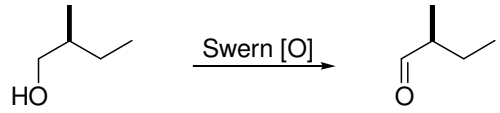
6.2.2 Synthesis of the chiral ketone fragments 122 and 123

Preparation of $(^{c}C_6H_{11})_2BCl$



To a solution of cyclohexene (7 mL, 69 mmol) in Et_2O (35 mL) was added, at 0 °C, $BH_2Cl.Me_2S$ (3.3 mL, 32 mmol). The resulting mixture was stirred at room temperature for 2 hours before removing the volatiles in *vacuo*. The resulting white solid was purified by distillation (68-70 °C at 0.05 mmHg) to give $(^{c}C_6H_{11})_2BCl$ as a clear, colourless oil which was maintained under N_2, and stored in the freezer.

(2*S*)-2-methylbutyraldehyde (125)

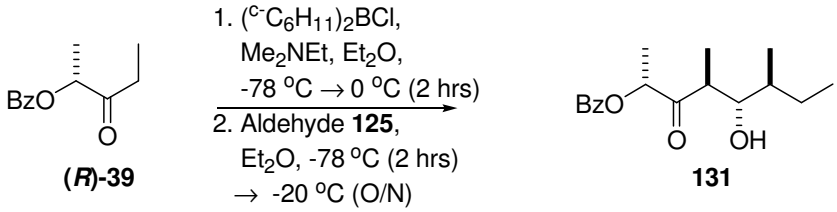


(2*S*)-2-methylbutan-1-ol **125**

Oxalyl chloride (4.26 mL, 8.51 mol) was added dropwise to a solution of DMSO (1.21 mL, 17.0 mmol) in CH_2Cl_2 (24 mL) at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes before dropwise addition of (2*S*)-2-methylbutan-1-ol (0.61 mL, 5.67 mmol) in CH_2Cl_2 (3 mL, 2 mL, 1 mL) *via* a cannula. The resulting solution was stirred for 45 minutes at -78 °C. NEt_3 (4.74 mL, 34.0 mmol) was added dropwise over several minutes and the resulting white solution was maintained at -78 °C for 30 minutes before warming to 0 °C and stirring for a further 30 minutes. The reaction was quenched by addition of NH_4Cl (sat. aq., 20 mL) and the solution poured onto NH_4Cl (sat. aq., 50 mL). The product was extracted with CH_2Cl_2 (3 x 50 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Due to the volatility of the aldehyde **125** the solvent was not completely removed in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.45) and careful concentration in *vacuo* (leaving some solvent) yielded aldehyde **125** (yield assumed to be 80 %), with spectroscopic data consisted with that reported.[304]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (1H, d, *J* = 2.1 Hz, C*H*(O)); 2.28 (1H, qd, *J* = 7.2, 2.1 Hz, CH(O)C*H*(CH_3)); 1.75 (1H, dq, *J*= 7.5, 7.5 Hz, CH_AH$_B$$CH_3$); 1.45 (1H dq, *J* = 7.5, 7.5 Hz, $CH_AH_BCH_3$); 1.09 (3H, d, *J* = 7.2 Hz, CH(O)CH(CH_3)); 0.95 (3H, t, *J* = 7.5 Hz, CH_2CH_3).

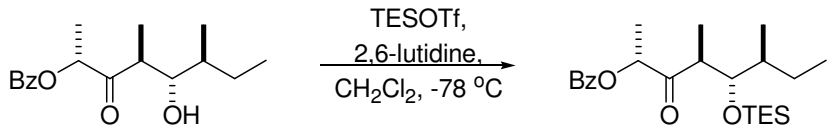
(2*R*, 4*S*, 5*S*, 6*S*)-2-benzoyloxy-5-hydroxy-4,6-dimethyloctan-3-one (131)



To a solution of dicyclohexylboron chloride (1.58 mL, 7.28 mmol) in Et_2O (19.5 mL) at –78 °C was added dimethylethylamine (0.95 mL, 8.73 mmol), dropwise, followed by ketone **(*R*)-39** (1.0 g, 4.85 mmol) in Et_2O (19.5 mL). The resulting milky white solution was slowly warmed to 0 °C and stirred for 2 hours before cooling to –78 °C and addition of aldehyde **125** (0.63 g, 7.28 mmol), dropwise. The solution was stirred for a further 2 hours at –78 °C before being placed in the freezer overnight. After this time the solution was placed in a 0 °C bath and was stirred for 30 minutes. The reaction was quenched by addition of methanol (20 mL), pH 7 phosphate buffer (20 mL) and H_2O_2 (30 %, 20 mL), at 0 °C. The solution was warmed to room temperature and stirred for 2.5 hours before partitioning onto H_2O (300 mL) and extracting with CH_2Cl_2 (3 x 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, $R_f = 0.26$) to yield 1.17 g (83 %, 90 % ds) of adduct **131** as a white, crystalline solid (m.p. 60-63 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.07 (2H, m, Ar*H*); 7.62-7.57 (1H, m, Ar*H*); 7.49-7.44 (2H, m, Ar*H*); 5.46 (1H, q, *J* = 7.2 Hz, BzOC*H*); 3.60-3.53 (1H, m, C*H*OH); 3.08 (1H, apt qn, *J* = 6.9 Hz, C(=O)C*H*(CH_3)); 2.39 (1H, d, *J* = 7.2 Hz, O*H*); 1.62-1.48 (1H, m, C*H*(CH_3)CH_2); 1.57 (3H, d, *J* = 7.2 Hz, BzOCH(C*H*$_3$)); 1.27 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)); 1.31-1.13 (2H, m, C*H*$_2$$CH_3$); 0.93 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)CH_2); 0.90 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.4; 133.4, 129.8; 129.5; 128.5; 78.2; 77.2; 74.7; 44.8; 37.1; 22.7; 16.3; 16.0; 14.8; 11.6; **IR** (film, cm^{-1}) 2967; 2936; 2876; 1718; 1453; 1316; 1268; 1118; 1006; 713; 667; $[\alpha]_D^{20} = -43.1$ (*c* 1.1, $CHCl_3$); **HRMS (ESI)** found 293.1747, $C_{17}H_{24}O_3H^+$ requires 293.1747; **LREIMS** 292 (1 %); 235 (5 %); 150 (25 %) 113 (8 %); 105 (100 %); 97 (19 %); 77 (34 %); 57 (28 %); 51 (12 %).

(2*R*, 4*S*, 5*S*, 6*S*)-2-benzoyloxy-5-triethylsilyloxy-4,6-dimethyloctan-3-one (132)

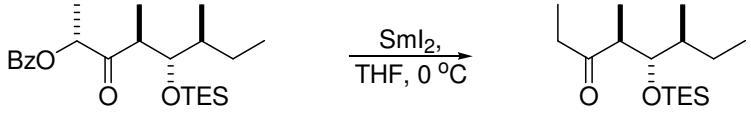


131 **132**

To a solution of alcohol **131** (0.42 g, 1.45 mmol) in CH_2Cl_2 (14.5 mL) at –78 °C was added dropwise, 2,6-lutidine (0.67 g, 5.78 mmol) followed immediately by TESOTf (0.98 mL, 4.35 mmol). The resulting solution was stirred at –78 °C for 1 hour before quenching with $NaHCO_3$ (sat. aq., 30 mL). The product was partitioned onto H_2O (30 mL) extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.40) yielding 0.57 g (97 %) of silyl ether **132** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar*H*); 7.59-7.53 (1H, m, Ar*H*); 7.46-7.41 (2H, m, Ar*H*); 5.44 (1H, q, *J* = 6.9 Hz, C*H*(CH_3)OBz)); 3.94 (1H, dd, *J* = 9.0, 2.1 Hz, C*H*OTES); 3.11 (1H, dq, *J* = 9.0, 6.9 Hz, (C=O)C*H*(CH_3)); 1.57-1.39 (1H, m, CH(OTES)C*H*(CH_3)); 1.51 (3H, d, *J* = 6.9 Hz, BzOCH(C*H*$_3$); 1.23-1.12 (2H, m, C*H*$_2$$CH_3$); 1.09 (3H, d, *J* = 6.9Hz, (C=O)CH(CH_3)); 0.95 (3H, d, *J* = 6.9 Hz; CH(C*H*$_3$)CH_2CH_3); 0.92 (9H, t, *J* = 7.9 Hz, Si(CH_2C*H*$_3$)$_3$); 0.89 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 0.56 (6H, q, *J* = 7.2 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.2; 165.6; 133.1; 129.7; 128.3; 78.1; 75.0; 45.9; 38.9; 23.8; 15.6; 15.4; 14.2; 12.5; 6.9; 5.2; **IR** (film, cm^{-1}) 2962; 2914; 2878; 1724; 1454; 1382; 1316; 1301; 1268; 1177; 1116; 1059; 1027; 1006; 834; 739; 711; 687; $[\alpha]_D^{20} = +7.1$ (*c* 1.1, $CHCl_3$).

(4*S*, 5*S*, 6*S*)-(5-*tert*-butyldimethylsilyloxy-4,6-dimethyloctan-3-one (122)



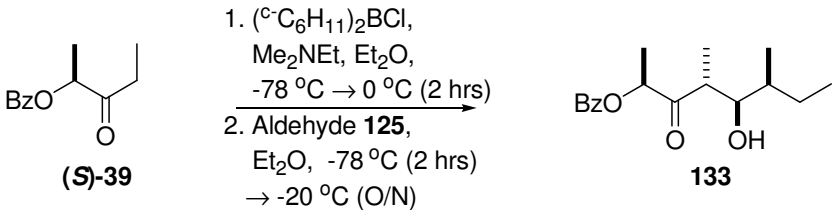
132 **122**

To a solution of benzoate **132** (0.82 g, 2.03 mmol) in THF (24.5 mL) and methanol (12.7 mL) at 0 °C was added (*via* a cannula) a solution of samarium diiodide (3-4 eq.) in THF (0.1 M) until TLC analysis indicated reaction completion. The reaction was quenched by addition of K_2CO_3 (sat. aq., 120 mL) and the product extracted with Et_2O (3 x 150 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column

chromatography (40 % CH_2Cl_2/mixed hexanes, R_f = 0.58) yielding 0.54 g (93 %) of ketone **122** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (1H, dd, *J* = 7.8, 2.7Hz; C*H*(OTES)); 2.78 (1H, apt qn, *J* = 7.2Hz, C(=O)C*H*(CH_3)); 2.48 (2H, dq, *J* = 18.3, 7.2Hz; CH_3CH_2C(=O)); 1.53-1.41 (1H, m, CH(OTES)C*H*(CH_3)); 1.22-1.03 (2H, m, CH(CH_3)CH_2CH_3); 1.00 (3H, t, *J* = 7.2Hz, CH_3CH_2C(=O)); 0.94 (3H, d, *J* = 7.2Hz, C(=O)CH(CH_3)); 0.91 (9H, t, *J* = 8.1Hz, Si(CH_2CH_3)$_3$); 0.90-0.85 (6H, m, CH(CH_3)CH_2CH_3, CH(CH_3)CH_2CH_3); 0.54 (6H, q, *J* = 8.1 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.5; 78.7; 49.6; 38.7; 36.7; 23.7; 15.7; 13.9; 12.3; 7.3; 6.9; 5.2; **IR** (film, cm^{-1}) 2962; 2939; 2879; 1721; 1460; 1414; 1378; 1240; 1133; 1115; 1090; 1058; 1008; 975; 835; 738; $[\alpha]_D^{20}$ = +33.3 (*c* 1.1, $CHCl_3$); **HRMS (ESI)** found 287.2401, $C_{16}H_{34}O_2SiH^+$ requires 287.2401; **LREIMS** 257 (81 %); 229 (14 %); 201 (10 %); 171 (65 %); 143 (12 %); 115 (14 %); 103 (18 %); 84 (43 %); 75 (31 %); 57 (100 %); 51 (19 %).

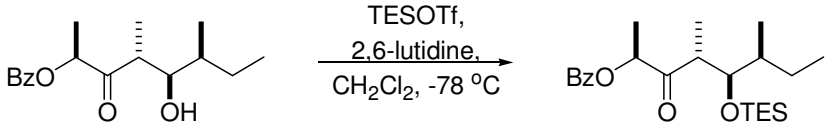
(2*S*, 4*R*, 5*R*, 6*S*)-2-benzoyloxy-5-hydroxy-4,6-dimethyloctan-3-one (133)



As per the procedure for **131** using ketone **(*S*)-39** (1.00 g, 4.85 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.21) yielded 1.18 g (83 %, >95 % ds) of the adduct **133** as a white, crystalline solid (m.p. = 85-87 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.07 (2H, m, Ar*H*); 7.62-7.56 (1H, m, Ar*H*); 7.49-7.43 (2H, m, Ar*H*); 5.46 (1H, q, *J* = 6.9 Hz, BzOC*H*(CH_3)C(=O)); 3.81 (1H, dd, *J* =8.7, 2.7, C*H*(OH)); 3.04 (1H, dq, *J* = 8.7, 6.9 Hz, C(=O)C*H*(CH_3)); 1.57 (3H, d, *J* = 6.9 Hz, BzOC*H*(CH_3)C(=O)); 1.54-1.24 (3H, m, CH(CH_3)CH_2CH_3), C*H*(CH_3)CH_2CH_3); 1.18 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)CH(OH)); 0.92 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2CH_3); 0.87 (3H, d, *J* = 6.6 Hz, CH(OH)CH(CH_3)CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.8; 165.9; 133.3; 129.8; 129.6; 128.4; 75.3; 74.8; 45.7; 36.1; 26.8; 15.8; 14.1; 12.0; 11.8; **IR** (film, cm^{-1}) 3538; 2968; 2925; 2877; 1732; 1699; 1455; 1319; 1298; 1274; 1228; 1001; 713; 683; $[\alpha]_D^{20}$ = +32.7 (*c* 1.0, $CHCl_3$).

(2*S*, 4*R*, 5*R*, 6*S*)-2-benzoyloxy-5-triethylsilyloxy-4,6-dimethyloctan-3-one (134)

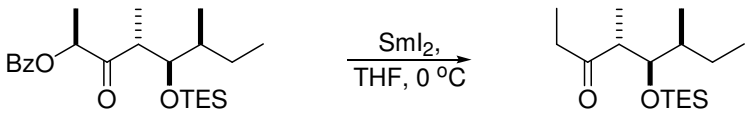


133 **134**

As per the procedure for **132** using alcohol **133** (1.18 g, 4.03 mmol), purification by column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.34) yielded 1.61 g (83 %) of the silyl ether **134** as clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.07 (2H, m, Ar*H*); 7.61-7.55 (1H, m, Ar*H*); 7.49-7.43 (2H, m, Ar*H*); 5.44 (1H, q, *J* = 6.9 Hz, BzOC*H*(CH_3)C(=O)); 3.96 (1H, dd, *J* = 9.3, 1.5 Hz, CH(OTES)); 3.07 (1H, dq, *J* = 9.3, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES)); 1.52 (3H, d, *J* = 6.9 Hz BzOCH(C*H*$_3$)C(=O)); 1.48-1.36 (1H, m, CH(OTES)C*H*(CH_3));1.26-1.13 (2H, m, CH(OTES)CH(CH_3)C*H*$_2$); 1.09 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)CH(OTES)); 0.92 (9H, t, *J* = 8.1 Hz, Si(CH_2C*H*$_3$)$_3$); 0.91 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); 0.84 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)CH_2CH_3); 0.56 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$$CH_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.5; 165.7; 133.2; 129.8; 128.4; 77.1; 75.1; 46.4; 37.9; 26.8; 15.6; 14.4; 12.7; 12.4; 7.0; 5.3 (note: two aromatic C signals are coincident); **IR** (film, cm^{-1}) 2962; 2878; 1723; 1453; 1267; 1115; 1060; 1008; 738; 711; $[\alpha]_D^{20}$ = +0.917 (*c* 2.2, $CHCl_3$); **LREIMS** 254 (6 %); 177(6 %); 162 (13 %); 149 (7.3 %); 105 (100 %); 86 (15 %); 85 (16 %); 77 (32 %); 57 (24 %); 55 (16 %).

(4*R*, 5*R*, 6*S*)-(5-*tert*-butyldimethylsilyloxy-4,6-dimethyloctan-3-one (123)



134 **123**

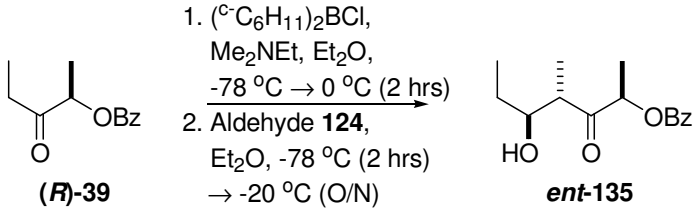
As per the procedure for **122** using benzoate **134** (1.61 g, 3.96 mmol), purification by column chromatography (40 % CH_2Cl_2/mixed hexanes, R_f = 0.26) yielded 1.01 g (89 %) of ketone **123** as clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (1H, dd, *J* = 8.7, 1.8 Hz, C*H*(OTES)); 2.76 (1H, dq, *J* = 8.7, 6.9 Hz, C(=O)C*H*(CH_3)); 2.54 (1H, dq, *J* = 18.9, 7.2 Hz, CH_3C*H*$_A$H$_B$C(=O)); 2.43 (1H, dq, *J* = 18.9, 7.2 Hz, CH_3CH$_A$*H*$_B$C(=O)); 1.45-1.32 (2H, m, C*H*(CH_3)CH_2CH_3, C*H*$_A$H$_B$$CH_3$); 1.23-1.09 (1H, m, CH$_A$*H*$_B$$CH_3$); 1.02 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$C(=O)); 0.92 (9H, t, *J* = 8.4 Hz, Si(CH_2C*H*$_3$)$_3$); 0.916 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)); 0.90 (3H, t, *J* = 7.2 Hz,C(CH_3)CH_2C*H*$_3$); 0.83 (3H, d, *J* =

6.6 Hz, CH(OTES)CH(C*H*$_3$)); 0.54 (6H, q, *J* = 8.4 Hz, Si(CH$_2$C*H*$_3$)$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.7; 77.5; 49.9; 37.8; 37.0; 26.8; 14.1; 12.6; 12.3; 7.3; 7.0; 5.3; **IR** (film, cm^{-1}) 2963, 2919; 2914; 2879; 1721; 1459; 1414; 1379; 1240; 1137; 1110; 1089; 1060; 1038; 1007; 976; 738; $[\alpha]_D^{20} = -31.8$ (*c* 1.5, $CHCl_3$).

6.2.3 Synthesis of the *anti*-aldehyde fragments 118 and 119

(2*R*, 4*S*, 5*S*)-2-benzoyloxy-5-hydroxy-4-methylpentan-3-one (*ent*-135)



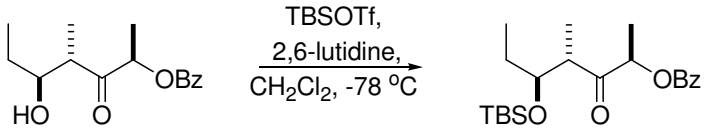
(*R*)-39 **ent-135**

To a solution of dicyclohexylboron chloride (0.89 mL, 4.1 mmol) in Et_2O (11 mL) at –78 °C was added dimethylethylamine (0.53 mL, 4.91 mmol), dropwise, followed by ketone **(*R*)-39** (0.56 g, 2.73 mmol) in Et_2O (11 mL). The resulting milky white solution was slowly warmed to 0 °C and stirred for 2 hours before dropwise addition of propionaldehyde (**124**) (0.79 mL, 10.9 mmol). The solution was stirred for a further 2 hours at –78 °C before being placed in the freezer overnight. After this time the solution was placed in a 0 °C bath and was stirred for 30 minutes. The reaction was quenched by addition of methanol (11 mL), pH 7 phosphate buffer (11 mL) and H_2O_2 (30 %, 11 mL) at 0 °C. The solution was warmed to room temperature and stirred for 1 hour before partitioning onto H_2O (150 mL) and extracting the product with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (60 % Et_2O/mixed hexanes, $R_f = 0.35$) to yield 0.63 g (87 %, >95 % ds) of ***ent*-135** as a low melting point, white, crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (2H, m, Ar*H*); 7.58 (1H, m, ArH); 7.45 (2H, m, ArH); 5.43 (1H, q, *J* = 7.2 Hz, C*H*(CH_3)OBz); 3.69 (1H, ddd, *J* = 10.8, 7.2, 3.3 Hz, C*H*OH); 2.88 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.44 (1H, bs, O*H*); 1.64-1.55 (1H, m, $CH_3CH_AH_B$); 1.56 (3H, d, *J* = 7.2 Hz, CH(C*H*$_3$)OBz); 1.48-1.33 (1H, m, $CH_3CH_AH_B$); 1.25 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 0.97 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$); **^{13}C NMR** (75.5MHz, $CDCl_3$) δ 211.9; 165.8; 133.3; 129.7; 129.4; 128.4; 74.7; 74.6; 47.8; 27.3; 15.8; 14.4; 9.7; **IR** (film, cm^{-1}) 3386; 2990; 2979; 2956; 2933; 2924; 2901; 2881; 1733; 1723; 1459; 1316; 1300; 1282; 1268; 1119; 1029; 1008;

710; $[\alpha]_D^{20} = -47$ (*c* 1.0, $CHCl_3$); **LREIMS** 137 (38 %); 121 (33 %); 105 (17 %); 85 (71 %); 83 (100 %); 77 (15 %); 57 (12 %).

(2*R*, 4*S*, 5*S*)-2-benzoyloxy-5-*tert*-butyldimethylsilyloxy-4-methylpentan-3-one (*ent*-136)

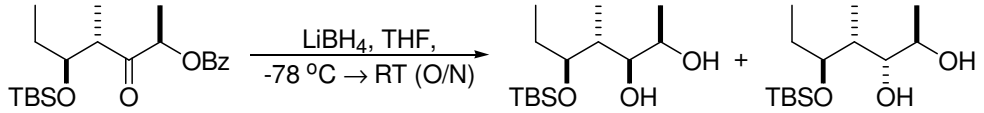


***ent*-135** ***ent*-136**

To a solution of alcohol ***ent*-135** (0.31 g, 1.16 mmol) in CH_2Cl_2 (11.6 mL) at –78 °C was added dropwise, 2,6-lutidine (0.27 mL, 2.32 mmol) followed immediately by TBSOTf (0.04 mL, 1.74 mmol). The resulting solution was stirred at –78 °C for 1 hour before quenching with $NaHCO_3$ (25 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.36) yielding 0.44g (99 %) of ***ent*-136** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar*H*); 7.61-7.55 (1H, m, Ar*H*); 7.48-7.42 (2H, m, Ar*H*); 5.42 (1H, q, *J* = 6.9 Hz, C(=O)C*H*(CH_3)OBz); 4.04 (1H, dt, *J* = 8.7, 3.9 Hz, C*H*(OTBS)); 3.03 (1H, dq, *J* = 8.4, 7.2 Hz, CH(OTBS)C*H*(CH_3)); 1.60-1.50 (2H, m, CH_3CH_2); 1.52 (3H, d, *J* = 6.9 Hz, CH(CH_3)OBz); 1.09 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(CH_3)); 0.88 (3H, t, *J* = 7.5 Hz, CH_3CH_2CH(OTBS)); 0.84 (9H, s, OSiC(CH_3)$_3$); 0.03 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); –0.05 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.3; 165.7; 133.2; 129.8; 129.7; 128.4; 74.9; 73.3; 46.4; 25.8; 25.7; 18.0; 15.4; 13.3; 7.0; –4.7; –4.8; **IR** (film, cm^{-1}) 2960; 2933; 2885; 2859; 1723; 1604; 1472; 1463; 1453; 1382; 1361; 1316; 1268; 1177; 1120; 1100; 1072; 1027; 999; 862; 835; 777; 711; $[\alpha]_D^{20} = +15.1$ (*c* 1.0, $CHCl_3$); **HRMS (ESI)** found 401.2110, $C_{22}H_{34}NaO_4Si^+$ requires 401.2119; **LREIMS** 321 (4.8 %); 279 (6.0 %); 254 (27 %); 199 (33 %); 179(100 %); 167 (14 %); 149 (40 %); 127 (12 %); 115 (12 %); 105 (62 %); 85 (51 %); 83 (71 %); 77 (25 %); 75 (39 %); 73 (37 %); 57 (40 %); 55(20 %).

(2*R*, 3*S*, 4*R*, 5S)/(2*R*, 3*R*, 4*R*, 5*S*)-5-*tert*-butylsilyloxy-4-methyl-heptan-2,3-diol (*ent*-137a/b)



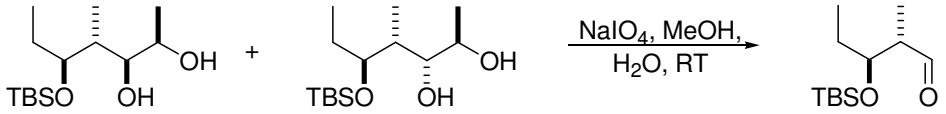
***ent*-136** ***ent*-137a** ***ent*-137b**

To a cooled (–78 °C) solution of the benzoate ester ***ent*-136** (0.44 g, 1.16 mmol) in THF (14 mL) was added a solution of $LiBH_4$ (2 M in THF, 11.6 mL, 23.2 mmol). The solution was placed in an ice/H_2O bath for 10 minutes before warming to room temperature. After stirring overnight the solution was cooled to 0 °C before quenching with H_2O (14 mL). The mixture was partitioned between H_2O (14 mL) and Et_2O (4 x 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (20 % Et_2O/CH_2Cl_2, R_f(**ent-137a**) = 0.25, R_f(**ent-137b**) = 0.41) yielding 0.23 g (73 %) of ***ent*-137a** and ***ent*-137b** (ratio 2.5:1) as clear, colourless oils.

(2*R*, 3*S*, 4*R*, 5S) (*ent*-137a) - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (1H, qd, *J* = 6.3, 3.9 Hz, CH(OH)C*H*(CH_3)OH); 3.74 (1H, apt q, *J* = 5.4 Hz, C*H*(OTBS)); 3.56 (1H, dd, *J* = 8.4, 3.9 Hz, CH(CH_3)C*H*(OH)); 2.88 (2H, br s, O*H*, O*H*); 1.73 (1H, m, CH(OTBS)CH(C*H*$_3$)); 1.53 (2H, m, CH_3CH_2CH(OTBS)); 1.16 (3H, d, *J* = 6.3 Hz, CH(OH)CH(C*H*$_3$)OH); 0.901 (9H , s, SiC(C*H*$_3$)$_3$); 0.895 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$); 0.81 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)CH(OH)); 0.10 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.09 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 77.4; 76.6; 67.9; 39.6; 26.4; 25.9; 18.0; 16.2; 12.2; 9.2; –4.4; –4.7; **IR** (film, cm^{-1}) 3410; 2960; 2932; 2887; 2859; 1473; 1464; 1407; 1388; 1361; 1304; 1286; 1256; 1141; 1107; 1069; 1012; 1004; 989; 923; 866; 836; 792; 774; 665; $[\alpha]_D^{20}$ = +11.3 (*c* 0.8, $CHCl_3$).

(2*R*, 3*R*, 4*R*, 5*S*) (*ent*-129b) - NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = +15.8 (*c* 1.1, $CHCl_3$).

(2*S*, 3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanal (119)

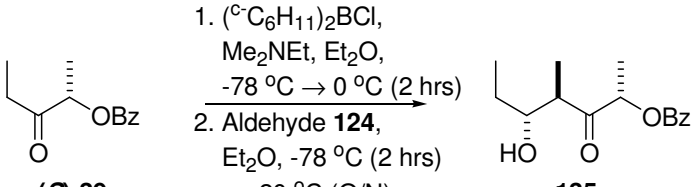


***ent*-137a** ***ent*-137b** **119**

To a stirred solution of the diols ***ent*-137a** and ***ent*-137b** (0.22 g, 0.81 mmol) in MeOH (8 mL) and H_2O (4 mL) at room temperature was added $NaIO_4$ (1.04g, 4.84 mmol) and the resulting suspension stirred for 15 min at room temperature. The reaction mixture was diluted with H_2O (24 mL) and extracted with Et_2O (3 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/mixed hexanes, R_f = 0.39) to give 0.16 g (87 %, >95 % ds) of aldehyde **119** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (1H, d, *J* = 2.1 Hz, C*H*(=O)); 3.86 (1H, apt q, *J* = 5.2 Hz, C*H*(OTBS)); 2.51 (1H, qdd, *J* = 6.9, 4.8, 2.4 Hz, CH(OTBS)C*H*(CH_3)CH(=O)); 1.55 (2H, m, CH_3CH_2CH(OTBS)); 1.06 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)CH(=O)); 0.90 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$); 0.87 (9H, s, SiC(C*H*$_3$)$_3$); 0.06 (3H, s, Si(C*H*$_3$)$_A$($CH_3$)$_B$); 0.05 (3H, s, Si($CH_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.2; 74.5; 50.6; 27.4; 25.7; 18.0; 10.5; 8.9; –4.3; –4.8; **IR** (film, cm^{-1}) 2960; 2933; 2885; 2860; 2712; 1729; 1473; 1464; 1389; 1382; 1362; 1257; 1156; 1119; 1088; 1068; 1044; 1017; 1006; 938; 838; 815; 790; 776; 668; $[\alpha]_D^{20}$ = +44.6 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** found 253.1588, $C_{12}H_{26}O_2SiNa^+$ requires 253.1594; **LREIMS** 469 (13 %); 327 (9.8 %); 257 (34 %); 201 (66 %); 173 (100%); 115 (48 %); 103 (17 %); 87 (18 %); 75 (49 %); 74 (28 %).

(2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-hydroxy-4-methylpentan-3-one (135)

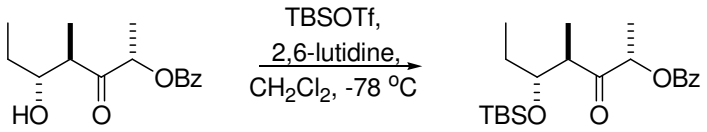


(*S*)-39 **135**

As per the procedure for ***ent*-135** using ketone **(*S*)-39** (1.0 g, 4.85 mmol), purification by column chromatography (60 % Et_2O/mixed hexanes, R_f = 0.38) yielded 1.13 g (88 %, >95 % ds) of the ketone **135** as clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = +44.7 (*c* 1.0, $CHCl_3$).

(2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-*tert*-butyldimethylsilyloxy-4-methylpentan-3-one (136)

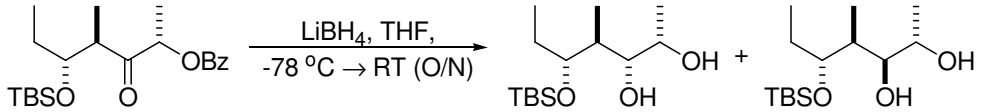


135 **136**

As per the procedure for ***ent*-136** using alcohol **135** (1.13 g, 4.28 mmol), purification by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.48) yielded 1.59 g (98 %) of the silyl ether **136** as clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20} = -17.1$ (*c* 1.1, $CHCl_3$).

(2*S*, 3*R*, 4*S*, 5*R*)/(2*S*, 3*S*, 4*S*, 5*R*)-5-*tert*-butylsilyloxy-4-methylheptan-2,3-diol (137a/b)



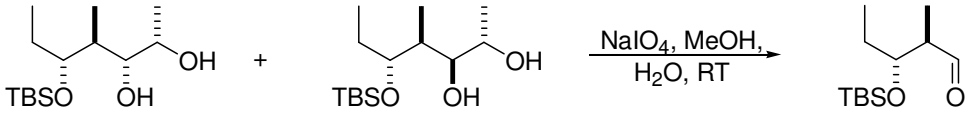
136 **137a** **137b**

As per the procedure for ***ent*-137a/b** using benzoate ester **136** (1.59 g, 4.2 mmol), purification by column chromatography (20 % Et_2O/CH_2Cl_2, R_f(**137a**) = 0.26, R_f(**137b**) = 0.40) yielded 0.80 g (99 %) of the diols **137a** and **137b** (2.5:1) as clear, colourless oils.

(2*S*, 3*R*, 4*S*, 5*R*) (137a) - NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20} = -8.46$ (*c* 1.0, $CHCl_3$); **HRMS (ESI)** found 277.2193, $C_{15}H_{32}O_3SiH^+$ requires 277.2193; **LREIMS** 201 (48 %); 173 (80 %); 143 (15 %); 133 (26 %); 115 (32 %); 109 (12 %); 85 (71 %); 83 (100 %); 57 (86 %); 55 (8 %).

(2*S*, 3*S*, 4*S*, 5*R*) (129b) - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77-3.61 (3H, m, C*H*(OTBS), C*H*(OH)CH(CH_3)OH, CH(OH)C*H*(CH_3)OH); 3.07 (2H, br s, O*H*, O*H*); 1.76-1.55 (3H, m, CH_3CH_2, CH(OTBS)C*H*(CH_3)); 1.08 (3H, d, *J* = 6.0 Hz, CH_3CH(OH)); 0.97 (3H, d, *J* = 6.9 Hz, CH(OH)CH(CH_3)CH(CHOTBS)); 0.89 (9H, s, Si(CH_3)$_2$); 0.83 (3H, t, *J* = 7.5 Hz, CH_3CH$_2$); 0.08 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 80.2; 75.2; 69.0; 34.5; 27.7; 25.8; 18.1; 17.9; 11.7; 9.8; –4.4; –4.9; **IR** (film, cm^{-1}) 3430; 2960; 2933; 2885; 2859; 1473; 1464; 1256; 1102; 1076; 1062; 1047; 1033; 1014; 1005; 837; 775; $[\alpha]_D^{20} = -16.8$ (*c* 1.0, $CHCl_3$).

(2*R*, 3*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanal (118)

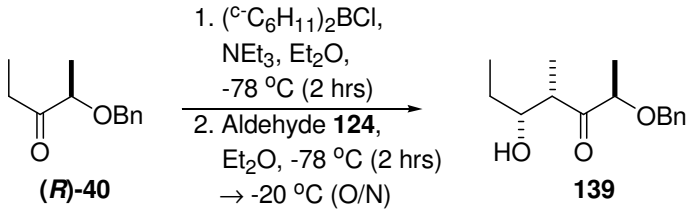


As per the procedure for **119** using diols **137a** and **137b** (0.20 g, 0.72 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.45) yielded 0.15 g (93 %) of the aldehyde **118** as clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = –45.0 (*c* 0.5, $CHCl_3$). Spectroscopic data is consistent with that reported.[209]

6.2.4 Synthesis of *syn*-aldehyde fragments 120 and 121

(2*R*, 4*S*, 5*R*)-2-benzyloxy-5-hydroxy-4-methylheptan-3-one (139)

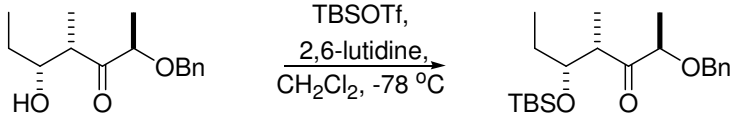


To a solution of dicyclohexylboron chloride (1.24 mL, 5.72 mmol) in Et_2O (12 mL) at –78 °C was added triethylamine (0.95 mL, 6.8 mmol) dropwise, followed by ketone **(*R*)-40** (0.73 g, 3.79 mmol) in Et_2O (12 mL). The resulting milky white solution was stirred at –78 °C for 2 hours before dropwise, addition of propionaldehyde (**124**) (1.1 mL, 15.2 mmol). The solution was stirred for a further 2 hours at –78 °C before being placed in the freezer overnight. After this time the solution was placed in a 0 °C bath and was stirred for 30 minutes. The reaction was quenched by addition of methanol (12 mL), pH 7 phosphate buffer (12 mL) and H_2O_2 (30 %, 12 mL)), at 0 °C. The solution was warmed to room temperature and stirred for 1 hour before extracting the product with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % Et_2O/CH_2Cl_2, R_f = 0.34) yielded 0.69 g (73 %, 95 % ds) of the adduct **139** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (5H, m, Ar*H*); 4.57 (1H, d, *J* = 11.7 Hz, OCH_AH_BPh); 4.51 (1H, d, *J* = 11.7 Hz, OCH_AH_BPh); 4.06 (1H, q, *J* = 6.9 Hz, $C(=O)CH(CH_3)O$); 3.76 (1H, ddd, *J* = 8.1, 5.1, 3.0 Hz, $CH_3CH_2CH(OH)$); 3.01 (1H, dq, *J* = 7.2, 3.0 Hz, $CH(OH)CH(CH_3)C(=O)$); 2.31 (1H, s, OH); 1.56-1.28 (2H, m,

CH_3CH_2); 1.38 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)O); 1.12 (3H, d, *J* = 7.2 Hz, CH(OH)CH(CH_3)C(=O)); 0.93 (3H, t, *J* = 7.5 Hz, CH_3CH_2CH(OH)); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.1; 137.5; 128.5; 128.0; 127.8; 79.5; 72.5; 71.7; 44.8; 26.9; 17.3; 10.4; 10.0; **IR** (film, cm^{-1}) 3467; 2976; 2937; 2880; 1716; 1456; 1373; 1116; 1027; 973; 736; 698; $[\alpha]_D^{20}$ = +18.1 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** found 273.1471, $C_{15}H_{22}O_3Na^+$ requires 273.1416; **LREIMS** 181 (7 %); 144 (10 %); 135 (11 %); 91 (100 %); 69 (11 %); 65 (12 %); 59 (14 %).

(2*R*, 4*S*, 5*R*)-2-benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methylheptan-3-one (140).

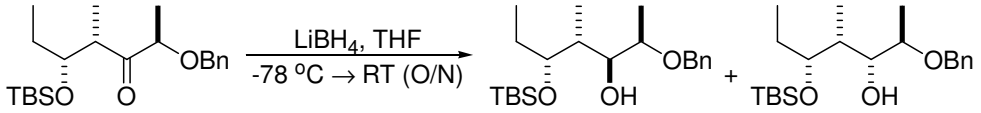


139 **140**

To a solution of the alcohol **139** (0.69 g, 2.77 mmol) in CH_2Cl_2 (30 mL) at –78 °C was added dropwise, 2,6-lutidine (640 μL, 5.48 mmol) followed immediately by TBSOTf (0.95 mL, 4.12 mmol). The resulting solution was stirred at –78 °C for 1 hour before quenching with $NaHCO_3$ (sat. aq., 70 mL). The product was extracted with CH_2Cl_2 (3 x 70 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (20 % mixed hexanes/CH_2Cl_2, R_f = 0.50) yielding 0.89 g (88 %) of the silyl ether **140** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m, Ar*H*); 4.56 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ph); 4.52 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ph); 4.08 (1H, q, *J* = 6.6 Hz, C(=O)C*H*(CH_3)OBn); 3.95 (1H, apt q, *J* = 5.7 Hz, C*H*(OTBS)); 3.08 (1H, apt qn, *J* = 6.9 Hz, CH(OTBS)C*H*(CH_3)); 1.56-1.32 (2H, m, CH_3CH_2); 1.35 (3H, d, *J* = 6.6 Hz, C(=O)CH(CH_3)OBn); 1.06 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(CH_3)); 0.87 (9H, s, SiC(CH_3)$_3$); 0.82 (3H, t, *J* = 7.5 Hz, CH_3CH_2); 0.03 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.00 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 213.4; 137.7; 128.5; 127.9 (2); 79.0; 73.4; 71.3; 46.4; 28.1; 25.9; 18.1; 16.4; 12.7; 9.1; –4.1; –4.5; **IR** (film, cm^{-1}) 2960; 2933; 2898; 2883; 2858; 1720; 1473; 1465; 1255; 1120; 1105; 1046; 1030; 1006; 991; 835; 775; 736; 697; 667; $[\alpha]_D^{20}$ = +39.0 (*c* 1.1, $CHCl_3$); **HRMS (ESI)** found 387.2327, $C_{21}H_{36}O_3SiNa^+$ requires 387.2326; **LREIMS** 249 (40 %); 173 (19 %); 157 (23 %); 143 (10 %); 115 (21 %); 91 (100 %); 76 (18 %); 73 (48 %).

(2*R*, 3*S*, 4*S*, 5*R*)/(2*R*, 3*R*, 4*S*, 5*R*)-2-benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methylheptan-3-ol (141)



140 **141a** **141b**

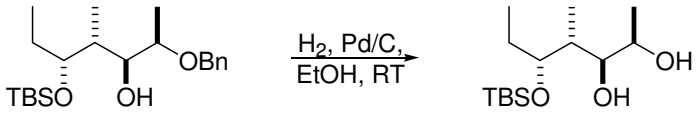
To a cooled (–78 °C) solution of the ketone **140** (0.89 g, 2.44 mmol) in THF (30 mL) was added dropwise, a solution of $LiBH_4$ (2 M in THF, 7.3 mL, 14.6 mmol). The reaction mixture was placed in an ice bath for 10 minutes before warming slowly to room temperature. After stirring overnight the solution was cooled to 0 °C before quenching by addition of H_2O (50 mL). The product was extracted with Et_2O (4 x 50 mL). The combined Et_2O extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (80 % CH_2Cl_2/mixed hexanes, R_f = 0.42 and 0.36) to yield the major isomer **141a** (0.65g, 65 %) and the minor isomer **141b** (0.24g, 24 %) as clear, colourless oils.

(2*R*, 3*S*, 4*S*, 5*R*) (133a) - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, Ar*H*); 4.60 (1H, d, *J* = 12.0 Hz, OCH_AH$_B$Ph); 4.53 (1H, d, *J* = 12.0 Hz, OCH$_A$$H_B$Ph); 3.92 (1H, dt, *J* = 2.1, 7.2 Hz, C*H*(OTBS)); 3.80 (1H, dd, *J* = 3.6, 9.0 Hz, C*H*(OH)); 3.57 (1H, dq, *J* = 3.6, 6.3 Hz, C*H*(CH$_3$)OBn); 1.68 (1H, dqd, *J* = 3.0, 7.2, 10.2 Hz, CH(OTBS)C*H*(CH$_3$)); 1.52 (2H, m, CH$_3$CH_2CH(OTBS); 1.20 (3H, d, *J* = 6.3 Hz, CH(OH)CH(CH_3)OBn); 0.91 (9H, s, SiC(CH_3)$_3$); 0.87 (3H, t, *J* = 7.5 Hz, CH_3CH$_2$); 0.76 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(CH_3)); 0.10 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); 0.08 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.6; 128.3; 127.6; 127.5; 75.8; 74.9; 73.6; 70.2; 37.8; 26.6; 25.9; 18.1; 12.8; 10.6; 9.8; –4.1; –4.6; **IR** (film, cm^{-1}) 3569; 3486; 2959; 2932; 2885; 2858; 1472; 1463; 1456; 1383; 1253; 1073; 1046; 1028; 1005; 983; 834; 775; 734; 697; 667; $[\alpha]_D^{20} = +1.99$ (*c* 1.5, $CHCl_3$); **HRMS (ESI)** found 267.2664, $C_{21}H_{38}O_3SiNa^+$ requires 267.2663; **LREIMS** 231 (7 %); 201 (15 %); 191 (19 %); 181 (23 %); 173 (46 %); 159 (8 %); 143 (7 %); 133 (12 %); 115 (14 %); 91 (100 %); 84 (26 %); 75 (27 %); 57 (20 %); 55 (12 %).

(2*R*, 3*R*, 4*S*, 5*R*) (133b) - **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.27 (5H, m, Ar*H*); 4.67 (1H, d, *J* = 11.4 Hz, OCH_AH$_B$Ph); 4.45 (1H, d, *J* = 11.4 Hz, OCH$_A$$H_B$Ph); 3.64 (1H, apt q, *J* = 5.4 Hz, C*H*(OTBS)); 3.57-3.53 (2H, m, C*H*(OH), C*H*(CH$_3$)OBn); 1.74-1.63 (1H, m, CH(OTBS)C*H*(CH$_3$)); 1.63-1.50 (2H, m, CH$_3$CH_2); 0.90 (3H, d, *J* = 8.4 Hz, CH(OTBS)CH(CH_3)); 0.89 (9H, s, SiC(CH_3)$_3$); 0.84 (3H, t, *J* = 7.5 Hz, CH$_3$CH$_2$); 0.05 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$);0.03 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR**

(75.5 MHz, $CDCl_3$) δ 138.4; 128.4; 127.8; 127.7; 77.1; 75.6; 75.2; 71.1; 38.0; 26.4; 25.9; 18.1; 15.5; 9.0; 8.9; –4.1, –4.5; **IR** (film, cm^{-1}) 3578; 2960; 2931; 2885; 2858; 1463; 1456; 1255; 1080; 1064; 1027; 1012; 1006; 836; 773; 697; 674; 667; $[\alpha]_D^{20} = -19.8$ (*c* 1.2, $CHCl_3$).

(2*R*, 3*R*, 4*S*, 5*R*)-5-*tert*-butylsilyloxy-4-methylheptan-2,3-diol (142a)

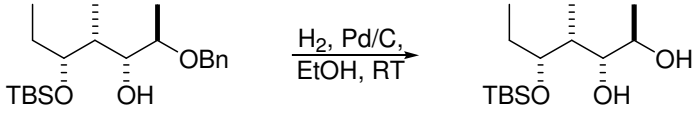


141a **142a**

To a solution of the benzyl ether **141a** (0.58 g, 1.58 mmol) in ethanol (16 mL), under an atmosphere of nitrogen, was added palladium on activated carbon (10 %, 60 mg). The flask was flushed with nitrogen followed by hydrogen and the solution stirred under an atmosphere of hydrogen for 2 hours, or until TLC analysis indicated starting material was consumed. The reaction mixture was diluted with ether (60 mL) and filtered through a pad of Celite and concentrated in *vacuo* to yield 0.44 g (99 %) of **142a** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77-3.67 (3H, m, C*H*(CH_3)OH, C*H*(OH), C*H*(OTBS)); 1.78-1.68 (1H, m, C*H*(CH_3)); 1.62-1.52 (2H, m, CH(OTBS)C*H*$_2$); 1.45 (3H, d, *J* = 6.3 Hz, CH(CH_3)OH); 0.94 (3H, t, *J* = 7.2 Hz, CH_2CH_3); 0.91 (9H, s, OSiC(CH_3)$_3$); 0.77 (3H, d, *J* = 7.2 Hz, CH(C*H*$_3$)); 0.11 (3H, s, OSi(C*H*$_3$)$_A$(CH_3)$_B$); 0.09 (3H, s, OSi(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 79.1; 75.9; 68.8; 39.3; 25.8; 24.3; 18.4; 15.5; 12.4; 11.3; –4.5; –4.6; **IR** (film, cm^{-1}) 3423; 2961; 2934; 2885; 2860; 1473; 1464; 1385; 1255; 1130; 1105; 1069; 1046; 1016; 1003; 987; 870; 836; 776; 675; 667; $[\alpha]_D^{20} = +20.6$ (*c* 1.6, $CHCl_3$).

(2*R*, 3*S*, 4*S*, 5*R*)-5-*tert*-butylsilyloxy-4-methylheptan-2,3-diol (142b)



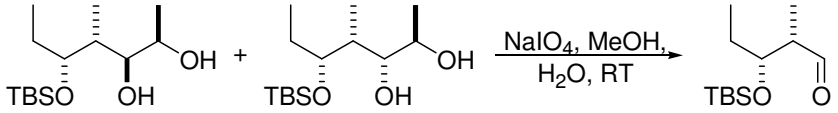
141b **142b**

As per the procedure for **142a** using benzyl ether **141b** (0.22 g, 5.88 mmol) yielding 0.15 g (91 %,) of alcohol **142b** as white semi-solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81-3.72 (2H, m, C*H*(OTBS), C*H*(CH_3)OH); 3.44 (1H, dd, *J* = 2.1, 7.2 Hz, C*H*(OH)); 2.87 (2H, br s, O*H*, O*H*); 1.75-1.66 (1H, m, CH(OH)C*H*(CH_3)); 1.60-1.50 (2H, m, CH(OTBS)CH_2); 1.14 (3H, d, *J* = 6.3 Hz,

CH(C*H*$_3$)OH); 0.89 (9H, s, OSiC(C*H*$_3$)$_3$); 0.87 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 0.83 (3H, t, *J* = 7.5 Hz, CH_2CH_3); 0.09 (6H, s, OSi(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 79.4; 78.9; 68.9; 36.4; 27.0; 25.9; 18.8; 18.0; 9.8; 6.5; –3.7; –4.5; **IR** (film, cm^{-1}) 3401; 2961; 2932; 2885; 2859; 1473; 1464; 1381; 1362; 1256; 1132; 1103; 1078; 1051; 1014; 1006; 984; 860; 872; 836; 792; 773; 676; 667; $[\alpha]_D^{20}$ = –11.5 (*c* 1.5, $CHCl_3$); **HRMS (ESI)** found 277.2195, $C_{14}H_{22}O_3SiH^+$ requires 277.2193; **LREIMS** 201 (35 %); 173 (67 %); 143 (17 %); 133 (51 %); 115 (41 %); 75 (100 %); 73 (64 %); 57 (26 %).

(2*S*, 3*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanal (120)

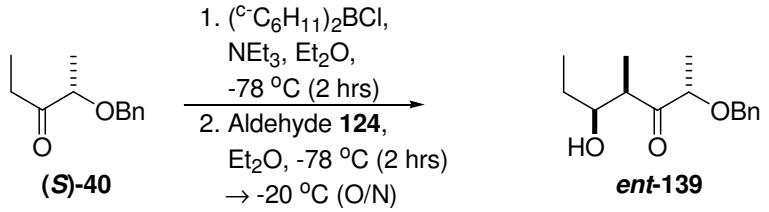


142a **142b** **120**

To a stirred solution of the diols **142a** and **142b** (0.44 g, 1.58 mmol) in MeOH (16 mL) and H_2O (8 mL) at room temperature was added $NaIO_4$ (2.06 g, 9.6 mmol) and the resulting suspension stirred for 15 minutes at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O (3 x 60 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/mixed hexanes, R_f = 0.45) to give 0.35 g (97 %) of the aldehyde **120** as a clear, colourless oil with spectroscopic data consistent with that reported.[211,212]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (1H, d, *J* = 0.9 Hz, C*H*(=O)); 4.03 (1H, dt, *J* = 3.6, 6.6 Hz, C*H*(OTBS)); 2.46 (1H, ddq, *J* = 0.9, 3.6, 6.9 Hz, CH(=O)C*H*(CH$_3$)); 1.64-1.45 (2H, m, CH(OTBS)C*H*$_2$); 1.05 (3H, d, *J* = 6.9 Hz, CH(=O)CH(C*H*$_3$)); 0.88 (3H, t, *J* = 7.5 Hz, CH_2CH_3); 0.86 (9H, s, OSiC(C*H*$_3$)$_3$); 0.06 (3H, s, OSi(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.03 (3H, s, OSi(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.5; 73.4; 50.8; 27.4; 25.7; 18.0; 10.1; 7.6; –4.2; –4.7; **IR** (film, cm^{-1}) 2960; 2933; 2884; 2860; 1727; 1473; 1464; 1254; 1141; 1103; 1048; 1030; 1006; 837; 775; 667; $[\alpha]_D^{20}$ = +53.7 (*c* 0.7, $CHCl_3$).

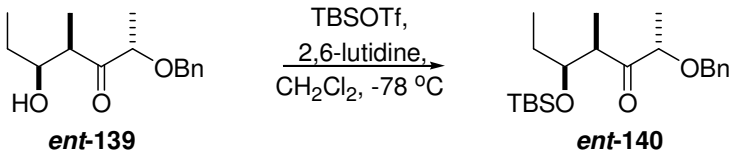
(2*S*, 4*R*, 5*S*)-2-benzyloxy-5-hydroxy-4-methylheptan-3-one (*ent*-139)



As per the procedure for **139** using ketone **(*S*)-40** (1.22g, 6.35 mmol), purification by column chromatography (50 % Et_2O/mixed hexanes, R_f = 0.27) yielded 1.58 g (99 %, 95 % ds) of ***ent*-139** as a clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = –19.6 (*c* 1.0, $CHCl_3$).

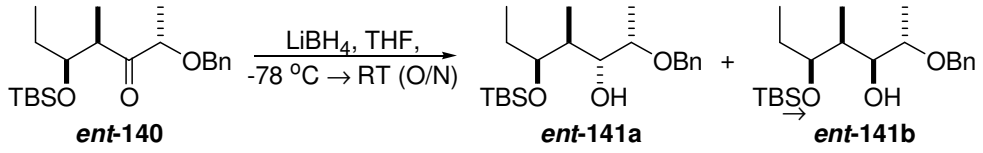
(2*S*, 4*R*, 5*S*)-2-benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methylheptan-3-one (*ent*-140)



As per the procedure for **140** using alcohol ***ent*-139** (1.04 g, 4.14 mmol) purification by column chromatography (20 % mixed hexanes/CH_2Cl_2, R_f = 0.47) yielded 1.44 g (95 %) of ***ent*-140** as a clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = –36.4 (*c* 1.1, $CHCl_3$).

(2*S*, 3*S*, 4*R*, 5*S*)/(2*S*, 3*R*, 4*R*, 5*S*)-2-benzyloxy-5-*tert*-butyldimethylsilyloxy-4-methylheptan-3-ol (*ent*-141a/b)

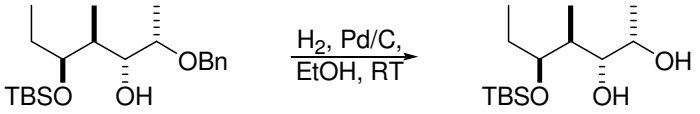


As per the procedure for **141a/b** using ketone ***ent*-140** (1.95 g, 5.35 mmol) purification by column chromatography (80 % CH_2Cl_2/mixed hexanes, R_f = 0.42 and 0.36) to yield 1.78 g, (91 %) of both ***ent*-141a** and ***ent*-141b** isomers (ratio 3.5:1) as clear, colourless oils.

(2*S*, 3*S*, 4*R*, 5*S*)(*ent*-141a) - NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = –2.0 (*c* 4.0, $CHCl_3$).

(2*S*, 3*R*, 4*R*, 5*S*) (*ent*-141b) - **NMR** and **IR** data as for the enantiomer; $[\alpha]_D^{20}$ = +29.7 (*c* 1.2, $CHCl_3$).

(2*S*, 3*S*, 4*R*, 5*S*)-5-*tert*-butylsilyloxy-4-methylheptan-2,3-diol (*ent*-142a)

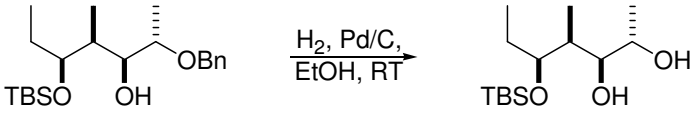


***ent*-141a** ***ent*-142a**

As per the procedure for **142a** using benzyl ether ***ent*-141a** (0.89 g, 2.43 mmol), yielding 0.67 g (99 %) of the diol ***ent*-142a** as a clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20} = -19.8$ (*c* 1.5, $CHCl_3$).

(2*S*, 3*R*, 4*R*, 5*S*)-5-*tert*-butylsilyloxy-4-methylheptan-2,3-diol (*ent*-142b)

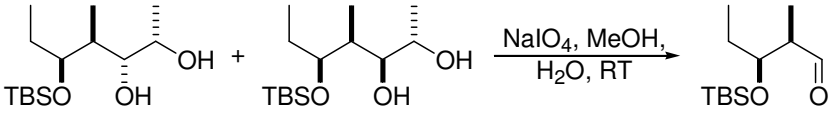


***ent*-141b** ***ent*-142b**

As per the procedure for **142a** using benzyl ether ***ent*-141b** (0.28 g, 7.56 mmol), yielding 0.20 g (95 %) of the diol ***ent*-142b** as a clear, colourless oil.

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20} = +15.1$ (*c* 1.0, $CHCl_3$).

(2*R*, 3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylpentanal (121)



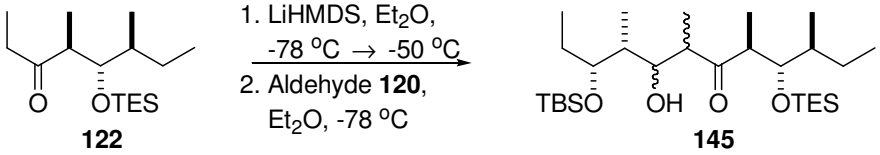
***ent*-142a** ***ent*-142b** **121**

As per the procedure for **120** using diols ***ent*-142a** and ***ent*-142b** (0.73g, 2.65mmol) purification by column chromatography (5 % Et_2O/mixed hexanes, R_f = 0.35) yielded 0.52 g (85 %) of aldehyde **121** as a clear, colourless oil with spectroscopic data consistent with that reported.[213]

NMR and **IR** data as for the enantiomer; $[\alpha]_D^{20} = -52.2$ (*c* 1.2, $CHCl_3$).

6.2.5 Synthesis of (-)-maurenone (14)

(3*S*, 4*S*, 5*S*, 9*S*, 10*R*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (145)



122 **145**

To a solution of ketone **122** (105 mg, 0.368 mmol) in THF (0.74 mL) at –78 °C was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 552 μL, 0.552 mmol). The resulting yellow solution was stirred at –78 °C for 30 minutes then warmed to –50 °C for 30 minutes. The solution was then cooled to –78 °C and aldehyde **120** (127 mg, 0.552 mmol) added. The resulting solution was stirred at –78 °C for 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer solution (2 mL) and the organics extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (5 % Et_2O/hexanes, R_f = 0.21, 0.13 and 0.05) to yield 108 mg (57 %) of the aldol adducts **145** as a mixture of diastereomers (0.74:0.08:0.18) and clear, colourless oils.

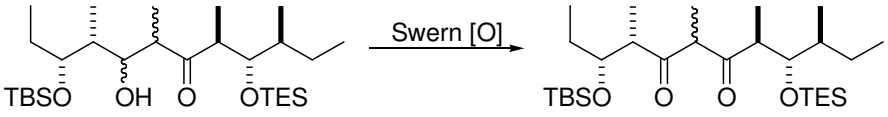
145a - **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.04-3.98 (2H, m, C*H*(OH), C*H*(OTBS)); 3.87 (1H, dd, *J* = 8.1, 3.0 Hz, C*H*(OTES)); 3.32 (1H, br s, O*H*); 3.06 (1H, dq, *J* = 7.8, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES)); 2.63 (1H, qd, *J* = 7.2, 1.8 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.63-1.43 (6H, m, CH_3CH_2, CH(OTBS)C*H*(CH_3), CH(OTES)C*H*(CH_3), CH_2CH_3); 1.15 (3H, d, *J* = 7.5Hz, CH(OH)CH(C*H*$_3$)C(=O)); 0.98-0.83 (12H, m, CH_3CH_2, CH_2CH_3, C(=O)CH(C*H*$_3$)CH(OTES), CH(OTES)CH(C*H*$_3$)CH_2); 0.93 (9H, t, *J* = 7.5 Hz, Si(CH_2CH_3)$_3$); 0.88 (9H, s, SiC(C*H*$_3$)$_3$); 0.72 (3H, d, *J* = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH(OH)); 0.55 (6H, q, *J* = 7.5 Hz, Si(CH_2CH_3)$_3$); 0.09 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.07 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 219.1; 79.1; 73.0; 70.6; 48.6; 47.3; 39.3; 38.0; 27.4; 25.9; 24.4; 18.1; 15.4; 14.0; 12.5; 10.6; 9.0; 8.0; 7.0; 5.3; –4.4; –4.5; **IR** (film, cm^{-1}) 3533; 2961; 2938; 2880; 2859; 1699; 1463; 1381; 1251; 1150; 1130; 1107; 1059; 1006; 973; 871; 835; 775; 739; 729; 666; $[\alpha]_D^{20} = +52.1$ (*c* 0.9, $CHCl_3$).

145b – not characterised due to small amount isolated.

145c - **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.95 (1H, apt t, *J* = 5.4 Hz, C*H*(OH)); 3.93 (1H, dd, *J* = 6.0, 2.7 Hz, C*H*(OTES)); 3.71 (1H, ddd, *J* = 8.4, 6.0, 2.4 Hz, C*H*(OTBS)); 2.96 (1H, dq, *J* = 8.4, 7.5 Hz, C(=O)C*H*(CH_3)CH(OTES)); 2.86 (1H,

qd, *J* = 7.2, 6.0 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.65-1.46 (5H, m, $CH_3CH_AH_B$ or $CH_AH_BCH_3$, CH_3CH_2 or CH_2CH_3, CH(OTBS)C*H*(CH_3), CH(OTES)C*H*(CH_3)); 1.22-1.12 (1H, m, $CH_3CH_AH_B$ or $CH_AH_BCH_3$); 1.16 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)C(=O)); 0.97-0.78 (15H, m, CH(OTBS)CH(C*H*$_3$), C(=O)CH(C*H*$_3$), CH(OTES)CH(C*H*$_3$), C*H*$_3$CH$_2$, CH$_2$C*H*$_3$); 0.94 (9H, t, *J* = 8.1 Hz, Si(CH_2CH_3)$_3$); 0.90 (9H, s, SiC(C*H*$_3$)$_3$); 0.59 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$); 0.11 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.09 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.6; 77.54; 77.51; 74.1; 49.2; 48.9; 39.1; 37.5; 27.4; 25.9; 24.3; 18.0; 15.7; 13.7; 12.6; 11.0; 10.2; 7.4; 7.0; 5.3; –3.7; –4.4; **IR** (film, cm^{-1}) 3524; 2961; 2938; 2879; 2861; 1712; 1463; 1415; 1380; 1361; 1255; 1132; 1113; 1056; 1006; 977; 872; 835; 814; 774; 738; 667; $[\alpha]_D^{20} = -2.47$ (*c* 2.0, $CHCl_3$).

(3*R*, 4*S*, 8*S*, 9*S*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (146)



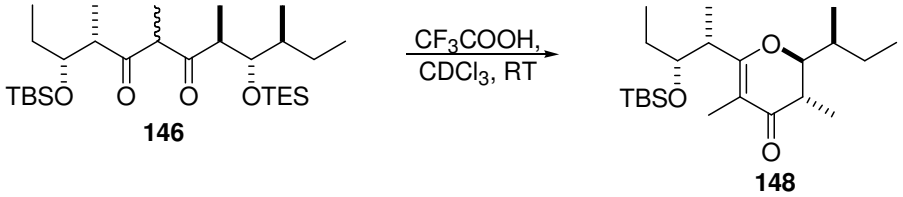
145 **146**

Oxalyl chloride (152 µL, 0.305 mmol) was added dropwise to a solution of DMSO (43 µL, 0.609 mmol) in CH_2Cl_2 (870 µL) at –78 °C and the solution stirred for 30 minutes. Alcohol **145** (108 mgs, 0.209 mmol) was added *via* a cannula and the resulting solution stirred for 45 minutes at –78 °C. Et_3N (170 µL, 0.122 mmol) was then added dropwise over several minutes and stirred at –78 °C for 30 minutes before warming to 0 °C and stirring for 1 hour. The reaction was quenched by pouring onto $NaHSO_4$ (1 M, 10 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organics were concentrated in *vacuo*, taken up in Et_2O (50 mL), washed $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (sat. aq., 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. (Alternatively the reaction was quenched by addition of NH_4Cl (sat. aq., 20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*). Purification by column chromatography yielded dione **146** (85 mg, 79 %) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) (predominantly keto form) δ 4.00 (1H, q, *J* = 7.2 Hz, C(=O)C*H*(CH_3)C(=O)); 3.86 (1H, apt q, *J* = 5.7 Hz, C*H*(OTBS)); 3.75 (1H, dd, *J* = 8.4, 2.4 Hz, C*H*(OTES)); 2.93 (1H, qd, *J* = 6.9. 6.0 Hz, CH(OTBS)C*H*(CH_3)); 2.83

(1H, dq, *J* = 8.7, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES)); 1.67–1.12 (5H, m, CH_3CH_2, C*H*(CH_3)CH_2CH_3, CH(CH_3)C*H*$_2CH_3$); 1.26 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)C(=O)); 1.08 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)C(=O)); 1.01 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)CH(OTES)); 0.95-0.86 (18H, m, Si(CH_2C*H*$_3$)$_3$), C*H*$_3CH_2$, CH_2C*H*$_3$, CH(OTES)CH(C*H*$_3$)CH_2); 0.91 (9H, s, SiC(C*H*$_3$)$_3$); 0.53 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2CH_3$)$_3$); 0.083 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.075 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.2; 210.2; 80.0; 74.5; 61.8; 49.7; 49.4; 40.1; 27.6; 25.9; 24.6; 18.2; 15.2; 14.2; 13.8; 12.6; 12.2; 9.4; 6.9; 5.2; –4.3; –4.4; **IR** (film, cm^{-1}) 2960; 2937; 2879; 2860; 1727; 1701; 1462; 1379; 1362; 1254; 1130; 1115; 1054; 1005; 873; 836; 793; 776; 738; 725; 673.

(2*S*, 3*S*)-2,3-dihydro-6-[1'*S*,2'*R*]-(2-*tert*-butyldimethylsilyloxy-1-methylbutyl)-2-[1"*S*]-(1-methylpropyl)-3,5-dimethyl-pyran-4-one (148)

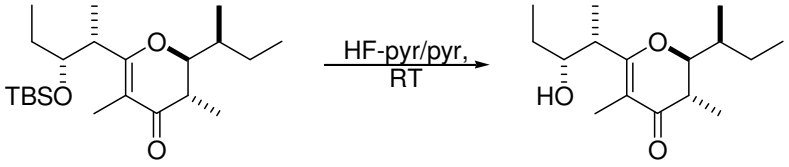


To a solution of dione **146** (88.6 mg, 0.172 mmol) in $CDCl_3$ (3 mL) was added trifluoroacetic acid (5 drops) at room temperature with stirring. The solution was stirred for approximately 1 hour or until TLC analysis showed consumption of starting material. The solution was diluted with Et_2O (50 mL) and washed with $NaHCO_3$ (sat. aq., 30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.31) yielding 41.7 mg (63 %) of compound **148** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, dt, *J* = 9.0, 4.2 Hz, C*H*(OTBS)); 3.71 (1H, dd, *J* = 12.3, 3.3 Hz, CH(CH_3)C*H*(O)CH(CH_3)); 2.81 (1H, dq, *J* = 9.0, 7.2 Hz, CH(OTBS)C*H*(CH_3)); 2.46 (1H, dq *J* = 12.3, 6.9 Hz, C(=O)C*H*(CH_3)CH(O)); 1.74 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.80-1.66 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.62-1.44 (2H, m, CH_3C*H*$_A$$H_B$CH(OTBS), CH($CH_3$)C*H*$_A$$H_B$$CH_3$); 1.41-1.19 (2H m, CH_3CH_A*H*$_B$CH(OTBS), CH(CH_3)CH_A*H*$_B$$CH_3$); 1.14 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)); 1.06 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)CH(O)); 1.02 (3H, d, *J* = 6.9 Hz, CH(O)CH(C*H*$_3$)CH_2); 0.94 (3H, t, *J* = 7.5 Hz, CH(CH_3)CH_2C*H*$_3$); 0.90 (9H, s, SiC(C*H*$_3$)$_3$); 0.84 (3H, t, *J* = 7.2 Hz, C*H*$_3CH_2$); 0.07 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.06 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.9; 173.4; 108.6; 86.6; 74.5; 41.2; 40.5; 35.2; 27.8; 25.9; 22.0; 18.2; 16.1 (2); 11.8; 10.6; 9.4; 8.0; –

4.2; –4.5; **IR** (film, cm^{-1}) 2962; 2933; 2881; 2859; 1668; 1618; 1472; 1462; 1376; 1359; 1354; 1254; 1191; 1157; 1144; 1106; 1073; 1054; 1035; 1005; 879; 856; 836; 794; 775; 675; $[\alpha]_D^{20} = -99.8$ (*c* 0.4, $CHCl_3$).

(2*S*, 3*S*)-2,3-dihydro-6-[(1'*S*, 2'*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (14)



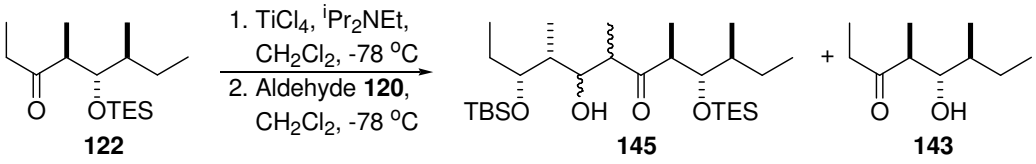
148 **14**

A solution of silyl ether **148** (41.7 mg, 0.109 mmol) in HF-pyr/pyr (750 μL; from a stock solution containing dry THF 10 mL, pyridine 5 mL, pyridinium hydrofluoride 2.1 g) and H_2O (80 μL) was stirred at room temperature in a Teflon® screw cap jar for 12 days or until TLC analysis indicated consumption of the starting material. The solution was diluted with Et_2O (30 mL), washed with $CuSO_4$ (sat. aq., 15 mL), $NaHCO_3$ (sat. aq., 15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/CH_2Cl_2, $R_f = 0.33$) yielding 26.4 mg (90 %) of the product **14** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (1H, dd, *J* = 12.3, 3.3 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.65 (1H, ddd, *J* = 8.4, 6.6, 3.9 Hz, C*H*(OH)); 2.77 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.49 (1H, dq, *J* = 12.3, 6.6 Hz, C(=O)C*H*(CH_3)); 1.88 (1H, br s, O*H*); 1.73 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.76-1.70 (1H, m, CH(O)C*H*(CH_3)CH_2CH_3); 1.60-1.53 (1H, m, CH(CH_3)C$H_A$$H_B$$CH_3$); 1.52-1.45 (1H, m, CH_3C$H_A$$H_B$CH(OH)); 1.43-1.35 (1H, m, $CH_3H_A$$H_B$CH(OH)); 1.28-1.22 (1H, m, CH(CH_3)$CH_A$$H_B$$CH_3$)); 1.20 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 1.08 (3H, d, *J* = 6.6 Hz, C(=O)CH(C*H*$_3$)); 1.03 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)CH_2CH_3); 0.96 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$CH(OH); 0.94 (3H, d, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.7; 173.0; 108.6; 87.0; 75.1; 41.6; 40.6; 35.1; 28.0; 22.0; 16.2; 13.2; 11.7; 10.6; 10.2; 9.3; **^{1}H** and **^{13}C NMR** (600 MHz, $CDCl_3$) Reported in Table 2.2; **IR** (film, cm^{-1}) 3435; 2967; 2935; 2878; 1664; 1650; 1609; 1459; 1378; 1357; 1196; 1144; 1070; 1029; 977; $[\alpha]_D^{20} = -137.5$ (*c* 0.9, $CHCl_3$); **UV** ($CHCl_3$) 275nm (ε 20100).

6.2.6 Synthesis of the seven stereoisomers of (-)-maurenone (12,13,15-19)

Attempted $TiCl_4$ Aldol Coupling



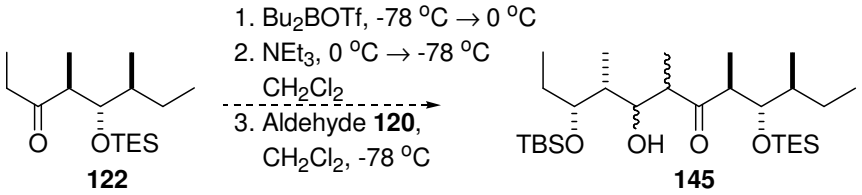
122 **145** **143**

Titanium tetrachloride (1.05 eq.) was added dropwise to a solution of ketone **122** (1 eq.) in CH_2Cl_2 (0.2 M) at -78 °C, producing a yellow solution. After 5 minutes $^iPr_2NEt$ (1.1 eq.) was added dropwise and the resulting deep red solution was stirred at -78 °C for 1 hour. The aldehyde **120** (1 eq.) was added as a solution in CH_2Cl_2 and the solution stirred at -78 °C for 1.5 hours. The reaction was quenched at -78 °C by the addition of NH_4Cl (sat. aq.) and the solution warmed to room temperature. The solution was diluted with Et_2O, washed with H_2O, $NaHCO_3$ (sat. aq.) and brine, dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography indicated that triethylsilylether cleavage of the ketone had predominantly occurred to give alcohol **143** however a small amount of the desired product **145** had formed in high diastereoselectivity (one isomer by NMR).

Attempted modifications to the procedure; increasing the reagents relative to the ketone (1.5-4 eq. aldehyde, 1.2 eq. $TiCl_4$, 1.4 eq. $^iPr_2NEt$), cooler temperatures (-105 °C), replacing the $^iPr_2NEt$ with TMEDA (2.5 eq.) and reduction in the time allowed for complexation of the $TiCl_4$ and the ketone (2 minutes). The highest yield obtained using this procedure was an unacceptable 22 %.

Alcohol 143 - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (1H, apt q, *J* = 5.7 Hz, C*H*(OH)); 2.83 (1H, qd, *J* = 7.2, 6.3 Hz, C(=O)C*H*(CH_3)); 2.72 (1H, d, *J* = 7.5 Hz, O*H*); 2.59 (1H, dq, *J* = 18.0, 6.9 Hz, $CH_3CH_AH_BC(=O)$); 2.46 (1H, dq, *J* = 18.0, 6.9 Hz, $CH_3CH_AH_BC(=O)$); 1.67-1.40 (3H, m, CH(OH)C*H*(CH_3)CH_2, CH(OH)CH(CH_3)CH_2); 1.14 (3H, d, *J* = 7.2 Hz, C(=O)CH(CH_3)); 1.04 (3H, t, *J* = 6.9 Hz, C$H_3CH_2C(=O)$); 0.90 (3H, d, *J* = 6.9 Hz, CH(OH)CH(CH_3)CH_2); 0.89 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2CH_3).

Attempted Boron Aldol Coupling



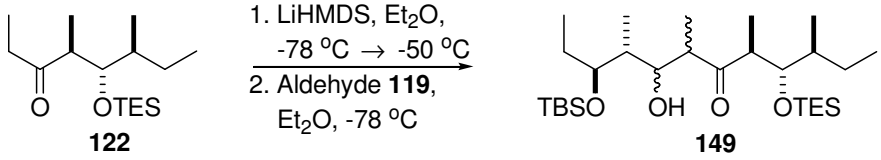
122 **145**

To a stirring solution of the ketone **122** (1 eq.) in CH_2Cl_2 (0.1 M) and at -78 °C was added a solution of Bu_2BOTf (1 M in CH_2Cl_2) and the solution warmed slowly to 0 °C and stirred for 30 minutes. NEt_3 (1.3 eq.) was added at 0 °C and the solution stirred for a further 30 minutes. The solution was cooled to -78 °C and a solution of the aldehyde **120** in CH_2Cl_2 was added and stirring continued at -78 °C for 20 minutes. The solution was then warmed to 0 °C and stirred for 4 hours. The reaction was quenched by the addition of pH 7 buffer, MeOH and H_2O_2 (30 % aq.):MeOH (2:1) at 0 °C and the solution stirred for 1 hour at room temperature. The solvent was removed in *vacuo* and the product extracted with CH_2Cl_2 (3x). The combined extracts were washed with $NaHCO_3$ (sat. aq.), brine, dried ($MgSO_4$) and concentrated in *vacuo*. ^1H NMR analysis showed that triethylsilyl ether cleavage of the ketone had occurred and no product was detected.

General Procedure for Lithium-mediated Aldol Coupling

To a solution of the ketone (~100 mg) in THF (~800 μL, 0.5 M) at –78 °C was added dropwise a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 1.5 eq.). The resulting yellow solution was stirred at –78 °C for 30 minutes then warmed to –50 °C for 30 minutes. The solution was then cooled to –78 °C and the aldehyde (1.5 eq.) added in THF (~300 μL). The resulting solution was stirred at –78 °C for 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer solution (5 mL) and the organics extracted with Et_2O (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography to yield, in most instances, the aldol adducts (mixture of diastereomers) as clear, colourless oils.

(3*S*, 4*S*, 5*S*, 9*S*, 10*S*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (149)



122 **149**

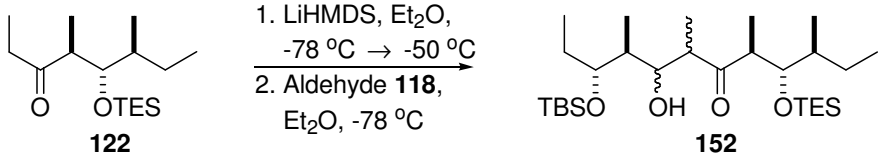
As per the general procedure using ketone **122** (60 mg, 0.21 mmol) and aldehyde **119** (73 mg, 0.315 mmol), purification by column chromatography (35 % CH_2Cl_2/mixed hexanes → 100 % CH_2Cl_2, R_f = 0.23, 0.12) yielded 67 mg (61 %) of the adduct **149** as a mixture of diastereomers (0.72:0.28) as clear, colourless oils.

149a - ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (1H, dd, *J* = 8.4, 2.1 Hz, C*H*(OH)); 3.89 (1H, dd, *J* = 7.8, 3.0 Hz, C*H*(OTES)); 3.61-3.55 (2H, m, C*H*(OTBS)); 2.88 (1H, apt qn, *J* = 7.2 Hz, C(=O)C*H*(CH_3)CH(OTES)); 2.76 (1H, qd, *J* = 7.2, 1.5 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.76-1.43 (6H, m, CH_3CH_2, CH(OTBS)C*H*(CH_3), C*H*(CH_3)CH_2CH_3, CH(CH_3)CH_2CH_3); 1.19 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 0.99 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)); 0.96-0.83 (30H, m, CH_3CH_2, C(=O)CH(C*H*$_3$), CH(C*H*$_3$)CH_2CH_3, CH(CH_3)CH_2CH_3, Si(CH_2CH_3)$_3$, SiC(C*H*$_3$)$_3$); 0.57 (6H, q, *J* = 7.5 Hz, Si(CH_2CH_3)$_3$); 0.07 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.7; 79.9; 77.1; 71.1; 50.1; 48.8; 39.0; 36.1; 27.4; 25.8; 24.4; 17.9; 15.7; 13.3; 13.1; 12.4; 11.6; 10.0; 7.0; 5.3; –4.4; –4.8; **IR** (film, cm^{-1}) 3504; 2959; 2937; 2878; 1711; 1463; 1380; 1255; 1102; 1058; 1004; 976; 836; 775; 738; $[\alpha]_D^{20}$ = +11.5 (*c* 1.0, $CHCl_3$).

149b - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, ddd, *J* = 9.3, 3.6, 2.7 Hz, C*H*(OTBS)); 3.81 (2H, m, C*H*(OH), C*H*(OTES)); 3.29 (1H, br s, C*H*(OH)); 3.02 (1H, apt qn, *J* = 7.1 Hz, C*H*(CH_3)CH(OTES)); 2.66 (1H, dq, *J* = 7.2, 2.7 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.77 (1H, m, CH(OTBS)C*H*(CH_3)); 1.56-1.19 (5H, m, CH_3CH_2CH(OTBS), CH(OTES)C*H*(CH_3)CH_2CH_3, CH(OTES)CH(CH_3)CH_2CH_3); 1.12 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)C(=O)); 0.98 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)CH(OTES); 0.95-0.89 (9H, m, CH_3CH_2, CH(CH_3)CH_2C*H*$_3$, CH(C*H*$_3$)CH_2CH_3); 0.93 (9H, t, *J* = 8.1 Hz, OSi(CH_2C*H*$_3$)$_3$); 0.90 (9H, s, OSiC(C*H*$_3$)$_3$); 0.75 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)C(=O)); 0.55 (6H, q, *J* = 8.1 Hz, OSi(CH_2CH_3)$_3$); 0.06 (6H, s, OSi(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 219.8; 79.5; 73.7; 71.3; 48.2; 47.4; 40.8; 39.9; 25.9; 24.7; 23.3; 18.1; 15.1; 14.5; 12.5; 11.1; 9.4; 7.8; 6.9; 5.3; –4.4; –4.6; **IR** (film, cm^{-1}) 3513; 2959; 2878; 1699;

1463; 1379; 1250; 1104; 1057; 1004; 974; 835; 774; 736; $[\alpha]_D^{20}$ = +50.2 (*c* 0.9, $CHCl_3$).

(3*S*, 4*S*, 5*S*, 9*R*, 10*R*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (152)

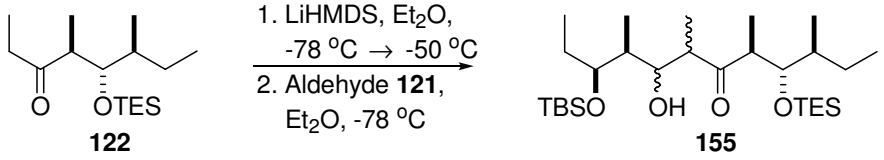


122 **152**

As per the general procedure using ketone **122** (22 mg, 0.077 mmol) and aldehyde **118** (0.028mg, 0.124 mmol), purification by column chromatography (40 % CH_2Cl_2/mixed hexanes, R_f = 0.27) yielded 13 mg (33 %) of the adduct **152** as single diastereomer as clear, colourless oils.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89-3.80 (3H, m, C*H*(OTBS), C*H*OH, C*H*(OTES)); 3.44 (1H, br s, O*H*); 3.08-2.98 (1H, dq, *J* = 8.7, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES); 2.73-2.65 (1H, qd, *J* = 6.9, 1.7Hz, CH(OH)C*H*(CH_3)C(=O)); 1.82-1.71 (1H, m, CH(OTBS)C*H*(CH_3)CH(OH)); 1.56-1.34 (5H, m, CH(OTES)C*H*(CH_3)CH_2CH_3, CH_3CH_2CH(OTBS), CH(CH_3)CH_2CH_3); 1.07 (3H, d, *J* = 6.9 Hz, CH(OH)CH(CH_3)C(=O)); 0.98-0.89 (30H, m, C(=O)CH(CH_3), CH(OTES)CH(CH_3)CH_2CH_3, CH_3CH_2CH(OTBS), CH(CH_3)CH_2CH_3, Si(CH_2CH_3)$_3$, Si(C(CH_3)$_3$)); 0.79 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(CH_3)); 0.55 (6H, q, J = 7.8 Hz, OSi(CH_2CH_3)$_3$); 0.09 (3H, s, OSi(CH_3)$_A$(CH_3)$_B$); 0.08 (3H, s, OSi(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.7; 78.7; 75.5; 73.0; 48.3; 47.7; 40.4; 39.2; 25.9; 25.0; 24.2; 18.1; 15.5; 14.2; 12.6; 11.4; 10.0; 7.1; 7.0; 5.2; –4.47; –4.51.

(3*S*, 4*S*, 5*S*, 9*R*, 10*S*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (155)



122 **155**

As per the general procedure using ketone **122** (100 mg, 0.349 mmol) and aldehyde **121** (121 mg, 0.524 mmol), purification by column chromatography (5 % Et_2O/mixed hexanes, R_f(**155a/b**) = 0.18, R_f=(**155c**) = 0.06, isomers **155a** and **155b** were inseparable and submitted to repeat column chromatography 50 % CH_2Cl_2/mixed hexanes, R_f(**155a**) = 0.28, R_f(**155b**) = 0.25) yielded 122 mg (68 %) of

the adducts **155a-c** as a mixture of diastereomers (0.20:0.06:0.74) as clear, colourless oils.

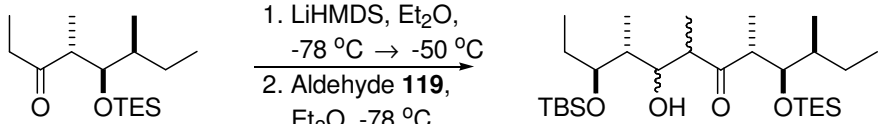
155a - ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89 (1H, dd, *J* = 7.2, 3.0 Hz, C*H*(OTES)); 3.84 (1H, apt d, *J* = 8.4 Hz, C*H*(OH)); 3.71 (1H, dt, *J* = 6.6, 4.8 Hz, C*H*(OTBS)); 2.95 (1H, apt qn, *J* = 7.2 Hz, C(=O)C*H*(CH_3)CH(OTES)); 2.87 (1H, br d, *J* = 2.4 Hz, O*H*); 2.79 (1H, dq, *J* = 8.4, 7.2 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.67 (1H, qdd, *J* = 7.2, 4.8, 2.4 Hz, CH(OTBS)C*H*(CH_3)CH(OH)); 1.60-1.53 (2H, m, CH_3CH_2); 1.52-1.50 (1H, m, CH(OTES)C*H*(CH_3)); 1.20-1.07 (2H, m, $CH(CH_3)CH_2CH_3$); 0.97 (3H, d, *J* = 7.2 Hz, C(=O)CH(CH_3)CH(OTES)); 0.96 (3H, d, *J* = 7.2 Hz, CH(OH)CH(CH_3)C(=O)); 0.92 (9H, t, *J* = 7.8 Hz, $Si(CH_2CH_3)_3$); 0.90-0.85 (18H, m, $SiC(CH_3)_3$, CH_2CH_3, CH(OTBS)CH(CH_3), CH(OTES)CH(CH_3)); 0.81 (3H, t, *J* = 7.2 Hz, CH_3CH_2); 0.57 (6H, q, *J* = 7.8 Hz, $Si(CH_2CH_3)_3$); 0.05 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.7; 77.8; 77.4; 75.5; 51.0; 48.8; 39.1; 36.5; 27.2; 25.9; 24.5; 18.0; 15.6; 13.0; 12.8; 12.4; 9.4; 7.0; 6.6; 5.3; –3.8; –4.5; **IR** (film, cm^{-1}) 3544; 2961; 2937; 2879; 2860; 1710; 1462; 1381; 1361; 1255; 1127; 1115; 1103; 1073; 1059; 1004; 977; 835; 774; 738; 728; 675; 667; $[\alpha]_D^{20}$ = +24.9 (*c* 1.2, $CHCl_3$).

155b - ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (1H, apt t, *J* = 5.4 Hz, C*H*(OH) or C*H*(OTES)); 3.83 (1H, dd, *J* = 6.6, 4.2 Hz, C*H*(OH) or C*H*(OTES)); 3.65 (1H, ddd, *J* = 8.4, 6.0, 2.4 Hz, C*H*(OTBS)); 3.14 (1H, br s, OH); 3.01 (1H, apt qn, *J* = 6.6 Hz, $CH(CH_3)$C(=O) or C(=O)C*H*(CH_3)); 2.88 (1H, dd, *J* = 7.2, 5.4 Hz, C*H*(CH_3)C(=O) or C(=O)C*H*(CH_3)); 1.70-1.65 (1H, m, CH(OTBS)C*H*(CH_3) or CH(OTES)C*H*(CH_3)); 1.58-1.43 (5H, m, CH(OTBS)C*H*(CH_3) or CH(OTES)C*H*(CH_3), CH_3CH_2CH(OTBS), C*H*(CH_3)CH_2, $CH(CH_3)CH_2CH_3$); 1.13 (3H, d, *J* = 6.6 Hz); 1.01 (3H, d, *J* = 7.2 Hz); 0.93 (9H, t, *J* = 7.2 Hz, $Si(CH_2CH_3)_3$); 0.89-0.86 (9H, m); 0.89 (9H, s, $SiC(CH_3)_3$); 0.80 (3H, t, *J* = 7.2 Hz); 0.58 (6H, q, *J* = 7.8 Hz, $Si(CH_2CH_3)_3$); 0.07 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.06 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.8; 78.1; 77.6; 73.4; 49.0; 48.4; 39.6; 38.2; 27.0; 25.9; 25.1; 18.1; 15.4; 13.8; 12.3; 11.2; 10.3; 8.8; 7.0; 5.2; –3.8; –4.3; **IR** (film, cm^{-1}) 3525; 2960; 2937; 2879; 2860; 1702; 1462; 1381; 1255; 1106; 1054; 1005; 836; 774; 737; 726; 666; $[\alpha]_D^{20}$ = +19.3 (*c* 0.5, $CHCl_3$).

155c - ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.02 (1H, d, *J* = 9.6 Hz, C*H*(OH)); 3.85-3.82 (2H, m, C*H*(OTBS) C*H*(OTES)); 3.53 (1H, br s, O*H*); 3.01 (1H, dq, *J* = 8.4, 7.2 Hz, C(=O)C*H*(CH_3)CH(OTES)); 2.66 (1H, qd, *J* = 7.2, 1.8 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.70 (1H, dqd, *J* = 7.8, 7.2, 1.8 Hz, CH(OTBS)C*H*(CH_3));

1.59-1.53 (2H, m, CH_3CH_2); 1.51-1.44 (1H, m, CH(OTES)C*H*(CH_3)); 1.18-1.09 (2H, m, CH(CH_3)C*H*$_2$$CH_3$); 1.01 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)C(=O)); 0.96 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)CH(OTES)); 0.92 (3H, t, *J* = 6.6 Hz, C*H*$_3$$CH_2$); 0.90 (9H, t, *J* = 7.8 Hz, Si(CH_2C*H*$_3$)$_3$); 0.91-0.87 (6H, m, CH_2C*H*$_3$, CH(OTES)CH(C*H*$_3$)CH_2); 0.86 (9H, s, SiC(CH_3)$_3$); 0.77 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)); 0.53 (6H, q, *J* = 7.8 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.06 (3H, s, Si(C*H*$_3$)$_A$($CH_3$)$_B$); 0.05 (3H, s, Si($CH_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.8; 79.0; 76.0; 71.8; 49.2; 47.6; 39.5; 39.1; 25.9; 24.1; 18.1; 15.6; 14.0; 12.5; 11.2; 11.0; 7.0; 6.9; 5.4; 5.3; –4.4; –4.6; **IR** (film, cm^{-1}) 3488; 2961; 2938; 2876; 2860; 1714; 1705; 1462; 1382; 1252; 1131; 1114; 1052; 1004; 975; 835; 775; 738; 668; $[\alpha]_D^{20}$ = +25.4 (*c* 1.0, $CHCl_3$).

(3*S*, 4*R*, 5*R*, 9*S*, 10*S*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (159)



123 **159**

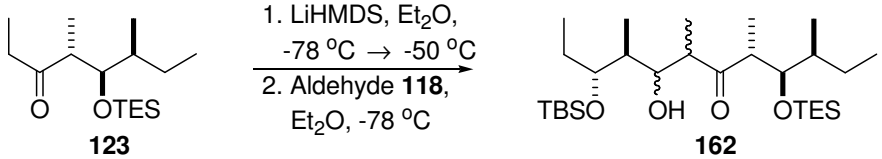
As per the general procedure using ketone **123** (102 mg, 0.357 mmol) and aldehyde **119** (123 mg, 0.533 mmol), purification by column chromatography (5 % Et_2O/mixed hexanes, R_f = 0.17, 0.13, 0.07) yielded 130 mg (71 %) of the adduct **159** as a mixture of diastereomers (0.27, 0.29, 0.44) as clear, colourless oils.

159a - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, ddd, *J* = 9.3, 3.6, 2.7 Hz, C*H*(OTBS)); 3.86-3.82 (2H, m, C*H*(OH), C*H*(OTES)); 3.21 (1H, br s, O*H*); 2.99 (1H, dq, *J* = 8.4, 6.9 Hz); 2.61 (1H, qd, *J* = 7.2, 1.2 Hz); 1.81-1.71 (1H, m, C*H*(OTBS) or C*H*(CH_3)CH_2); 1.52-1.08 (5H, m, CH_3C*H*$_2$CH(OTBS), CH(CH_3)C*H*$_2$, C*H*(OTBS) or C*H*(CH_3)CH_2); 1.14 (3H, d, *J* = 7.2 Hz); 0.97-0.86 (21H, m); 0.90 (9H, s, SiC(CH_3)$_3$); 0.75 (3H, d, *J* = 6.9 Hz); 0.54 (6H, q, *J* = 7.8 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.06 (6H, s, Si(C*H*$_3$)$_2$) **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 219.8; 78.6; 73.8; 71.3; 48.8; 48.1; 40.8; 38.6; 26.3; 25.9; 23.4; 18.1; 14.7; 13.4; 12.4; 11.1; 9.4; 7.9; 7.0; 5.4; –4.4; –4.6; **IR** (film, cm^{-1}) 3544; 2960; 2937; 2879; 2858; 1701; 1462; 1414; 1380; 1360; 1309; 1289; 1251; 1134; 1105; 1059; 1005; 974; 942; 874; 836; 814; 792; 775; 738; 677; 667; $[\alpha]_D^{20}$ = –51.6 (*c* 1.4, $CHCl_3$); **HRMS** (ESI) found 539.3918, $C_{28}H_{60}O_4Si_2Na^+$ requires 539.3922.

159b – ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, ddd, *J* = 9.3, 3.9, 3.0 Hz, C*H*(OTBS)); 3.91 (1H, dd, *J* = 8.7, 1.8 Hz, C*H*(OH) or C*H*(OTES)); 3.77 (1H, br s, C*H*(OH) or C*H*(OTES)); 3.37-3.26 (1H, m, C*H*(CH_3)C(=O) or C(=O)CH(CH_3)); 2.88-2.80 (1H, m, C*H*(CH_3)C(=O) or C(=O)C*H*(CH_3)); 1.81-1.13 (6H, m, CH_3CH_2CH(OTBS), CH(OTBS)C*H*(CH_3), CH(C*H*$_3$)CH_2, CH(CH_3)C*H*$_2$); 1.26 (3H, d, *J* = 7.2 Hz); 0.97-0.83 (33H, m); 0.57 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.06 (3H, s, Si(C*H*$_3$)$_A$($CH_3$)$_B$); 0.02 (3H, s, Si($CH_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 218.8; 77.5; 76.2; 74.2; 50.5; 46.7; 42.7 38.1; 26.8; 25.9; 23.7; 18.1; 14.3; 13.4; 13.1; 12.4; 11.5; 10.9; 7.0; 5.4; –4.4; –4.5; **IR** (film, cm^{-1}) 3491; 2960; 2937; 2879; 2859; 1699; 1460; 1417; 1381; 1362; 1253; 1133; 1104; 1058; 1006; 980; 854; 836; 813; 792; 744; 737; 675.

159c - ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (1H, dd, *J* = 8.7, 2.4 Hz, C*H*(OH) or C*H*(OTES)); 3.93 (1H, dd, *J* = 8.1, 1.8 Hz, C*H*(OH) or C*H*(OTES)); 3.59 (1H, m, CH(OTBS)); 2.86 (1H, dq, *J* = 8.1, 6.9 Hz, CH(CH_3)C*H*(=O) or C(=O)C*H*(CH_3)); 2.76 (1H, dq, *J* = 8.7, 7.2 Hz, C*H*(CH_3)C(=O) or C(=O)C*H*(CH_3)); 1.77-1.12 (6H, m, CH_3CH_2CH(OH), CH(OTBS)C*H*(CH_3), C*H*(CH_3)CH_2CH_3, CH(CH_3)C*H*$_2CH_3$); 1.20 (3H, d, *J* = 7.2 Hz); 1.00 (3H, d, *J* = 6.9 Hz); 0.96-0.87 (15H, m, C*H*$_3$$CH_2$CH(OTBS), CH($CH_3$)$CH_2$C*H*$_3$, Si($CH_2$C*H*$_3$)$_3$); 0.90 (9H, s, Si(C*H*$_2$$CH_3$)$_3$); 0.86 (3H, d, *J* = 6.6 Hz); 0.57 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.081 (3H, s, Si(C*H*$_3$)$_A$($CH_3$)$_B$); 0.078 (3H, s, Si($CH_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.7; 80.0; 76.1; 71.0; 50.3; 48.7; 38.1; 36.1; 27.5; 27.0; 25.9; 17.9; 13.5; 13.2; 13.0; 12.4; 11.6; 10.0; 7.0; 5.4; –4.4, –4.8; **IR** (film, cm^{-1}) 3508; 2961; 2937; 2879; 2861; 1712; 1381; 1255; 1134; 1103; 1060; 1014; 1005; 976; 850; 837; 790; 775; 738; 683; $[\alpha]_D^{20} = -11.86$ (*c* 1.3, $CHCl_3$).

(3*S*, 4*R*, 5*R*, 9*R*, 10*R*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (162)



123 **162**

As per the general procedure using ketone **162** (99 mg, 0.346 mmol) and aldehyde **118** (119 mg, 0.518 mmol), purification by column chromatography (5 → 10 % Et_2O/mixed hexanes, R_f (5 % Et_2O/mixed hexanes) = 0.26, 0.20, 0.15, 0.11) yielded

130 mg (73 %) of the adduct **162** as a mixture of diastereomers (0.20:0.20:0.35:0.45) as clear, colourless oils.

162a - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, ddd, *J* = 9.6, 6.6, 2.7 Hz, C*H*(OTBS)); 3.86-3.82 (2H, m, CH(OH), CH(OTES)); 3.20 (1H, br s, O*H*); 2.99 (1H, dq, *J* = 8.4, 6.9 Hz); 2.61 (1H, qd, *J* = 7.5, 1.5 Hz); 1.80-1.72 (1H, m); 1.51-1.09 (5H, m); 1.14 (3H, d, *J* = 7.2 Hz); 0.97-0.86 (30H, m); 0.75 (3H, d, *J* = 7.2 Hz); 0.54 (6H, q, *J* = 8.1 Hz, $Si(CH_2CH_3)_3$); 0.06 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 219.9; 78.6; 73.8; 71.3; 48.8; 48.1; 40.8; 38.6; 26.3; 25.9; 23.4; 18.1; 14.7; 13.4; 12.4; 11.1; 9.4; 7.9; 7.0; 5.4; –4.4; –4.6 **IR** (film, cm^{-1}) 3550; 2960; 2938; 2879; 2859; 1700; 1463; 1413; 1380; 1361; 1309; 1251; 1133; 1105; 1058; 1005; 974; 942; 873; 835; 815; 792; 774; 737; 727; $[\alpha]_D^{20} = -48.9$ (*c* 1.6, $CHCl_3$).

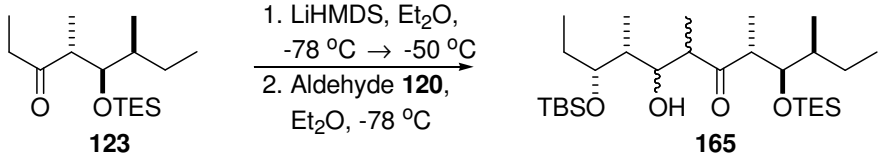
162b - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, ddd, *J* = 9.0, 6.9, 3.9 Hz, C*H*(OTBS)); 3.92 (1H, dd, *J* = 8.7, 1.8 Hz) 3.80-3.72 (1H, m); 2.89-2.76 (2H, m, CH(OH)C*H*(CH_3)C(=O), C(=O)C*H*(CH_3)CH(OTES)); 1.83-1.74 (1H, m); 1.52-1.06 (5H, m); 1.26 (3H, d, *J* = 7.5 Hz); 0.96-0.83 (3H, m); 0.57 (6H, m, *J* = 7.2 Hz, $Si(CH_2CH_3)_3$); 0.06 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.02 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 218.8; 77.5; 76.2; 74.2; 50.5; 46.7; 42.7; 38.1; 26.8; 25.9; 23.9; 18.1; 14.3; 13.4; 13.1; 12.4; 11.6; 10.9; 7.0; 5.4; –4.4; –4.5.

162c - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86-3.80 (3H, m, C*H*(OTBS), C*H*(OH), C*H*(OTES)); 3.35-2.88 (1H, m, CH(OH)C*H*(CH_3)C(=O) or C(=O)C*H*(CH_3)CH(OTES)); 2.86-2.82 (1H, m, CH(OH)CH(CH_3)C(=O) or C(=O)C*H*(CH_3)CH(OTES));1.83-1.14 (6H, m, CH_3CH_2CH(OH), CH(OTBS)C*H*(CH_3), C*H*(CH_3)CH_2, CH(CH_3)CH_2CH_3); 1.08 (3H, d, *J* = 6.9 Hz); 1.00-0.86 (12H, m); 0.94 (9H, t, *J* = 7.8 Hz, $Si(CH_2CH_3)_3$); 0.91 (9H, s, $SiC(CH_3)_3$); 0.81 (3H, d, *J* = 6.9 Hz); 0.56 (6H, q, *J* = 8.1 Hz, $Si(CH_2CH_3)_3$); 0.103 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.096 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.7; 77.7; 75.7; 73.0; 48.5; 48.1; 40.4; 38.1; 26.6; 25.9; 25.2; 18.1; 14.4; 13.0; 12.4; 11.6; 10.0; 7.0; 5.4; –4.46; –4.51.

162d - ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (1H, dd, *J* = 8.7, 2.4 Hz); 3.92 (1H, dd, *J* = 8.4, 2.1 Hz); 3.59 (1H, ddd, *J* = 8.4, 5.7, 2.1 Hz, C*H*(OTBS)); 2.85 (1H, dq, *J* = 8.1, 7.2 Hz); 2.75 (1H, *J* = 8.7, 7.2 Hz); 1.79-1.34 (6H, m, CH_3CH_2, C*H*(CH_3)CH_2, CH_2CH_3, CH(OTBS)C*H*(CH_3)); 1.19 (3H, d, *J* = 7.2 Hz); 0.99 (3H, d, *J* = 7.2 Hz); 0.95-0.84 (30H, m); 0.57 (6H, q, *J* = 8.1 Hz, $Si(CH_2CH_3)_3$); 0.08 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 214.7; 80.0; 76.1; 70.9; 50.3; 48.7; 38.1; 36.1; 27.5;

26.9; 25.8; 17.9; 13.5; 13.2; 13.0; 12.4; 11.6; 10.0; 7.0; 5.3; –4.4; –4.8 **IR** (film, cm^{-1}) 3507; 2960; 2937; 2879; 2861; 1712; 1463; 1415; 1382; 1255; 1134; 1102; 1060; 1014; 1006; 976; 837; 789; 776; 738; 680.

(3*S*, 4*R*, 5*R*, 9*S*, 10*R*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (165)



123 **165**

As per the general procedure using ketone **123** (100 mg, 0.349 mmol), and aldehyde **120** (121 mg, 0.523 mmol) purification by column chromatography (5 % Et_2O/mixed hexanes, R_f = 0.15,0.09, 0.06) yielded 81 mg (45 %) of the adduct **165** as a mixture of diastereomers (0.47:0.14:0.26) as clear, colourless oils.

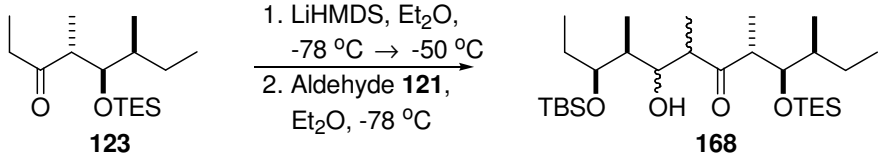
165a - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (1H, dd, *J* = 9.0, 2.1 Hz, C*H*(OTES)); 3.89 (1H, dd, *J* = 7.5, 3.3 Hz, C*H*(OH)); 3.73 (1H, apt q, *J* = 6.3 Hz, C*H*(OTBS)); 2.96-2.86 (2H, m, O*H*, C(=O)C*H*(CH_3)CH(OTES)); 2.77 (1H, dq, *J* = 8.7, 7.2 Hz, CH(OH)C*H*(CH_3)C(=O)); 1.71-1.66 (1H, m, CH(OTBS)C*H*(CH_3)); 1.62-1.53 (2H, m, CH_3CH_2); 1.49-1.08 (3H, m, CH(OTES)C*H*(CH_3), CH_2CH_3); 0.99-0.85 (24H, m, CH(OTBS)CH(C*H*$_3$), CH(OH)CH(C*H*$_3$), C(=O)CH(C*H*$_3$), CH(OTES)CH(C*H*$_3$), CH_2CH_3,Si(CH_2CH_3)$_3$); 0.88 (9H, s, SiC(C*H*$_3$)$_3$); 0.83 (3H, t, *J* = 7.5 Hz, CH_3CH_2); 0.58 (6H, q, *J* = 7.5 Hz, Si(CH_2CH_3)$_3$); 0.07 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.06 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.6; 77.6; 76.4; 74.9; 51.0; 48.9; 38.1; 36.6; 27.1; 26.8; 25.9; 18.1; 15.3; 13.3; 13.0; 12.4; 9.3; 7.1; 6.8; 5.4; –3.9; –4.5; **IR** (film, cm^{-1}) 3539; 2962; 2938; 2880; 2860; 1710; 1461; 1415; 1381; 1361; 1255; 1132; 1112; 1060; 1005; 977; 948; 879; 837; 817; 792; 774; 739; 678; $[\alpha]_D^{20}$ = –21.2 (*c* 1.7, $CHCl_3$).

165b - ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, apt t, *J* = 5.4 Hz,C*H*(OTES)); 3.86 (1H, dd, *J* = 7.2, 2.7 Hz, C*H*(OH)); 3.67 (1H, ddd, *J* = 7.2, 6.0, 0.6 Hz, CH(OTBS)); 3.18 (1H, br s, O*H*); 3.01 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)C(=O)); 2.87 (1H, qd, *J* = 6.9, 5.1 Hz, C(=O)C*H*(CH_3)CH(OTES)); 1.72-1.38 (6H, m, CH_3CH_2, CH(OTBS)C*H*(CH_3), CH(OTES)C*H*(CH_3), CH_2CH_3); 1.16 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)); 1.01 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 0.95 (3H, t, *J* = 6.9 Hz, CH_2CH_3); 0.95 (9H, t, *J* = 7.8 Hz, Si(CH_2CH_3)$_3$); 0.92-0.89 (12H, m, SiC(C*H*$_3$)$_3$, CH(OTES)CH(C*H*$_3$)); 0.87 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 0.81 (3H, t, *J*

= 7.5 Hz, C*H*$_3$CH$_2$); 0.59 (6H, q, *J* = 7.8 Hz, Si(C*H*$_2$CH$_3$)$_3$); 0.09 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.08 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 217.0; 77.7; 77.3; 73.4; 49.3; 49.1; 38.6; 38.2; 27.0; 26.8; 25.9; 18.1; 13.91; 13.87; 12.2; 11.2; 10.3; 8.6; 7.0; 5.2; –3.8; –4.3; **IR** (film, cm^{-1}) 3525; 2961; 2937; 2880; 2860; 1702; 1463; 1415; 1381; 1361; 1255; 1134; 1109; 1054; 1005; 974; 872; 856; 836; 816; 790; 774; 738; 726; 667; $[\alpha]_D^{20} = -19.2$ (*c* 0.7, $CHCl_3$).

165c - ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (1H, dd, *J* = 9.6, 2.1 Hz, C*H*(OH)); 3.90-3.82 (2H, m, C*H*(OTBS), C*H*(OTES)); 3.00 (1H, dq, *J* = 8.7, 6.9 Hz, C(=O)C*H*(CH$_3$)); 2.63 (1H, qd, *J* = 7.2, 2.1 Hz, CH(OH)C*H*(CH$_3$)C(=O)); 1.76-1.68 (1H, m, CH(OTBS)C*H*(CH$_3$)); 1.68-1.36 (5H, m, CH$_3$C*H*$_2$, CH(OTES)C*H*(CH$_3$), C*H*$_2$CH$_3$); 1.04 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 0.97 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)CH(OTES)); 0.95-0.87 (6H, m, C*H*$_3$CH$_2$, CH$_2$C*H*$_3$); 0.92 (9H, t, *J* = 8.1 Hz, Si(CH$_2$C*H*$_3$)$_3$); 0.88 (9H, s, SiC(C*H*$_3$)$_3$); 0.86 (3H, d, *J* = 6.9 Hz, CH(OTES)CH(C*H*$_3$)CH$_2$); 0.79 (3H, d, *J* = 6.9Hz, CH(OTES)CH(C*H*$_3$)); 0.54 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$); 0.09 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.07 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.9; 78.0; 76.1; 71.9; 49.4; 48.0; 39.5; 38.0; 26.7; 25.9; 25.8; 18.1; 14.2; 12.9; 12.4; 11.3; 11.0; 7.0; 6.8; 5.4; –4.4; –4.6; **IR** (film, cm^{-1}) 3485; 2961; 2937; 2879; 2860; 1713; 1705; 1462; 1415; 1382; 1361; 1253; 1134; 1110; 1056; 1005; 976; 939; 871; 835; 816; 793; 775; 738; 667; $[\alpha]_D^{20} = -18.8$ (*c* 1.9, $CHCl_3$).

(3*S*, 4*R*, 5*R*, 9*R*, 10*S*)-10-*tert*-butyldimethylsilyloxy-4-triethylsilyloxy-8-hydroxy-3,5,7,9-tetramethyldodeca-6-one (168)



123 **168**

As per the general procedure using ketone **123** (106 mg, 0.370 mmol) and aldehyde **121** (128 mg, 0.555 mmol), purification by column chromatography (10 % Et_2O/mixed hexanes, R_f = 0.17) yielded 110 mg (57 %) the adduct **168** as a single diastereomer as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.94-3.91 (2H, m, C*H*(OH), C*H*(OTES)); 3.68 (1H, ddd, *J* = 8.4, 6.0, 2.4 Hz, C*H*(OTBS)); 3.02 (1H, br s, O*H*); 2.89 (1H, dq, *J* = 8.4, 7.2 Hz, CH(OH)C*H*(CH$_3$)C(=O) or C(=O)C*H*(CH$_3$)CH(OTES)); 2.82 (1H, qd, *J* = 7.2, 6.6 Hz, CH(OH)C*H*(CH$_3$)C(=O) or C(=O)C*H*(CH$_3$)CH(OTES)); 1.63-1.15 (6H, m,

$CH_3CH_2CH(OH)$, $CH(OH)CH(CH_3)$, $CH(OTES)CH(CH_3)$, $CH(CH_3)CH_2CH_3$); 1.13 (3H, d, J = 7.2 Hz, $CH(OH)CH(CH_3)C(=O)$ or $C(=O)CH(CH_3)CH(OTES)$); 0.92 (3H, d, J = 7.2 Hz, $CH(CH_3)C(=O)$ or $C(=O)CH(CH_3)$); 0.91 (9H, t, J = 7.8 Hz, $Si(CH_2CH_3)_3$); 0.90 (3H, d, J = 6.6 Hz); 0.89 (3H, t, J = 7.2 Hz, $CH_3CH_2CH(OH)$ or $CH(CH_3)CH_2CH_3$); 0.87 (9H, s, J = $SiC(CH_3)_3$); 0.84 (3H, d, J = 6.6 Hz); 0.78 (3H, t, J = 7.2 Hz, $CH_3CH_2CH(OH)$ or $CH(CH_3)CH_2CH_3$); 0.55 (6H, qd, J = 7.8, 1.8 Hz, $Si(CH_2CH_3)_3$); 0.07 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.06 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 215.4; 78.0; 76.8; 74.0; 49.6; 49.4; 38.2; 38.1; 27.7; 27.4; 26.1; 18.2; 14.1; 13.0; 12.6; 11.7; 10.1; 7.8; 7.4; 5.9; –3.7; –4.4; **IR** (film, cm^{-1}) 3525; 2961; 2938; 2879; 2860; 1712; 1706; 1462; 1381; 1255; 1135; 1108; 1058; 1006; 977; 856; 774; 737; $[\alpha]_D^{20}$ = +7.77 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** found 539.3906, $C_{28}H_{60}NaO_4Si_2^+$ requires 539.3922; **LREIMS** 500 (5.8 %); 460 (7.0 %); 257 (24 %); 229 (5.8 %); 201 (10 %); 173 (41 %); 171 (23 %); 162 (5.8 %); 143 (10 %); 127 (9.3 %); 115 (45 %); 103 (17 %); 85 (71 %); 83 (100 %); 57 (44 %).

General Procedure for Swern Oxidation

Oxalyl chloride (1.5 eq.) was added dropwise to a solution of DMSO (3 eq.) in CH_2Cl_2 (0.7 M) at –78 °C and the solution stirred for 30 min. The alcohol (1 eq.) was added *via* a cannula and the resulting solution stirred for 45 min at –78 °C. Et_3N (6 eq.) was added dropwise over several minutes and stirred at –78 °C for 30 min before warming to 0 °C and stirring for 1 hour.

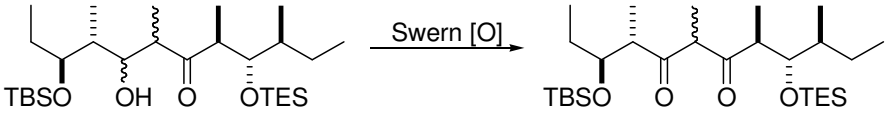
Two alternative product isolation procedures were used:

A. The reaction was quenched by pouring onto $NaHSO_4$ (1 M, 10 mL) and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organics were concentrated in *vacuo*, taken up in Et_2O (50 mL), washed $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (sat aq., 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*.

B. The reaction was quenched by addition of NH_4Cl (sat. aq., 20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*.

Column chromatography was performed as required.

(3*S*, 4*S*, 8*S*, 9*S*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (150)

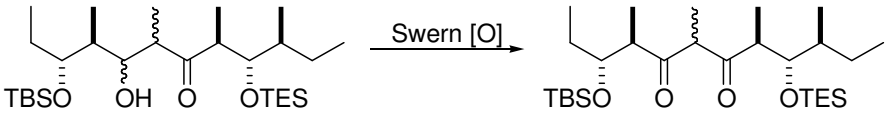


149 **150**

As per the general procedure using alcohol **149** (124 mg, 0.240 mmol), purification by column chromatography (5 % Et_2O/mixed hexanes, R_f(keto) = 0.24, R_f(enol) = 0.64) yielded 48 mg (71 %) of the dione **150** as an inseperable mixture of keto-enol forms as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00-3.83 (3H, m, C*H*(OTBS), C(=O)C*H*(CH_3)C(=O), C*H*(OTES)); 3.11-2.89 (2H, m, CH(OTBS)C*H*(CH_3), CH(OTES)C*H*(CH_3)); 1.91 (1.2H, s, C(OH)=C(C*H*$_3$)); 1.62-1.42 (5H, m, CH_3CH_2CH(OTBS), CH(OTES)C*H*(CH_3)CH_2, CH(CH_3)CH_2CH_3); 1.30 (1.8H, d, *J* = 7.2 Hz); 1.01-0.80 (33H, m, C*H*$_3$$CH_2$CH(OTBS), CH(OTBS)CH(C*H*$_3$), C(=O)CH(C*H*$_3$)C(=O), C(=O)CH(C*H*$_3$)CH(OTES), CH(OTES)CH(C*H*$_3$), CH(CH_3)CH_2C*H*$_3$, SiC(C*H*$_3$)$_3$, Si(CH_2C*H*$_3$)$_3$); 0.60 (3.6H, q, *J* = 7.8 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.49 (2.4H, q, *J* = 8.1 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.04 (1.8H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.00 (1.2H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); –0.03 (1.8H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); –0.10 (1.2H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$) **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.6; 210.5; 197.1; 196.0; 78.8; 78.5; 75.3; 74.4; 62.1; 49.7; 48.1; 42.1; 41.7; 39.2; 37.6; 29.7; 26.1; 26.0; 25.8; 25.8; 24.7; 22.2; 18.0; 16.8; 15.8; 14.5; 13.6; 13.5; 12.8; 12.5; 12.4; 12.2; 7.1; 7.0; 6.7; 5.3; 5.2; –4.6; –4.8; –5.4.

(3*R*, 4*R*, 8*S*, 9*S*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (153)



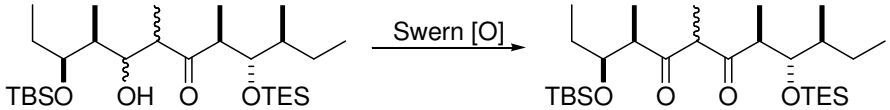
152 **153**

As per the general procedure using alcohol **152** (25.2 mg, 0.049 mmol), purification by column chromatography (5 % Et_2O/mixed hexanes, R_f = 0.38) yielding 16 mg (62 %) of the dione **153**, in predominantly the keto form, as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95-3.81 (3H, m, C*H*(OTBS), C(=O)C*H*(CH_3)C(=O), C*H*(OTES)); 2.90-2.78 (2H, m, CH(OTBS)C*H*(CH_3), C(=O)C*H*(CH_3)CH(OTES)); 1.60-1.00 (5H, m, CH_3CH_2CH(OTBS), C*H*(CH_3)CH_2, CH(CH_3)CH_2CH_3); 1.21 (3H, d, *J* = 7.2 Hz); 1.06-0.84 (33H, m); 0.55 (6H, q, *J* =

7.8 Hz, Si(CH_2CH$_3$)$_3$); 0.04 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); –0.05 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.9; 210.3; 78.5; 73.8; 61.4; 50.0; 49.5; 39.5; 25.8; 25.8; 24.2; 18.0; 15.5; 14.0; 12.8; 12.6; 11.4; 8.7; 7.0; 5.2; –4.71; –4.74; **IR** (film, cm^{-1}) 2961; 2934; 2879; 2859; 1727; 1712; 1459; 1379; 1253; 1117; 1059; 1005; 835; 776; 738; 727; 667; **HRMS (ESI)** found 537.3766 $C_{28}H_{58}O_4Si_2Na^+$ requires 537.3766; **LREIMS** 257 (26 %); 201 (70 %); 173 (75 %); 115 (88 %); 85 (71 %); 83 (100 %); 57 (67 %); 55 (41 %).

(3*S*, 4*R*, 8*S*, 9*S*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (156)

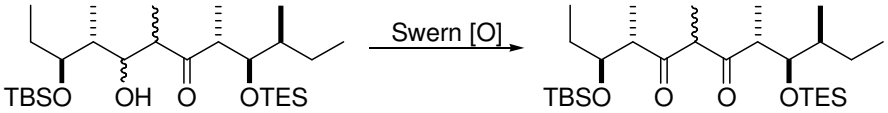


155 **156**

As per the general procedure using alcohol **155** (116 mg, 0.224 mmol), yielding 111 mg (96 %) of the dione **156**, in predominantly the keto form, as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, q, *J* = 6.9 Hz, C(=O)C*H*(CH$_3$)C(=O)); 3.89-3.82 (1H, m, CH(OTBS)); 3.77 (1H, dd, *J* = 9.0, 2.4 Hz, C*H*(OTES)); 2.89 (1H, apt qn, *J* = 7.2 Hz, CH(OTBS)C*H*(CH$_3$)); 2.80 (1H, dq, *J* = 9.0, 7.2 Hz, C(=O)C*H*(CH$_3$)CH(OTES)); 1.56-0.82 (35H, m, CH$_3$CH_2CH(OTBS), CH(OTES)C*H*(CH$_3$)CH$_2$, CH(OTES)CH(CH$_3$)CH_2, CH_3CH$_2$CH(OTBS), CH(CH$_3$)CH$_2$CH_3, C(=O)CH(CH_3)CH(OTES), CH(OTES)CH(CH_3)CH$_2$, Si(CH$_2$CH_3)$_3$, SiC(CH_3)$_3$); 1.23 (3H, d, *J* = 7.2 Hz, C(=O)CH(CH_3)C(=O)); 1.18 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(CH_3)); 0.53 (6H, q, *J* = 7.5 Hz, Si(CH_2CH$_3$)$_3$); 0.063 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); 0.059 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 211.3; 209.7; 79.4; 73.8; 60.8; 51.1; 49.1; 39.8; 27.5; 25.9; 24.4; 18.1; 15.3; 14.2; 13.5; 12.6; 11.9; 9.3; 6.9; 5.2; –4.3; –4.4; **IR** (film, cm^{-1}) 2961; 2937; 2879; 2860; 1728; 1703; 1462; 1415; 1380; 1362; 1338; 1289; 1254; 1118; 1056; 1006; 939; 874; 836; 794; 776; 739; 672.

(3*S*, 4*S*, 8*S*, 9*S*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (160)

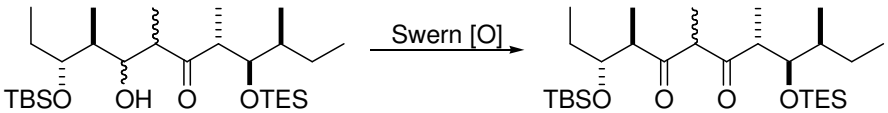


159 **160**

As per the general procedure using alcohol **159** (126 mg, 0.245 mmol), yielded 123 mg (97 %) of the dione **160**, in predominantly the keto form, as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (1H, ddd, *J* = 9.0, 5.1, 3.6 Hz, C*H*(OTBS)); 3.90 (1H, q, *J* = 7.2 Hz, C(=O)C*H*(CH_3)C(=O)); 3.77 (1H, dd, *J* = 9.0, 1.5 Hz, C*H*(OTES)); 3.09-2.95 (1H, m, CH(OTBS)C*H*(CH_3)); 2.76 (1H, dq, *J* = 9.0, 6.9 Hz, C(=O)CH(CH_3)CH(OTES)); 1.63-1.13 (5H, m, CH_3CH_2CH(OTBS), CH(OTES)C*H*(CH_3)CH_2, CH(CH_3)CH_2CH_3); 1.28 (3H, d, *J* = 7.2 Hz, C(=O)CH(CH_3)C(=O)); 1.03 (3H, d, *J* = 6.9Hz, CH(OTBS)CH(CH_3)); 0.98-0.84 (30H, m, CH_3CH_2CH(OTBS), C(=O)CH(CH_3)CH(OTES), CH(OTES)CH(CH_3)CH_2, CH(CH_3)CH_2CH_3, Si(CH_2CH_3)$_3$, SiC(CH_3)$_3$); 0.54 (6H, q, *J* = 8.1 Hz, Si(CH_2CH_3)$_3$); 0.09 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.07 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.8; 210.0; 79.2; 73.8; 61.5; 50.3; 50.0; 38.6; 26.4; 25.8; 25.7; 18.1; 14.2; 13.2; 12.4; 11.1; 9.5; 7.01; 6.97; 5.3; –4.6; –4.7; **IR** (film, cm^{-1}) 2960; 2937; 2879; 2860; 1727; 1698; 1462; 1415; 1380; 1361; 1255; 1135; 1114; 1058; 1006; 868; 836; 816; 794; 776; 738; 728; 667.

(3*R*, 4*R*, 8*R*, 9*R*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (163)



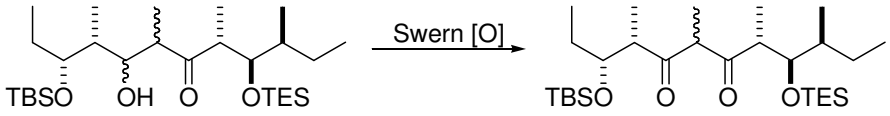
162 **163**

As per the general procedure using alcohol **162** (130 mg, 0.252 mmol), yielding 115 mg (89 %) of the dione **163**, in predominantly the keto form, as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (1H, ddd, *J* = 6.9, 5.1, 3.9 Hz, C*H*(OTBS)); 3.90 (1H, q, *J* = 6.9 Hz, C(=O)C*H*(CH_3)C(=O)); 3.77 (1H, dd, *J* = 9.0, 1.5 Hz C*H*(OTES)); 3.02 (1H, dq, *J* = 6.9, 5.1 Hz, CH(OTBS)C*H*(CH_3)); 2.77 (1H, dq, *J* = 9.0, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES)); 1.57-1.13 (5H, m, CH_3CH_2, C*H*(CH_3)CH_2, CH(CH_3)CH_2); 1.30 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)C(=O)); 1.03 (3H, d, *J* = 7.2

Hz, CH(OTBS)CH(C*H*$_3$)); 0.98-0.84 (30H, m, Si(CH$_2$C*H*$_3$)$_3$,SiC(C*H*$_3$)$_3$),CH$_3$C*H*$_2$, C*H*(CH$_3$)CH$_2$, CH(CH$_3$)C*H*$_2$); 0.55 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$); 0.08 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.07 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 210.7; 209.9; 79.2; 73.8; 61.5; 50.3; 50.0; 38.7; 27.0; 26.4; 25.8; 18.1; 14.2; 13.3; 12.41; 12.38; 11.1; 9.5; 7.0; 5.3; –4.6; –4.7; **IR** (film, cm^{-1}) 2961; 2937; 2879; 2860; 1727; 1706; 1698; 1462; 1380; 1254; 1135; 1114; 1057; 1006; 836; 776; 738; 728.

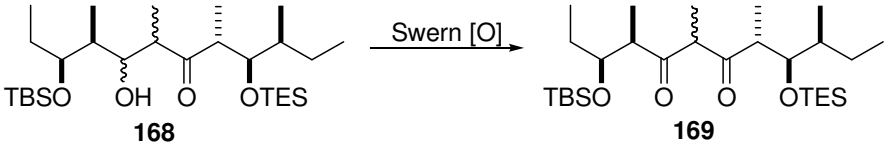
(3*R*, 4*S*, 8*R*, 9*R*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (166)



165 **166**

As per the general procedure using alcohol **165** (124 mg, 0.240 mmol), yielding 115 mg (93 %) of the dione **166**, in predominantly the keto form as a clear, colourless oil. **^{1}H NMR** (300 MHz, CDCl$_3$) δ 3.97 (1H, q, *J* = 6.9 Hz, C(=O)C*H*(CH$_3$)C(=O)); 3.85 (1H, apt q, *J* = 5.7 Hz, C*H*(OTBS)); 3.79 (1H, dd, *J* = 9.0, 1.5 Hz, C*H*(OTES)); 2.91 (1H, apt qn, *J* = 7.2 Hz, CH(OTBS)C*H*(CH$_3$)); 2.76 (1H, dq, *J* = 9.0, 6.9 Hz, C(=O)C*H*(CH$_3$)CH(OTES)); 1.60–1.04 (5H, m, CH$_3$C*H*$_2$, C*H*(CH$_3$)CH$_2$CH$_3$, CH(CH$_3$)C*H*$_2$CH$_3$); 1.24 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)C(=O)); 1.19 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)C(=O)); 0.97-0.83 (12H, m, C*H*$_3$CH$_2$, CH$_2$C*H*$_3$, C(=O)CH(C*H*$_3$)CH(OTES), CH(OTES)CH(C*H*$_3$)CH$_2$); 0.92 (9H, t, *J* = 8.1 Hz, Si(CH$_2$C*H*$_3$)$_3$); 0.89 (9H, s, SiC(C*H*$_3$)$_3$); 0.53 (6H, q, *J* = 8.1 Hz, Si(C*H*$_2$CH$_3$)$_3$); 0.070 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.065 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 211.3; 209.9; 78.6; 73.9; 60.8; 51.3; 49.7; 38.4; 27.5; 26.5; 25.9; 18.1; 14.4; 13.5; 13.0; 12.4; 11.9; 9.3; 7.0; 5.3; –4.3; –4.4; **IR** (film, cm^{-1}) 2961; 2937; 2879; 2860; 1728; 1704; 1463; 1417; 1380; 1362; 1255; 1136; 1115; 1057; 1006; 875; 836; 816; 794; 775; 738; 667.

(3*S*, 4*R*, 8*R*, 9*R*, 10*S*)-3-*tert*-butyldimethylsilyloxy-4,6,8,10-tetramethyl-9-triethylsilyloxydodecan-5,7-dione (169)



168 **169**

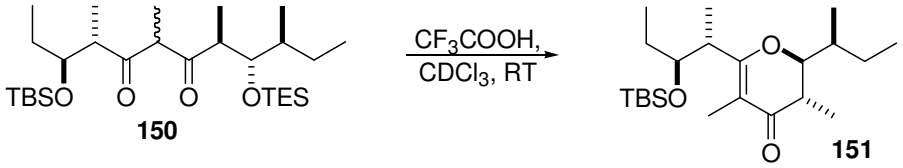
As per the general procedure using alcohol **168** (138 mg, 0.267 mmol), yielding 128 mg (93 %) of the dione **169**, in predominantly the keto form, as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, q, *J* = 7.2 Hz, C(=O)C*H*(CH_3)C(=O)); 3.87 (1H, m, C*H*(OTBS)); 3.76 (1H, dd, *J* = 9.0, 1.5 Hz, C*H*(OTES)); 2.93 (1H, qd, *J* = 6.9, 6.0 Hz, CH(OTBS)C*H*(CH_3)); 2.79 (1H, dq, *J* = 9.0, 6.9 Hz, C(=O)C*H*(CH_3)CH(OTES)); 1.74-1.12 (5H, m, CH_3CH_2CH(OTBS), CH(OTES)C*H*(CH_3)CH_2, CH(OTES)CH(CH_3)CH_2); 1.26 (3H, d, *J* = 7.2 Hz, C(=O)CH(CH_3)C(=O)); 1.08 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(CH_3)); 0.99 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)CH(OTES)); 0.97-0.80 (27H, m, CH_3CH_2CH(OTBS), CH(CH_3)CH_2CH_3, CH(OTES)CH(CH_3)CH_2, Si(CH_2CH_3)$_3$, SiC(CH_3)$_3$); 0.53 (6H, q, *J* = 7.8 Hz, Si(CH_2CH_3)$_3$); 0.08 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.07 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.1; 210.3; 79.2; 74.6; 61.7; 50.0(2); 38.6; 27.6; 26.4; 25.9; 18.2; 14.3; 13.8; 13.2; 12.4; 12.3; 9.4; 7.0; 5.3; –4.3; –4.4; **IR** (film, cm^{-1}) 2960; 2937; 2879; 2860; 1726; 1701; 1463; 1416; 1380; 1362; 1255; 1136; 1112; 1056; 1006; 872; 836; 815, 794; 776; 739; 667.

General Procedure for Acid-Catalysed Cyclisation/Dehydration

To a solution of the dione (~100 mg) in $CDCl_3$ (~3 mL) was added trifluoroacetic acid (~5 drops) at room temperature with stirring. The solution was stirred for approximately 1 hour or until TLC analysis showed consumption of starting material. The solution was diluted with Et_2O (15 mL) and washed with $NaHCO_3$ (sat. aq., 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2) yielding a clear, colourless oil.

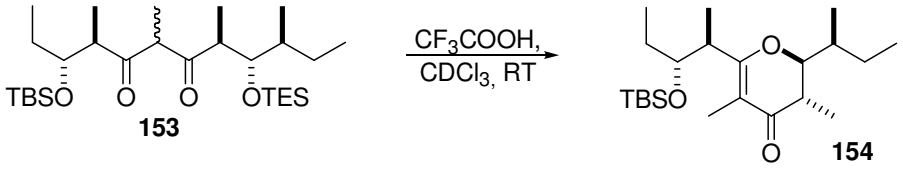
(2*S*, 3*S*)-2,3-dihydro-6-[(1'*S*, 2'S)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (151)



As per the general procedure using dione **150** (47.5 mg, 0.092 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.39) yielded 25.7 mg (73 %) of the product **151** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82-3.75 (2H, m, C*H*(OTBS), CH(CH_3)C*H*(O)); 2.95 (1H, apt qn, *J* = 6.9 Hz, CH(OTBS)C*H*(CH_3)); 2.46 (1H, dq, *J* = 13.8, 6.6 Hz, C(=O)C*H*(CH_3)); 1.75 (3H, s, C=C(CH_3)); 1.75-1.67 (1H, m, C(O)C*H*(CH_3)); 1.62-1.41 (2H, m, CH_3CH_2); 1.33-1.20 (2H, m, CH(CH_3)C*H*$_2$$CH_3$); 1.08 (3H, d, *J* = 6.9 Hz, C(O)CH(C*H*$_3$)CH_2CH_3); 1.05 (3H, d, *J* = 6.6 Hz, C(=O)CH(C*H*$_3$)); 1.02 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 0.94 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); 0.89 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$); 0.85 (9H, s, SiC(C*H*$_3$)$_3$); 0.04 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.00 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.5; 172.8; 109.2; 85.9; 73.9; 41.1; 40.1; 35.5; 25.8; 25.7; 21.8; 18.0; 16.2; 12.1; 11.9; 10.2; 9.5; 7.8; –4.3; –4.6; **IR** (film, cm^{-1}) 2964; 2935; 2881; 2859; 1666; 1616; 1463; 1389; 1378; 1367; 1256; 1195; 1145; 1125; 1111; 1082; 1056; 1035; 1012; 1006; 858; 836; 793; 774; $[\alpha]_D^{20}$ = –85.6 (*c* 1.0, $CHCl_3$).

(2*S*, 3*S*)-2,3-dihydro-6-[(1'*R*, 2'*R*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (154)

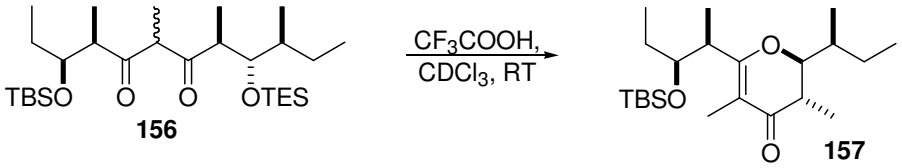


As per the general procedure using dione **153** (0.016 g, 0.042 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.40) yielded 8.4 mg (72 %) of the product **154** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, dt , *J* = 8.1, 4.2 Hz, C*H*(OTBS)); 3.71 (1H, dd, *J* = 14.1, 2.1 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 2.98 (1H, apt qn, *J* = 7.2 Hz, C*H*(CH_3)C(O)=C(CH_3)); 2.48 (1H, apt sextet, *J* = 6.9 Hz, C(=O)C*H*(CH_3)); 1.75 (3H, s, C(O)=C(CH_3)); 1.82-1.64 (1H, m, C(O)C*H*(CH_3)CH_2CH_3); 1.61-1.49 (2H, m, CH_3C*H*$_2$CH(OTBS)); 1.36-1.21 (2H, m, C(O)CH(CH_3)C*H*$_2$$CH_3$); 1.09 (3H, d, *J* =

6.9Hz, C(O)CH(C*H*$_3$)CH$_2$CH$_3$); 1.05 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)CH(O)); 0.98 (3H, t, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 0.95 (3H, t, *J* = 7.5 Hz, CH(CH$_3$)CH$_2$C*H*$_3$); 0.88 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$CH(OTBS)); 0.83 (9H, s, OSiC(CH$_3$)$_2$); –0.02 (3H, s, Si(CH$_3$)$_A$(CH$_3$)$_B$); –0.03 (3H, s, Si(CH$_3$)$_A$(CH$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 196.1; 173.7; 109.7; 87.8; 73.6; 41.0; 40.8; 35.7; 25.8; 25.7; 21.7; 17.9; 16.3; 12.5; 12.2; 9.8; 9.5; 7.6; –4.4; –4.7; **IR** (film, cm^{-1}) 2963; 2932; 2880; 2858; 1666; 1619; 1462; 1391; 1379; 1363; 1252; 1193; 1144; 1123; 1107; 1081; 1058; 1037; 1011; 1006; 835; 775; $[\alpha]_D^{20} = -144.4$ (*c* 0.5, $CHCl_3$); **HRMS (ESI)** found 383.2973, $C_{22}H_{42}O_3SiH^+$ requires 383.2976; **LREIMS** 325 (17 %); 210 (23 %); 173 (42 %); 117 (26 %); 111 (31 %); 85 (79 %); 83 (100 %); 57 (88 %); 55 (68 %).

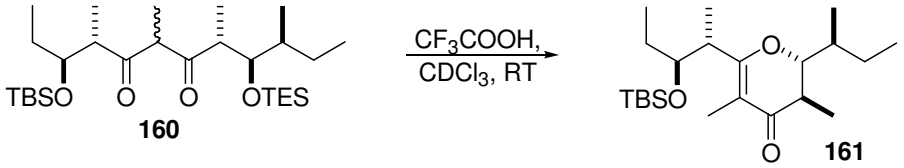
(2*S*, 3*S*)-2,3-dihydro-6-[(1'*R*, 2'*S*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (157)



As per the general procedure using dione **156** (0.111 g, 0.215 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.53) yielded 59 mg (71 %) of the product **157** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, dt, *J* = 8.7, 4.5 Hz, CH(OTBS)); 3.72 (1H, dd, *J* = 13.2, 2.7 Hz, C*H*(O)CH(CH$_3$)CH$_2$); 2.81 (1H, dq, *J* = 8.7, 6.9 Hz, CH(OTBS)C*H*(CH$_3$)); 2.44 (1H, dq, *J* = 13.2, 6.9 Hz, C(=O)C*H*(CH$_3$)); 1.79-1.65 (1H, m, CH(O)C*H*(CH$_3$)CH$_2$); 1.73 (3H, s, C(O)=C(C*H*$_3$)); 1.62-1.38 (4H, m, CH$_3$C*H*$_2$CH(OTBS), CH(CH$_3$)C*H*$_2$CH$_3$); 1.12 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 1.06 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)CH$_2$); 1.04 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)); 0.94 (3H, t, *J* = 7.5 Hz, CH(CH$_3$)CH$_2$C*H*$_3$); 0.90 (9H, s, SiC(C*H*$_3$)$_3$); 0.82 (3H, t, *J* = 7.5 Hz, C*H*$_3$CH$_2$); 0.06 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.9; 173.5; 108.6; 87.2; 74.2; 41.1; 40.6; 35.4; 27.8; 25.9; 21.9; 18.2; 16.1; 15.4; 11.9; 10.0; 9.3; 8.0; –4.2; –4.5; **IR** (film, cm^{-1}) 2963; 2933; 2881; 2859; 1668; 1619; 1463; 1376; 1355; 1254; 1191; 1145; 1120; 1102; 1076; 1054; 1035; 1005; 857; 836; 794; 774; $[\alpha]_D^{20} = -139.9$ (*c* 1.2, $CHCl_3$).

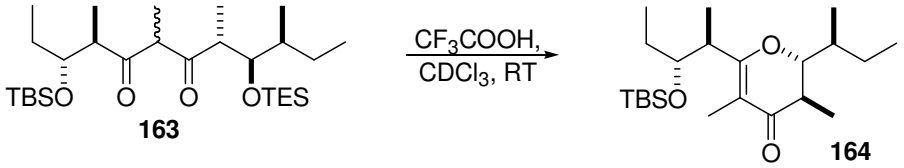
(2*R*, 3*R*)-2,3-dihydro-6-[(1'*S*, 2'*S*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (161)



As per the general procedure using dione **160** (0.123 g, 0.238 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.47) yielded 76.2 mg (84 %) of the product **161** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (1H, dd, *J* = 13.8, 2.1 Hz, C*H*(O)CH(CH_3)CH_2); 3.77 (1H, ddd, *J* = 7.2, 5.4, 3.6 Hz, CH(OTBS)); 2.95 (1H, apt qn, *J* = 7.2 Hz, CH(OTBS)C*H*(CH_3)); 2.43 (1H, dq, *J* = 13.8, 6.9 Hz, C(=O)C*H*(CH_3)); 1.75 (3H, s, C(O)=C(C*H*$_3$)); 1.68-1.38 (5H, m, CH(O)C*H*(CH_3)CH_2 ,CH_3CH_2CH(OTBS), CH(CH_3)CH_2CH_3); 1.04 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$); 1.03 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(C*H*$_3$)); 0.97-0.82 (18H, m, CH_3CH_2CH(OTBS),CH(CH_3)CH_2CH_3); CH(C*H*$_3$)CH_2, SiC(C*H*$_3$)$_3$); 0.04 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.01 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.4; 172.7; 109.3; 83.8; 73.9; 41.2; 40.1; 35.9; 26.6; 25.8; 25.6; 18.0; 12.1; 12.0; 11.9; 9.8; 9.5; 8.0; –4.4; –4.6; **IR** (film, cm^{-1}) 2964; 2935; 2882; 2860; 1666; 1616; 1471; 1471; 1463; 1389; 1377; 1367; 1257; 1194; 1149; 1125; 1112; 1082; 1055; 1035; 1011; 1006; 858; 836; 793; 774; $[\alpha]_D^{20}$ = + 77.7 (*c* 1.9, $CHCl_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*R*, 2'*R*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (164)

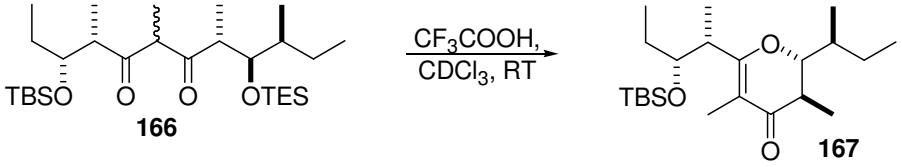


As per the general procedure using dione **163** (0.115 g, 0.223 mmol), purification by column chromatography (10 % mixed hexanes/CH_2Cl_2, R_f = 0.44) yielded 62 mg (73 %) of the product **164** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (1H, dd, *J* = 13.8, 2.1 Hz, C*H*(O)CH(CH_3)CH_2); 3.78 (1H, ddd, *J* = 7.5, 5.7, 3.6 Hz, CH(OTBS)); 2.95 (1H, apt qn, *J* = 6.9 Hz, CH(OTBS)C*H*(CH_3)); 2.43 (1H, dq, *J* = 13.8, 6.9 Hz, C(=O)C*H*(CH_3)); 1.75 (3H, s, C(O)=C(C*H*$_3$));1.70-1.58 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.58-1.39 (4H, m, CH_3CH_2CH(OTBS), CH(CH_3)CH_2CH_3);1.04 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$);

1.03 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 0.95 (3H, t, *J* = 7.5 Hz, C*H*$_3$CH$_2$CH(OTBS) or CH(CH$_3$)CH$_2$C*H*$_3$); 0.93 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)CH$_2$); 0.89 (3H, t, *J* = 7.5 Hz, C*H*$_3$CH$_2$CH(OTBS) or CH(CH$_3$)CH$_2$C*H*$_3$); 0.85 (9H, s, SiC(C*H*$_3$)$_3$); 0.04 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.00 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 195.4; 172.8; 109.3; 83.8; 73.9; 41.2; 40.1; 36.0; 26.6; 25.8; 25.6; 18.0; 12.1; 12.0; 11.9; 9.8; 9.5; 8.0; –4.4; –4.6; **IR** (film, cm^{-1}) 2963; 2933; 2881; 2859; 1666; 1617; 1462; 1389; 1367; 1256; 1194; 1149; 1125; 1111; 1082; 1052; 1035; 1006; 878; 858; 836; 793; 774; 666; $[\alpha]_D^{20}$ = + 83.7 (*c* 0.9, CHCl$_3$).

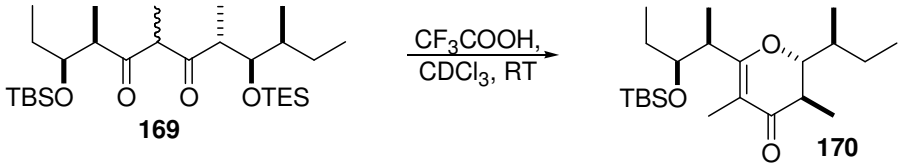
(2*R*, 3*R*)-2,3-dihydro-6-[(1'*R*, 2'*S*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (167)



As per the general procedure using dione **166** (0.129 g, 0.250 mmol), purification by column chromatography (100 % CH$_2$Cl$_2$, R$_f$ = 0.52) yielded 66 mg (70 %) of the product **167** as a clear, colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.82-3.76 (2H, m, CH(OTBS), C*H*(O)CH(CH$_3$)CH$_2$); 2.82 (1H, dq, *J* = 9.0, 6.9 Hz, CH(OTBS)C*H*(CH$_3$)); 2.43 (1H, dq, *J* = 13.5, 6.9 Hz, C(=O)C*H*(CH$_3$)); 1.75 (3H, s, C(O)=C(C*H*$_3$)); 1.68-1.25 (5H, m, CH(O)C*H*(CH$_3$)CH$_2$, CH$_3$C*H*$_2$CH(OTBS), CH(CH$_3$)C*H*$_2$CH$_3$); 1.16 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)); 1.05 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$)); 0.94 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)CH$_2$); 0.93 (3H, t, *J* = 6.9 Hz, C*H*$_3$CH$_2$CH(OTBS) or CH(CH$_3$)CH$_2$C*H*$_3$); 0.91 (9H, s, SiC(C*H*$_3$)$_3$); 0.85 (3H, t, *J* = 7.5 Hz, C*H*$_3$CH$_2$CH(OTBS) or CH(CH$_3$)CH$_2$C*H*$_3$); 0.08 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.07 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 195.9; 173.6; 108.8; 83.8; 74.6; 41.3; 40.5; 35.7; 27.9; 26.5; 25.9; 18.2; 16.1; 12.5; 11.8; 9.8; 9.5; 8.1; –4.2; –4.4 **IR** (film, cm^{-1}) 2963; 2933; 2881; 2860; 1668; 1618; 1463; 1376; 1353; 1255; 1191; 1147; 1107; 1073; 1053; 1034; 1006; 856; 836; 794; 775; $[\alpha]_D^{20}$ = +94.3 (*c* 1.3, CHCl$_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*S*, 2'*R*)-2-*tert*-butyldimethylsilyloxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (170)



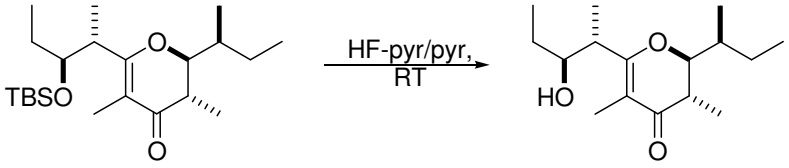
As per the general procedure using dione **169** (0.115 g, 0.224 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.42) yielded 54 mg (63 %) of the product **170** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84-3.78 (2H, m, C*H*(OTBS), $CH(CH_3)CH(O)CH(CH_3)$); 2.81 (1H, dq, *J* = 8.4, 6.9 Hz, $CH(OTBS)CH(CH_3)$); 2.40 (1H, dd, *J* = 13.8, 6.9 Hz, $C(=O)CH(CH_3)$); 1.74 (3H, s, $C(O)=C(CH_3)C(=O)$); 1.67-1.58 (1H, m, $CH(O)CH(CH_3)CH_2CH_3$); 1.57-1.40 (4H, m, CH_3CH_2, CH_2CH_3); 1.11 (3H, d, *J* = 6.9 Hz, $CH(OTBS)CH(CH_3)$); 1.03 (3H, d, *J* = 6.9 Hz, $C(=O)CH(CH_3)$); 0.94 (3H, t, *J* = 7.2 Hz, CH_3CH_2 or CH_2CH_3); 0.92 (3H, d, *J* = 6.9 Hz, $CH(O)CH(CH_3)CH_2$); 0.90 (9H, s, $SiC(CH_3)_3$); 0.82 (3H, t, *J* = 7.5 Hz, CH_3CH_2 or CH_2CH_3)); 0.06 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.7; 173.6; 108.7; 84.3; 74.3, 41.1; 40.6; 35.6; 27.8; 26.5; 25.9; 18.1; 15.4; 12.5; 11.8; 9.4; 9.3; 8.0; –4.3; –4.6; **IR** (film, cm^{-1}) 2967; 2933; 2882; 2860; 1459; 1392; 1373; 1359; 1353; 1253; 1197; 1153; 1107; 1077; 1052; 1029; 1009; 839; 792; 772; 666; $[\alpha]_D^{20}$ = +152.5 (*c* 1.2, $CHCl_3$).

General Procedure for Desilylation

To a solution of the silyl ether (~50 mg) in HF-pyr/pyr (1 mL; from a stock solution containing dry THF 10 mL, pyridine 5 mL, pyridinium hydrofluoride 2.1 g) and H_2O (100 μL) was stirred at room temperature for 1-3 weeks (or until TLC analysis showed consummation of starting material) in a Teflon® screw cap jar. The solution was diluted with Et_2O (30 mL), washed with $CuSO_4$ (sat. aq., 15 mL), $NaHCO_3$ (sat. aq., 15 mL), brine (15 mL) and dried ($MgSO_4$) and concentrated in *vacuo*. The resulting oil was purified by column chromatography.

(2*S*, 3*S*)-2,3-dihydro-6-[(1'*S*, 2'*S*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (12)

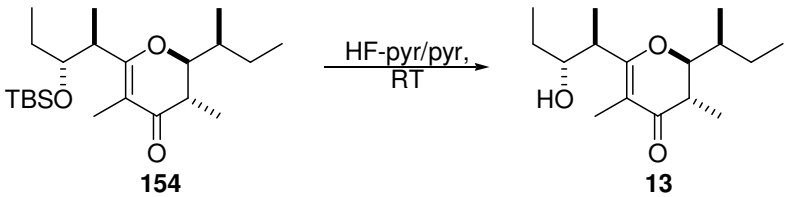


151 **12**

As per the general procedure using silyl ether **151** (8.4 mg, 0.022 mmol), purification by column chromatography (60 % Et_2O/mixed hexanes, R_f = 0.31) yielded 3.7 mg (69 %) of isomer **12** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (1H, dd, *J* = 12.0, 3.6 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.57 (1H, ddd, *J* = 8.4, 6.6, 3.6 Hz, C*H*(OH)); 2.87 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.50 (1H, dq, *J* = 12.0, 7.2 Hz, C(=O)C*H*(CH_3)); 1.79-1.73 (1H, m, CH(O)C*H*(CH_3)CH_2CH_3); 1.75 (3H, s, C(O)=C(C*H*$_3$)); 1.61-1.54 (2H, m, $CH_3CH_AH_B$, CH(CH_3)$CH_AH_BCH_3$); 1.45-1.37 (1H, m, $CH_3CH_AH_B$); 1.31-1.22 (1H, m, CH(CH_3)$CH_AH_BCH_3$); 1.17 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)C(O)); 1.10 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)); 1.06 (3H, d, *J* = 7.2 Hz, CH(O)CH(C*H*$_3$)CH_2CH_3); 1.00 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$); 0.94 (3H, t, *J* = 7.7 Hz, CH(CH_3)CH_2C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.6; 172.3; 109.7; 87.0; 75.4; 41.1; 40.6; 35.1; 28.1; 22.2; 16.3; 14.7; 11.7; 11.0; 10.0; 9.4; **IR** (film, cm^{-1}) 3460; 2968; 2937; 2879; 1661; 1647; 1608; 1462; 1392; 1381; 1367; 1198; 1145; 1116; 1078; 1018; 975; $[\alpha]_D^{20} = -139.3$ (*c* 0.7, $CHCl_3$).

(2*S*, 3*S*)-2,3-dihydro-6-[(1'*R*, 2'*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (13)



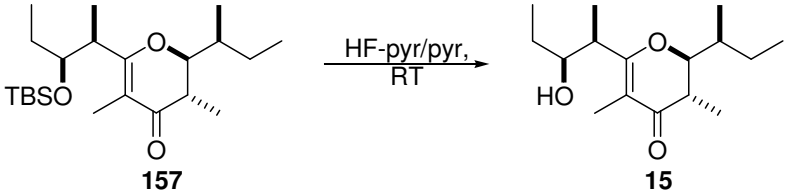
154 **13**

As per the general procedure using silyl ether **154** (7.7 mg, 0.020 mmol), purification by column chromatography (50 %, Et_2O/mixed hexanes, R_f = 0.21) yielded 3.7 mg (69 %) of isomer **13** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.80 (1H, dd, *J* = 13.2, 3.0 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.57 (1H, ddd, *J* = 8.4, 6.6, 4.2 Hz, C*H*(OH)); 2.85 (1H, apt q, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.52 (1H, dq, *J* = 13.1, 7.2 Hz,

C(=O)C*H*(CH_3)CH(O)); 1.77-1.72 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.74 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.68-1.53 (2H, m, $CH_3CH_AH_BCH(OH)$, O*H*); 1.50-1.40 (1H, m, $CH_3CH_AH_BCH(OH)$); 1.27-1.17 (2H, m, CH(CH_3)C*H*$_2$); 1.16 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 1.09 (3H, d, *J* = 7.2 Hz, CH(O)CH(C*H*$_3$)CH_2); 1.08 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)CH(O)); 0.99 (3H, t, *J* = 7.5 Hz, C*H*$_3$$CH_2$CH(OH)); 0.97 (3H, t, *J* = 7.5 Hz, CH(CH_3)CH_2C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.6; 172.4; 109.9; 87.8; 75.5; 41.1; 40.9; 35.4; 28.1; 22.0; 16.2; 14.7; 12.0; 10.1; 10.0; 9.4; **IR** (film, cm^{-1}) 3466; 2966; 2935; 2879; 1723; 1661; 1651; 1608; 1462; 1379; 1367; 1237; 1195; 1144; 1116; 1103; 1077; 1018; 975; 953 $[\alpha]_D^{20} = -133.6$ (*c* 0.2, $CHCl_3$).

(2*S*, 3*S*)-2,3-dihydro-6-[(1'*R*, 2'*S*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (15)

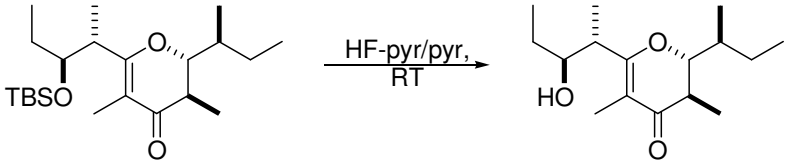


157 **15**

As per the general procedure using silyl ether **157** (59 mg, 0.153 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.54) yielded 33.3 mg (81 %) of isomer **15** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (1H, dd, *J* = 12.6, 3.0 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.67 (1H, ddd, *J* = 8.4, 6.6, 3.6 Hz, C*H*(OH)); 2.76 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.47 (1H, dq, *J* = 12.6, 7.2 Hz, C(=O)C*H*(CH_3)CH(O)); 1.91 (1H, br s, O*H*); 1.75-1.69 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.72 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.60-1.50 (2H, m, $CH_3CH_AH_BCH(OH)$, $CH(CH_3)CH_AH_B$); 1.47-1.38 (1H, m, $CH_3CH_AH_BCH(OH)$); 1.21-1.14 (1H, m, $CH(CH_3)CH_AH_BCH_3$); 1.18 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 1.06 (6H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)CH(O), CH(C*H*$_3$)CH_2CH_3); 0.95 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$CH(OH)); 0.94 (3H, d, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.7; 173.0; 108.5; 87.4; 74.8; 41.5; 40.7; 35.3; 27.8; 21.9; 16.1; 12.9; 11.9; 10.2; 10.2; 9.2; **IR** (film, cm^{-1}) 3443; 2967; 2878; 1661; 1651; 1607; 1462; 1378; 1194; 1144; 1072; 1028; 976; $[\alpha]_D^{20} = -181.8$ (*c* 1.0, $CHCl_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*S*, 2'*S*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (16)

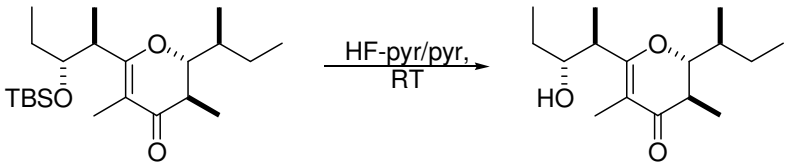


161 **16**

As per the general procedure using silyl ether **161** (76.2 mg, 0.199 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.43) yielded 42.6 mg (80 %) of isomer **16** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91 (1H, dd, *J* = 13.2, 3.0 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.54 (1H, ddd, *J* = 8.4, 6.6, 3.6 Hz, C*H*(OH)); 2.86 (1H, apt qn, *J* = 6.6 Hz, CH(OH)C*H*(CH_3)); 2.46 (1H, dq, *J* = 13.2, 6.6 Hz, C(=O)C*H*(CH_3)CH(O)); 1.82 (1H, br s, O*H*); 1.74 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.69-1.63 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.60-1.53 (1H, m, $CH_3CH_AH_BCH(OH)$); 1.51-1.36 (3H, m, $CH_3CH_AH_BCH(OH)$, $CH(CH_3)CH_2CH_3$); 1.16 (3H, d, *J* = 6.6 Hz, CH(OH)CH(C*H*$_3$)); 1.06 (3H, d, *J* = 6.6 Hz, C(=O)CH(C*H*$_3$)CH(O)); 0.98 (3H, t, *J* = 7.5 Hz, C*H*$_3$$CH_2CH(OH)$); 0.953 (3H, t, *J* = 7.2 Hz, $CH(CH_3)CH_2$C*H*$_3$); 0.947 (3H, d, *J* = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.5; 172.6; 109.8; 84.5; 75.3; 41.2; 40.6; 35.6; 28.1; 26.8; 14.6; 12.3; 11.9; 9.93; 9.91; 9.4; **IR** (film, cm^{-1}) 3951; 3890; 3869; 3854; 3839; 3835; 3822; 3787; 3858; 3747; 3743; 3732; 3683; 3675; 3648; 3629; 3486; 2962; 2934; 2878; 1654; 1604; 1457; 1377; 1197; 1146; 975; $[\alpha]_D^{20}$ = +144.6 (*c* 1.0, $CHCl_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*R*, 2'*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (17)



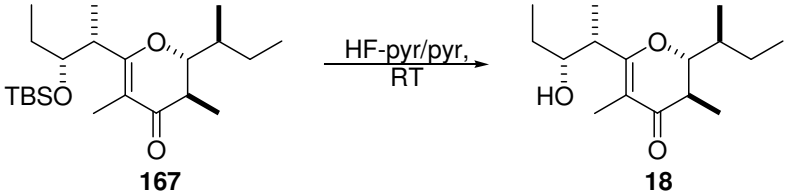
164 **17**

As per the general procedure using silyl ether **164** (62.1 mg, 0.162 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.27) yielded 36.3 mg (83 %) of isomer **17** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91 (1H, dd, *J* = 13.2, 3.0 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.55 (1H, ddd, *J* = 9.0, 7.2, 4.2 Hz, C*H*(OH)); 2.86 (1H,

apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.46 (1H, dq, *J* = 13.2, 6.6 Hz, C(=O)C*H*(CH_3)CH(O)); 1.84 (1H, br s, O*H*); 1.74 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.69-1.63 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.50-1.53 (1H, m, $CH_3CH_AH_BCH(OH)$); 1.50-1.36 (3H, m, $CH_3CH_AH_BCH(OH)$, CH(CH_3)C*H*$_2$); 1.16 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 1.06 (3H, d, *J* = 6.6 Hz, C(=O)CH(C*H*$_3$)CH(O)); 0.99 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$CH(OH)); 0.95 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); 0.95 (3H, d, *J* = 6.6 Hz, CH(O)CH(C*H*$_3$)CH_2); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.5; 172.6; 109.8; 84.5; 75.3; 41.2; 40.5; 35.6; 28.0; 26.8; 14.6; 12.3; 11.9; 9.9 (2); 9.4; **IR** (film, cm^{-1}) 3465; 2967; 2937; 2879; 1655; 1649; 1608; 1460; 1390; 1379; 1368; 1353; 1197; 1148; 1117; 1078; 1032; 1018; 975; $[\alpha]_D^{20}$ = +133.9 (*c* 1.8, $CHCl_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*S*, 2'*R*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (18)

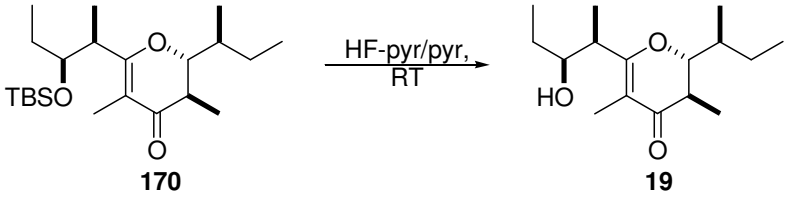


167 **18**

As per the general procedure using silyl ether **167** (54 mg, 0.141 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.35) yielded 30.4 mg (80 %) of isomer **18** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (1H, dd, *J* = 13.2, 2.4 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.68 (1H, ddd, *J* = 8.4, 6.0, 3.6 Hz, C*H*(OH)); 2.76 (1H, apt qn, *J* = 7.2 Hz, CH(OH)C*H*(CH_3)); 2.44 (1H, dq, *J* = 13.2, 7.2 Hz, C(=O)C*H*(CH_3)); 1.95 (1H, br s, O*H*); 1.73 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.68-1.62 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.59-1.37 (4H, m, CH_3C*H*$_2$CH(OH), CH(CH_3)C*H*$_2$$CH_3$); 1.17 (3H, d, *J* = 7.2 Hz, CH(OH)CH(C*H*$_3$)); 1.04 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)); 0.95 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); 0.94 (3H, t, *J* = 7.5 Hz, C*H*$_3$$CH_2$CH(OH)); 0.92 (3H, d, *J* = 7.2 Hz, CH(C*H*$_3$)CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.7; 173.2; 108.6; 84.7; 74.8; 41.5; 40.7; 35.5; 27.8; 26.5; 12.9; 12.4; 11.8; 10.2; 9.5; 9.2; **IR** (film, cm^{-1}) 3442; 2967; 2935; 2878; 1664; 1650; 1610; 1459; 1388; 1378; 1363; 1195; 1147; 1072; 1053; 1029; 977; $[\alpha]_D^{20}$ = +191.4 (*c* 1.0, $CHCl_3$).

(2*R*, 3*R*)-2,3-dihydro-6-[(1'*R*, 2'*S*)-2-hydroxy-1-methylbutyl]-3,5-dimethyl-2-[(1''*S*)-1-methylpropyl]-4H-pyran-4-one (19)



170 **19**

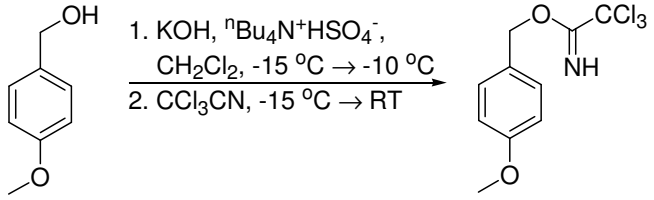
As per the general procedure using silyl ether **170** (66 mg, 0.172 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.38) yielded 36.3 mg (79 %) of isomer **19** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84 (1H, dd, *J* = 13.8, 2.4 Hz, C*H*(O)CH(CH_3)CH_2CH_3); 3.61 (1H, ddd, *J* = 8.4, 6.6, 3.6 Hz, C*H*(OH)); 2.77 (1H, apt qn, *J* = 6.6 Hz, CH(OH)C*H*(CH_3)); 2.45 (1H, dq, *J* = 13.8, 7.2 Hz, C(=O)C*H*(CH_3)CH(O)); 1.86 (1H, br s, O*H*); 1.73 (3H, s, C(O)=C(C*H*$_3$)C(=O)); 1.67-1.61 (1H, m, CH(O)C*H*(CH_3)CH_2); 1.53-1.34 (4H, m, CH_3CH_2CH(OH), CH(CH_3)C*H*$_2$); 1.21 (3H, d, *J* = 6.6 Hz, CH(OH)CH(C*H*$_3$)); 1.05 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$)CH(O)); 0.96 (3H, t, *J* = 7.2 Hz, C*H*$_3$$CH_2$CH(OH)); 0.94 (3H, d, *J* = 6.6 Hz, CH(O)CH(C*H*$_3$)); 0.93 (3H, t, *J* = 7.2 Hz, CH(CH_3)CH_2C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.7; 173.1; 108.7; 84.3; 75.2; 41.8; 40.5; 35.6; 28.0; 26.6; 13.4; 12.3; 11.8; 10.2; 9.7; 9.3; **IR** (film, cm^{-1}) 3443; 2967; 2934; 2878; 1661; 1651; 1607; 1462; 1378; 1194; 1144; 1072; 1028; 976; $[\alpha]_D^{20}$ = +115.4 (*c* 0.7, $CHCl_3$).

6.3 Experimental Procedures for Chapter 4

6.3.1 Model System One

2,2,2-trichloroacetimidic acid 4'-methoxybenzyl ester

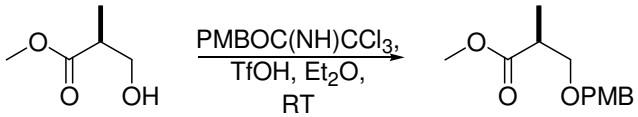


To a solution of 4-methoxybenzylalcohol (5.0 g, 4.51 mL, 36.2 mmol) in CH_2Cl_2 at -15 → -10 °C was added potassium hydroxide (50 % aq., 34 mL) and tetra-^{n}butyl ammonium hydrogen sulfate (75 mg. 0.22 mmol) and the resulting mixture stirred vigorously at -15 → -10 °C for 5 minutes. Trichloroactetonitrile was added dropwise

and the mixture stirred at -15 → -10 °C for 30 minutes. The solution was then warmed slowly to room temperature and stirred for an additional 30 minutes. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 35 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo* to approx. 25 mL. The solution was filtered through a 2 cm pad of Celite, washed through with CH_2Cl_2 (50 mL) and concentrated in *vacuo*. Purification of the clear, yellow oil by Kugelrohr distillation (76 °C at 0.3 mm Hg) yielded 10.2 g (100 %) of the PMBOC(NH)CCl_3 as a clear, colourless oil. (lit. b.p. 135-137 °C at 0.7 mmHg)[305]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (1H, br s, N*H*); 7.38 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.91 (2H, d, *J* = 8.7 Hz, Ar*H*); 5.28 (2H, s, CH_2O); 3.82 (3H, s, OCH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.5; 159.7; 129.7; 128.6; 127.4; 113.9; 70.6; 55.2; **IR** (film, cm^{-1}) 3338; 3002; 2956; 2910; 2836; 1663; 1613; 1515; 1463; 1442; 1378; 1303; 1249; 1176; 1078; 1035; 982; 822; 797; 648.

(*S*)-methyl-3-(4'-methoxybenzyloxy)-2-methylpropionate (221)

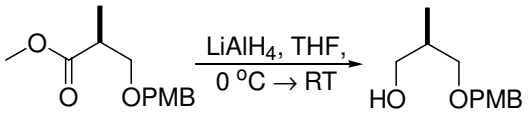


220 **221**

To a solution of the alcohol **220** (2.0 g, 15 mmol) and PMBOC(NH)CCl_3 (6.32 g, 22.5 mmol) in Et_2O (44 mL) was added, dropwise, triflic acid (4 μL, $4.5x10^{-5}$ mol). After stirring for 30 minutes, the reaction was monitored by TLC and successive additions of PMBOC(NH)CCl_3 and triflic acid were added until the reaction was complete. The reaction mixture was diluted with Et_2O (20 mL), washed with $NaHCO_3$ (sat. aq., 25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by distillation (108-120 °C at 0.05-0.01 mmHg) yielded 3.53 g (99 %) of PMB ether **221** as a clear, colourless oil with spectroscopic data consistent with that reported.[239]

^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.45 (2H, s, ArCH_2O); 3.80 (3H, s, OCH_3); 3.69 (3H, s, OCH_3); 3.63 (1H, dd, *J* = 9.0, 7.2 Hz, C$H_A$$H_B$OPMB); 3.46 (1H, dd, *J* = 9.0, 6.0 Hz, C$H_A$$H_B$OPMB); 2.77 (1H, qn, *J* = 7.2, 6.0 Hz, CH_2(OPMB)C*H*(CH_3)); 1.67 (3H, d, *J* = 7.2 Hz, CH_2(OPMB)CH(CH_3)); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.2; 129.2; 113.7; 72.7; 71.6; 71.6; 55.2; 51.7; 40.2; 14.0; **IR** (film, cm^{-1}) 2952; 1738; 1612; 1513; 1463; 1363; 1302; 1248; 1201; 1175; 1090; 1035; 822; $[\alpha]_D^{20}$ = +8.45 (*c* 1.1, $CHCl_3$).

(*S*)-3-(4'-methoxybenzyloxy)-2-methyl-propan-1-ol (222)

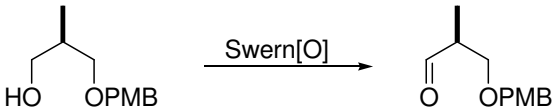


221 **222**

To a cooled (0 °C) suspension of $LiAlH_4$ (206 mg, 5.42 mmol) in dry THF (6 mL) was added, *via* a cannula, a solution of the ester **221** in THF (3 x 3 mL). The suspension was warmed to room temperature and stirred for 30 minutes. After this time the reaction was quenched at room temperature by addition of H_2O (250 μL), NaOH (5 M, 250 μL) and H_2O (250 μL). The mixture was diluted with Et_2O (10 mL), dried ($MgSO_4$) and vacuum filtered at the water pump. The solution was concentrated in *vacuo*. The product was purified by column chromatography (20 % Et_2O/CH_2Cl_2, R_f = 0.38) to yield 0.705 g (74 %) of the alcohol **222** as a clear, colourless oil with spectroscopic data consistent with that reported.[239]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.88 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.45 (2H, s, CH_2Ar); 3.81 (3H, s, OCH_3); 3.65-3.36 (4H, m, CH_2OH, CH_2OPMB); 2.45 (1H, br s, O*H*); 2.14-2.01 (1H, m, C*H*(CH_3)); 0.87 (3H, d, *J* = 7.2 Hz, CH(CH_3)); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.2; 130.1; 129.2; 113.8; 75.2; 73.0; 68.0; 55.3; 35.5; 13.4; **IR** (film, cm^{-1}) 3398; 2959; 2926; 2857; 1716; 1614; 1587; 1514; 1464; 1457; 1364; 1303; 1247; 1174; 1093; 1035; 818; 754; $[\alpha]_D^{20}$ = +15.7 (*c* 1.0, $CHCl_3$).

(*S*)-3-(4'-methoxybenzyloxy)-2-methylpropionaldehyde (219)



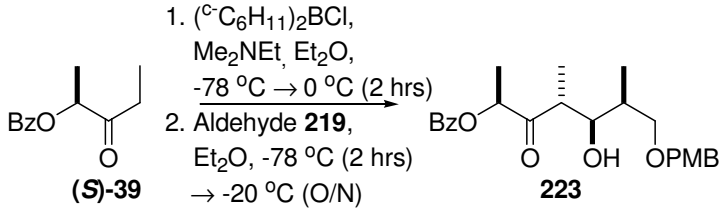
222 **219**

Oxalyl chloride (2.5 mL, 5.03 mmol) was added dropwise to a solution of DMSO (0.72 mL, 10.1 mmol) in CH_2Cl_2 (14.4 mL) at -78 °C. The resulting solution was stirred at -78 °C for 30 min. A solution of the alcohol **222** (0.71 g, 3.36 mmol) in CH_2Cl_2 (3 mL, 2 mL, 1 mL) was added *via* a cannula to the reaction mixture, dropwise. The resulting mixture was stirred for 45 minutes at -78 °C. Et_3N was added dropwise over several minutes and stirred at -78 °C for 30 minutes before warming to 0 °C and stirring for 30 minutes. The reaction mixture was quenched by addition of NH_4Cl (sat. aq., 30 mL), poured onto NH_4Cl (sat. aq., 70 mL) and extracted with

CH_2Cl_2 (3 x 75 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.41) yielding 0.56 g (80 %) aldehyde **219** as a clear, colourless oil with spectroscopic data consistent with that reported.[239]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (1H, d, *J* = 1.5 Hz, C*H*(O)); 7.24 (2H, d, *J* = 6.6 Hz, Ar*H*); 6.88 (2H, d, *J* = 6.6 Hz, Ar*H*); 4.46 (2H, s, OCH_2Ar); 3.81 (3H, s, OCH_3); 3.65 (1H, dd, *J* = 9.6, 6.9 Hz, CH_AH_BOPMB); 3.60 (1H, dd, *J* = 9.6, 5.4 Hz, CH_AH_BOPMB); 2.70-2.59 (1H, m, C*H*(CH_3)); 1.12 (3H, d, *J* = 7.2 Hz, CH(CH_3)); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 204.0; 159.2; 129.9; 129.2; 113.8; 72.9; 69.8; 55.3; 46.8; 10.7; **IR** (film, cm^{-1}) 2962; 2937; 2860; 2839; 1722; 1613; 1587; 1513; 1458; 1361; 1303; 1247; 1174; 1093; 1034; 819; $[\alpha]_D^{20}$ = +26.5 (*c* 1.1, $CHCl_3$).

(2*S*, 4*R*, 5*R*, 6*S*)-2-benzoyloxy-5-hydroxy-7-(4'-methoxybenzyloxy)-4,6-dimethylheptane-3-one (223)

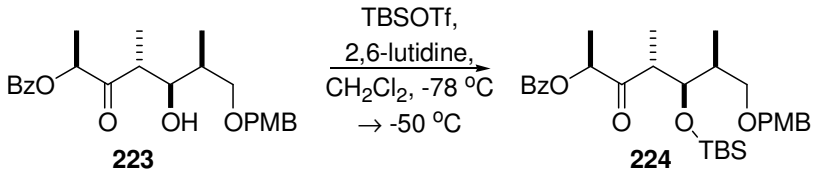


To a solution of dicyclohexylboron chloride (0.57 g, 0.58 mL, 2.69 mmol) in Et_2O (7 mL) at -78 °C was added Me_2NEt (0.24 g, 0.35 mL, 3.22 mmol), dropwise, followed by ketone **(*S*)-39** in Et_2O (7 mL), *via* a cannula. The resulting solution was allowed to warm slowly to 0 °C and stirred for 2 hours. The solution was again cooled to -78 °C and aldehyde **219** added in Et_2O (3 mL) *via* a cannula. The resulting solution was stirred at -78 °C for 2 hours before placing overnight in the freezer. The reaction was warmed to 0 °C for 30 minutes before quenching with MeOH (7 mL), pH 7 buffer (7 mL) and H_2O_2 (30 % aq., 7 mL). The solution was stirred for a further 1 hour at room temperature. The product was extracted with CH_2Cl_2 (3 x 75 mL) and the combined extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (5 % Et_2O/CH_2Cl_2, R_f = 0.30) yielded 0.69 g (94 %, >95 % ds) of adduct **223** as a white solid (m.p. 74-76 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (2H, d, *J* = 6.9 Hz, Ar*H*); 7.60-7.55 (1H, m, Ar*H*); 7.45 (2H, m, Ar*H*); 7.21 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 5.43 (1H, q, *J* = 6.9 Hz, BzOC*H*(CH_3)); 4.44 (1H, d, *J* = 11.4 Hz, CH_AH_BAr); 4.38 (1H, d, *J* = 11.4 Hz, CH_AH_BAr); 4.07 (1H, dd, *J* = 9.3, 2.1 Hz, C*H*(OH)); 3.80

(3H, s, OCH_3); 3.54 (1H, dd, J = 9.0, 4.2 Hz, CH_AH$_B$OPMB); 3.49 (1H, dd, J = 9.0, 4.2 Hz, CH$_A$$H_B$OPMB); 3.00 (1H, dq, J = 9.3, 7.2 Hz, C(=O)CH(CH$_3$)CH(OH)); 1.91-1.84 (1H, m, CH(OH)CH(CH$_3$)CH(OPMB)); 1.53 (3H, d, J = 6.9 Hz, BzOCH(CH_3)); 1.21 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)CH(OH)); 0.95 (3H, d, J = 6.9 Hz, CH(OH)CH(CH_3)CH$_2$(OPMB)); **^{13}C NMR** (75.5 MHz, CDCl$_3$) δ 211.1; 165.9; 159.2; 133.2; 130.0; 129.8; 129.6; 129.2; 128.4; 113.8; 75.1; 74.6; 73.0; 55.2; 45.7; 34.4; 15.5; 13.8; 9.5; (one signal missing); **IR** (film, cm^{-1}) 3512; 2968; 2938; 1718; 1613; 1514; 1453; 1301; 1269; 1250; 1116; 1072; 1034; 1006; 713; $[\alpha]_D^{20}$ = +11.3 (*c* 0.7, CHCl$_3$); **HRMS (ESI)** $C_{24}H_{30}O_6Na^+$ requires 437.1935, found 437.1936; **LRGCMS** 208 (3.7 %); 137 (74 %); 121 (100 %); 109 (8.9 %); 91 (3.7 %); 77 (8.9 %).

(2*S*, 4*R*, 5*R*, 6*S*)-2-benzoyloxy-5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-4,6-dimethylheptane-3-one (224)



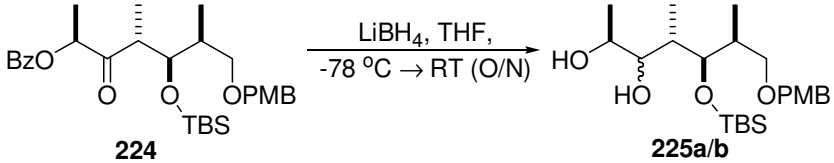
223 **224**

To a solution of alcohol **223** (6.02 g, 14.5 mmol) in CH_2Cl_2 (145 mL) at -78 °C was added 2,6-lutidine (3.4 mL, 29 mmol) followed immediately by TBSOTf (4.9 mL, 22 mmol). The resulting solution was stirred for 1 hour at -78 °C before warming to -50 °C for a further hour. TLC analysis showed the reaction was almost complete so the solution was warmed to 0 °C before quenching. The reaction mixture was poured onto $NaHCO_3$ (sat. aq., 200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2 → 5 % Et_2O/CH_2Cl_2, R_f(CH_2Cl_2) = 0.38) yielded 7.37 g (96 %) of silyl ether **224** as a clear, colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.08 (2H, m, ArH); 7.59 (1H, m, ArH); 7.46 (2H, m, ArH); 7.23 (2H, m, ArH); 6.86 (2H, m, ArH); 5.48 (1H, q, J = 6.9 Hz, CH$_3$(BzO)CH(C=O)); 4.44 (1H, d, J = 11.4 Hz, OCH_AH$_B$Ar); 4.36 (1H, d, J = 11.4 Hz, OCH$_A$$H_B$Ar); 4.21 (1H, dd, J = 8.7, 1.5 Hz, CH(OTBS)); 3.80 (3H, s, OCH$_3$); 3.39 (1H, dd, J = 9.0, 7.2 Hz, CH_AH$_B$OPMB); 3.24 (1H , dd, J = 9.0, 6.9 Hz, CH$_A$$H_B$OPMB); 3.10 (1H, dq, J = 8.1, 7.2 Hz, C(=O)CH(CH$_3$)CH(OTBS)); 1.93 (1H, m, CH(OTBS)CH(CH$_3$)CH$_2$OPMB); 1.51 (3H, d, J = 6.9 Hz, CH_3CH(OBz)C(=O)); 1.11 (3H, d, J = 7.2 Hz, C(=O)CH(CH_3)CH(OTBS)); 0.89

(3H, d, J = 6.9 Hz, CH(OTBS)CH(CH_3)CH$_2$OPMB); 0.83 (9H, s, SiC(CH_3)$_3$); 0.02 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); -0.09 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.0; 165.6; 159.1; 133.2; 130.6; 129.8; 129.2; 128.4; 113.7; 75.0; 72.9; 72.8; 72.5; 55.3; 46.9; 36.1; 26.2; 25.6; 18.6; 15.6; 14.0; 10.5; -3.6; -5.1; **IR** (film, cm^{-1}) 2954; 2928; 2855; 1721; 1613; 1513; 1462; 1452; 1250; 1115; 1039; 833; 711; $[\alpha]_D^{20}$ = -6.5 (*c* 0.77, $CHCl_3$); **HRMS (ESI)** $C_{30}H_{46}O_6NaSi^+$ requires 551.2799, found 551.2797; **LREIMS** 241 (4.2 %); 207 (4.2 %); 179 (6.7 %); 137 (11 %); 121 (100 %); 105 (26 %); 85 (15 %); 71 (23 %); 57 (34 %); 55 (22 %).

(2*S*, 3*R/S*, 4*R*, 5*R*, 6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-4,6-dimethylheptan-2,3-diol (225a/b)

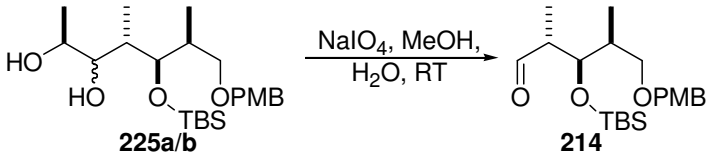


224 **225a/b**

To a cooled (-78 °C) solution of benzoate **224** (5.71 g, 10.8 mmol) in THF (130 mL) was added a solution of $LiBH_4$ (2 M in THF, 108 mL, 0.216 mol). The reaction mixture was placed in an ice/H_2O bath for 10 minutes before warming slowly to room temperature and the stirring continued overnight. The solution was cooled to 0 °C for 10 minutes before quenching with H_2O (200 mL). The mixture was extracted with Et_2O (4 x 200 mL), washed with brine (200 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (30 % mixed hexanes/Et_2O, R_f = 0.29) yielding 4.10g (89 %) of diols **225a/b** (ratio ~2:1) as a mixture of isomers as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.22 (2H, m, ArH); 6.91-6.86 (2H, m, ArH); 4.44 (2H, m, OCH_2Ar); 3.99 (1H, dd, J = 4.5, 2.7 Hz, plus 3.81-3.25 (4H, m, CH(OH), CH(OH), CH(OTBS), CH_2(OPMB)); 3.81 (3H, s, OCH_3); 2.47 (2H, br s, OH, OH); 2.10-1.95 and 1.70-1.63 (2H, m, CH(OH)CH(CH$_3$)CH(OTBS), CH(OTBS)CH(CH$_3$)CH$_2$(OPMB)); 1.15-0.79 (18H, m, CH_3CH(OH), CH(OH)CH(CH_3)CH(OTBS), CH(OTBS)CH(CH_3)CH$_2$(OPMB), SiC(CH_3)$_3$); 0.12-0.00 (6H, m, Si(CH_3)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ showed a complex mixture of isomers; **IR** (film, cm^{-1}) 3449; 2957; 2932; 2886; 2858; 1613; 1514; 1463; 1249; 1099; 1061; 1037; 837; **HRMS (ESI)** $C_{23}H_{42}O_5SiNa^+$ requires 449.2694, found 449.2694; **LREIMS** 323 (2.5 %); 243 (2.5 %); 187 (4.2 %); 173 (2.5 %); 137 (5.1 %); 122 (14 %); 121 (100 %); 115 (6.7 %); 91 (2.5 %); 75 (10 %); 73 (11 %).

(2*R*, 3*R*, 4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentanal (214)

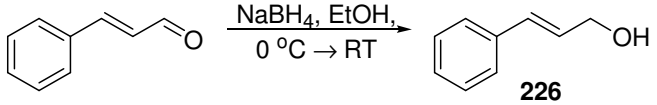


225a/b **214**

To a stirred solution of diol **225a/b** (1.18 g, 2.77 mmol) in methanol (27.7 mL) and H_2O (13.9 mL) at room temperature was added $NaIO_4$ (3.56 g, 8.08 mmol) and the resulting suspension stirred for 15 minutes (after this time TLC analysis showed consumption of starting material). The reaction mixture was diluted with H_2O (100 mL), extracted with Et_2O (3 x 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (30 % mixed hexanes/CH_2Cl_2, R_f = 0.39) to yield 0.37 g (93 %) of aldehyde **214** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, d, *J* = 2.7 Hz, C*H*(O)); 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.88 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.37 (2H, s, CH_2Ar); 4.05 (1H, dd, *J* = 5.7, 4.2 Hz, C*H*(OTBS)); 3.81 (3H, s, OCH_3); 3.35 (1H, dd, *J* = 9.0, 6.9 Hz, CH_AH$_B$(OPMB)); 3.26 (1H, dd, *J* = 9.0, 5.7 Hz, CH$_A$$H_B$(OPMB)); 2.61-2.51 (1H, m, CH(O)C*H*(CH$_3$)); 1.99-1.91 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$(OPMB)); 1.07 (3H, d, *J* = 6.9 Hz, CH(O)CH(CH_3)); 0.93 (3H, d, *J* = 6.6 Hz, CH(OTBS)CH(CH_3)CH$_2$(OPMB)); 0.87 (9H, s, Si(C(CH_3)$_3$); 0.05 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); 0.04 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 204.8; 159.2; 130.4; 129.2; 113.7; 74.1; 72.5; 72.0; 55.3; 50.9; 37.7; 25.9; 18.3; 12.2; 11.5; -4.2; -4.3; **IR** (film, cm^{-1}) 2956; 2931; 2884; 2857; 1725; 1613; 1514; 1463; 1361; 1249; 1173; 1088; 1037; 837; 775; $[\alpha]_D^{20}$ = -19.9 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** $C_{21}H_{36}O_4NaSi$ requires 403.2275, found 403.2286; **LRGCMS** 137 (2.2 %); 122 (9.6 %); 121 (100 %); 116 (2.2 %); 91 (0.7 %); 75 (2.9 %); 73 (3.7 %); 59 (2.2 %).

(2*E*)-3-phenylprop-2-en-1-ol (226)



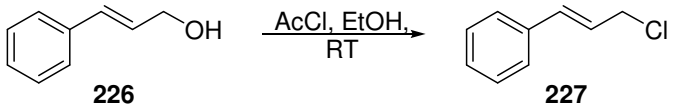
226

To a stirring solution of *E*-cinnamaldeyde (0.5g, 3.78 mmol) in EtOH (5.6 mL) at 0 °C was added $NaBH_4$ (0.143g, 3.78 mmol). The solution was stirred at 0 °C for 30

minutes before warming to room temperature and stirring for a further 30 minutes. After this time TLC analysis showed consumption of starting material and the reaction was quenched by the addition of HCl (1 M, 3 mL) until the fizzing stopped. The EtOH was removed in *vacuo* and the product extracted with EtOAc (3 x 20 mL). The combined extracts were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.33) yielded 0.46 g (90 %) of alcohol **226** as a clear, colourless oil with spectroscopic data consistent with that reported.[240]

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.21 (5H, m, Ar*H*); 6.62 (1H, d, *J* = 15.8 Hz, ArC*H*); 6.36 (1H, dt, *J* = 15.8, 5.6 Hz, ArCH=C*H*); 4.32 (2H, dd, *J* = 5.6, 1.4 Hz, CH_2OH); 1.78 (1H, s, O*H*); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 136.7; 131.1; 128.6; 128.5; 127.7; 126.4; 63.7; **IR** (film, cm^{-1}) 3328; 3083; 3060; 3028; 2924; 2868; 1599; 1494; 1450; 1422; 1373; 1093; 1070; 1011; 967; 744; 734; 692; 667; **HRMS (EI)** $C_9H_{10}O$ requires 134.0732, found 134.0737; **LREIMS** 134 (96 %); 115 (59 %); 105 (57 %); 92 (100 %); 91 (78 %); 78 (46 %); 77 (40 %); 63 (9.7 %); 55 (9.7 %); 51 (16 %).

(2*E*)-1-chloro-3-phenylprop-2-ene (227)



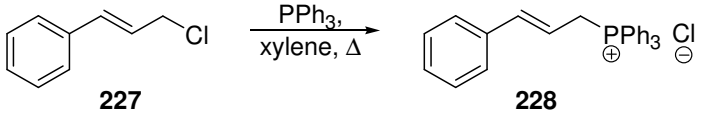
226 **227**

To a solution of the alcohol **226** (0.46 g, 3.4 mmol) in EtOH (1.6 mL) at room temperature was added AcCl (1.93 mL, 27.2 mmol), dropwise with a mild exotherm being observed. The reaction flask as stoppered and the solution stirred at room temperature for 30 minutes. After this time TLC analysis indicated no starting material remained. The volatiles were removed in *vacuo* and the solution was taken up in CH_2Cl_2 (20 mL) and washed with brine (10 mL). The aqueous was extracted again with CH_2Cl_2 (20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. ^{1}H and ^{13}C NMR data indicated the chloride **227** was of high purity so the clear oil (0.52 g, 100 % yield) was not further purified.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.26 (5H, m, Ar*H*); 6.67 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.30 (1H, dt, *J* = 15.6, 7.2 Hz, ArCH=C*H*); 4.25 (2H, dd, *J* = 7.2, 1.0 Hz, CH_2Cl); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 135.9; 134.1; 128.6; 128.3; 126.7; 124.9; 45.4; **IR** (film, cm^{-1}) 3085; 3063; 3029; 2955; 1740; 1497; 1450; 1440; 1249; 964;

749; 693; 674; 667; **HRMS (EI)** C_9H_9Cl requires 152.0393, found 152.0399; **LREIMS** 152 (23 %); 117 (100 %); 91 (13 %); 57 (6 %).

triphenyl-(3-phenylallyl)-phosphonium chloride (228)

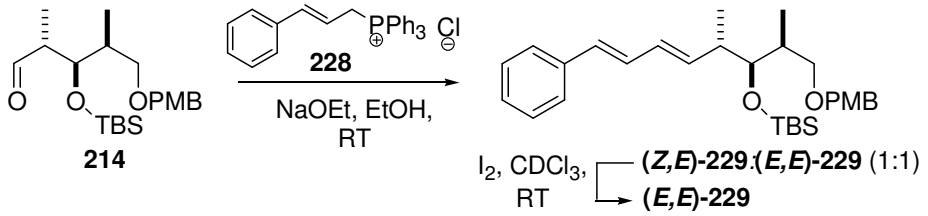


227 **228**

To a solution of the chloride **227** (0.519 g, 3.4 mmol) in xylene (2.6 mL) was added a solution of triphenylphosphine (1.19g, 4.53 mmol) in xylene (1.17 M, 3.86 mL). The mixture was heated under reflux overnight. The solid product was collected by vacuum filtration and washed with xylene yielding 1.41g (100 %) of the salt **228** as fine white crystals consistent with those reported in the literature.[236]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.61 (15H, m, Ar*H*); 7.22-7.13 (5H, m, Ar*H*); 6.67 (1H, dd, *J* = 10.6, 5.4 Hz, ArC*H*=); 5.98-5.86 (1H, m, ArCH=C*H*); 4.85 (2H, dd, *J* = 15.3, 7.2 Hz, ArCH=CHCH_2PPh$_3$).

(2*S*, 3*S*, 4*S*, 5*E*, 7*E*)-3-(*tert*-butyldimethylsilyloxy)-1-(4'-methoxybenzyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene ((*E*,*E*)-229)

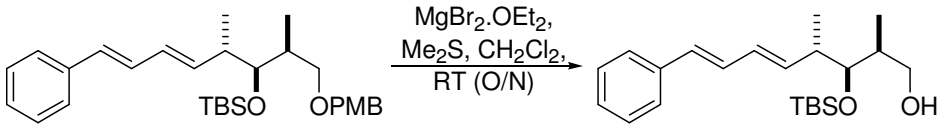


To a solution of triphenylcinnamylphosphonium chloride (**228**) (2.48 g, 5.99 mmol) and aldehyde **214** (0.455 g, 1.20 mmol) in EtOH (2 mL) was added a solution of NaOEt (1 M, 30 mL)) in EtOH. The solution immediately turned red indicating formation of the ylide. The reaction mixture was stirred at room temperature for a few days until TLC analysis showed consumption of starting material. The reaction was quenched by the addition of H_2O (25 mL) and the EtOH was removed in *vacuo*. The product was extracted with Et_2O (3 x 50 mL) and the combined extracts washed with brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.44) yielding 0.551 g (96 %) of a clear, colourless oil as a mixture of **(*E*,*E*)-229** and **(*Z*,*E*)-229** isomers. To a solution of mixture of isomers **(*Z*,*E*)-229** and **(*E*,*E*)-229** in $CDCl_3$ was added a few crystals of I_2 and the reaction monitored by ^{1}H NMR to see complete conversion of **(*Z*,*E*)-229** to **(*E*,*E*)-229** isomers. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with sodium metabisulfite (sat. aq., 10

mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined extracts dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.44) yielding 0.461 g (84 %) of **(*E,E*)-229** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 and 6.89-6.85 (9H, m, Ar*H*); 6.74 (1H, dd, *J* = 15.9, 10.5 Hz, ArCH=C*H*); 6.43 (1H, dd, *J* = 15.9, ArC*H*); 6.15 (1H, dd, *J* = 15.3, 10.5 Hz, ArCH=CHC*H*=CH); 5.80 (1H, dd, *J* = 15.3, 8.4 Hz, ArCH=CHCH=C*H*); 4.43 (1H, d, *J* = 11.4 Hz, CH_AH$_B$Ar); 4.37 (1H, d, *J* = 11.4 Hz, CH$_A$$H_B$Ar); 3.78 (3H, s, OC$H_3$); 3.70-3.67 (1H, m, C*H*(OTBS)); 3.38 (1H, dd, *J* = 9.0, 6.6 Hz, CH_AH$_B$OPMB); 3.21 (1H, dd, *J* = 9.0, 6.9 Hz, CH$_A$$H_B$OPMB); 2.49-2.40 (1H, m, =CHC*H*(CH$_3$)CH(OTBS)); 2.00-1.91 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$OPMB); 1.04 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)); 0.92-0.89 (12H, m, SiC(CH_3)$_3$, CH(OTBS)CH(CH_3)CH$_2$OPMB); 0.032 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); 0.025 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 138.9; 137.7; 130.2; 130.0; 129.6; 129.2; 129.1; 128.5; 127.1; 126.1; 113.7; 76.2; 73.3; 72.5; 55.2; 42.1; 37.3; 26.1; 18.4; 17.7; 12.3; -3.7; -4.1; **IR** (film, cm^{-1}) 3024; 2957; 2930; 2856; 1613; 1514; 1471; 1463; 1362; 1249; 1172; 1086; 1057; 1037; 990; 836; 773; 746; 691; $[\alpha]_D^{20}$ = -20.5 (*c* 0.1, $CHCl_3$); **HRMS (ESI)** $C_{30}H_{44}NaO_3Si^+$ requires 503.2952, found 503.2953; **LREIMS** 323 (4.3 %); 187 (11 %); 121 (100 %); 85 (26 %); 83 (58 %); 57 (24 %); 55 (16 %).

(2*S*, 3*S*, 4*S*, 5*E*, 7*E*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene-1-ol (230)



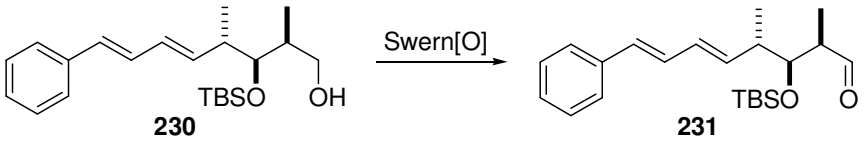
(*E,E*)-229 **230**

To a solution of PMB ether **(*E,E*)-229** (0.106g, 0.22 mmol) in dry CH_2Cl_2 (3.7 mL) at room temperature was added Me_2S (164 μL, 2.2 mmol) and powered $MgBr_2.OEt_2$ (0.170 g, 0.66 mmol). The mixture was stirred at room temperature overnight after which time TLC analysis showed consumption of the starting material. The reaction was quenched by the addition of NH_4Cl (sat. aq., 10 mL) and the product extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography

(30 % mixed hexanes/CH_2Cl_2, R_f = 0.27) yielded 0.061 g (77 %) of alcohol **230** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (5H, m, Ar*H*); 6.67 (1H, dd, *J* = 15.6, 10.2 Hz, ArCH=C*H*); 6.45 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.20 (1H, dd, *J* = 15.3, 10.2 Hz, ArCH=CHC*H*); 5.87 (1H, dd, *J* = 15.3, 7.8 Hz, ArCH=CHCH=C*H*); 3.72-3.58 (2H, m, CH_AH$_B$OH, C*H*(OTBS)); 3.47 (1H, dd, *J* = 10.5, 5.7, CH$_A$$H_B$OH); 2.59-2.46 (1H, m, =CHC*H*(CH_3)); 2.00-1.87 (1H, m, CH(OTBS)C*H*(CH_3)CH_2OH); 1.70 (1H, br s, O*H*); 1.07 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)); 0.93-0.89 (12H, m, SiC(CH_3)$_3$, CH(OH)CH(CH_3)); 0.09 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.07 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2; 137.6; 130.5; 130.3; 129.5; 128.5; 127.1; 126.2; 77.3; 65.9; 41.1; 39.8; 26.1; 18.4; 16.6; 12.2; -3.9; -4.1; **IR** (film, cm^{-1}) 3400; 3023; 2958; 2929; 2856; 1472; 1461; 1251; 1029; 989; 858; 836; 773; 745; 691; $[\alpha]_D^{20}$ = -10.2 (*c* 0.1, $CHCl_3$); **HRMS (ESI)** $C_{22}H_{36}NaO_2Si^+$ requires 383.2377, found 383.2375; **LREIMS** 259 (1.7 %); 203 (11 %); 185 (8.5 %) 173 (8.5 %); 157 (77 %); 145 (100 %); 131 (15 %); 115 (38 %); 111 (26 %); 85 (35 %); 75 (100 %); 55 (21 %).

(2*R*, 3*S*, 4*S*, 5*E*, 7*E*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-dienal (231)



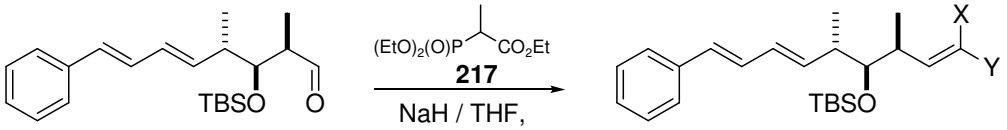
230 **231**

Oxalyl chloride (126 μL, 0.25 mol) was added dropwise to a solution of DMSO (36 μL, 0.50 mmol) in CH_2Cl_2 (720 μL) at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes before dropwise addition of a solution of alcohol **230** (0.031 g, 0.085 mmol) in CH_2Cl_2 (0.25 mL, 0.25 mL, 0.25 mL) *via* a cannula. The resulting mixture was stirred for 45 minutes at -78 °C. Et_3N (140 μL, 1.01mmol) was added dropwise over several minutes and stirred at -78 °C for 30 minutes before warming to 0 °C and stirring for 30 minutes. The reaction mixture was quenched by addition of $NaHSO_4$ (1 M, 10 mL), and the product extracted with Et_2O (3 x 10 mL). The combined extracts were concentrated in *vacuo*. The product was taken up in Et_2O (30 mL) and washed with $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (sat. aq., 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was

purified by column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.53) yielding 28.4 mg (94 %) of aldehyde **231** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (1H, d, *J* = 1.2 Hz, C*H*O); 7.40-7.18 (5H, m, Ar*H*); 6.73 (1H, dd, *J* = 15.6, 10.2 Hz, ArCH=C*H*); 6.46 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.17 (1H, dd, *J* = 15.3, 10.5 Hz, ArCH=CHC*H*); 5.73 (1H, dd, *J* = 15.3, 8.7 Hz, ArCH=CHCH=C*H*); 4.03 (1H, dd, *J* = 4.5, 4.5 Hz, C*H*(OTBS)); 2.57-2.46 (2H, m, C*H*(CH_3)CH(OTBS)CH(CH_3)C(=O), CH(CH_3)CH(OTBS)C*H*(CH_3)C(=O)); 1.11 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$) or CH(C*H*$_3$)CH=); 1.09 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$) or CH(C*H*$_3$)CH=) 0.91 (9H, s, SiC(C*H*$_3$)$_3$); 0.09 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.05 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 Hz, $CDCl_3$) δ 204.6; 137.4; 136.0; 132.0; 131.3; 128.9; 128.5; 127.3; 126.3; 75.8; 51.0; 41.5; 25.9; 18.2; 17.8; 9.4; -4.1; -4.2; **IR** (film, cm^{-1}) 2932; 2855; 1724; 1653; 1559; 1472; 1257; 1078; 1031; 991; 837; 776; 747; 692; $[\alpha]_D^{20}$ = -71.6 (*c* 1.2, $CHCl_3$); **HRMS (ESI)** $C_{22}H_{34}NaO_2Si^+$ requires 381.2220, found 381.2222; **LREIMS** 301 (4.3 %); 201 (31 %); 173 (31 %); 145 (17 %); 115 (59 %); 85 (40 %); 83 (44 %); 75 (44 %); 73 (100 %); 59 (21 %).

(2*E/Z*, 4*S*, 5*S*, 6*S*, 7*E*, 9*E*)-5-(*tert*-butyldimethylsilyloxy)-2,4-6-trimethyl-10-phenyldeca-2,7,9-trieneoic acid ethyl ester ((2*Z*,5*S*)-114 and (2*E*,5*S*)-114)



231

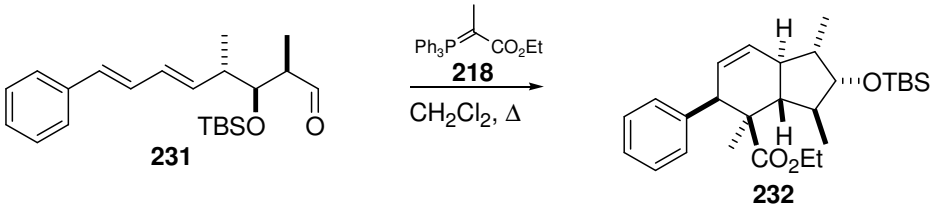
(2*Z*,5*S*)-114; X=CH_3, Y=CO_2Et
(2*E*,5*S*)-114; X=CO_2Et, Y=CH_3

To a solution of NaH (washed with mixed hexane and dried under N_2) (93 mg, 3.83 mmol) in THF (5.8 mL) at 0 °C was added the phosphonate **117** (0.80 mL, 3.7 mmol), dropwise. The solution was stirred at room temperature for 1 hour before cooling to 0 °C and addition of aldehyde **231** (0.42 g, 1.17 mmol). The solution was warmed slowly to room temperature and after 30 minutes no further reaction was occurring so the reaction was quenched by pouring on to NH_4Cl (sat. aq., 30 mL). The product was extracted with Et_2O (3 x 30 mL) and the combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (40 % CH_2Cl_2/mixed hexanes, R_f (2*E*) = 0.41, R_f (2*Z*) = 0.3) to give 120 mg (23 %) of **(2*Z*,5*S*)-114** and 373 mg (72 %) of

(2*E*,5*S*)-114 isomers. The **(2*E*,5*S*)-114** isomer spontaneously undergoes a [4π + 2π] cycloaddition reaction and was therefore not characterised.

(2*Z*,5*S*)-114 - **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39-7.17 (5H, m, Ar*H*); 6.73 (1H, dd, *J* = 15.6, 10.2 Hz, ArCH=C*H*); 6.42 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.10 (1H, dd, *J* = 15.3, 10.2 Hz, ArCH=CHC*H*); 5.82-5.71 (2H, m, ArCH=CHCH=C*H*, C*H*=C(CH_3)CO_2Et); 4.24-4.10 (2H, m, CO_2CH_2); 3.52-3.42 (1H, m, C*H*(OTBS)); 3.38-3.27 (1H, m, CH(OTBS)C*H*(CH_3)CH=); 2.44-2.34 (1H, m, CH=CHC*H*(CH_3)); 1.89 (3H, d, *J* = 1.5 Hz, CH=C(C*H*$_3$)CO_2Et); 1.27 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.05 (3H, d, *J* = 6.9 Hz, =CHCH(C*H*$_3$)CH(OTBS)); 0.99 (3H, d, *J* = 6.6 Hz, CH(OTBS)CH(C*H*$_3$)CH=); 0.92 (9H, s, SiC(C*H*$_3$)$_3$); 0.04 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.03 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 168.1; 146.1; 138.3; 130.7; 130.3; 130.2; 129.6; 128.5; 127.7; 127.0; 126.1; 79.9; 60.1; 42.5; 37.4; 26.1; 20.9; 18.4; 17.3; 15.9; 14.3; -3.5; -3.8; **IR** (film, cm^{-1}) 3025; 2960; 2928; 2857; 1716; 1253; 1219; 1092; 1030; 836; 773; 691; 667; $[\alpha]_D^{20}$ = +58.3 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** $C_{27}H_{42}NaO_3Si^+$ requires 465.2795, found 465.2800; **LREIMS** 385 (57 %); 339 (9.6 %); 310 (14 %); 285 (26 %); 239 (33 %); 237 (73 %); 221 (16 %); 195 (31 %); 181 (1 %); 157 (26 %); 153 (15 %); 129 (19 %); 115 (24 %); 103 (19 %); 91 (40 %); 84 (74 %); 75 (94 %); 73 (100 %); 57 (23 %); 51 (34 %).

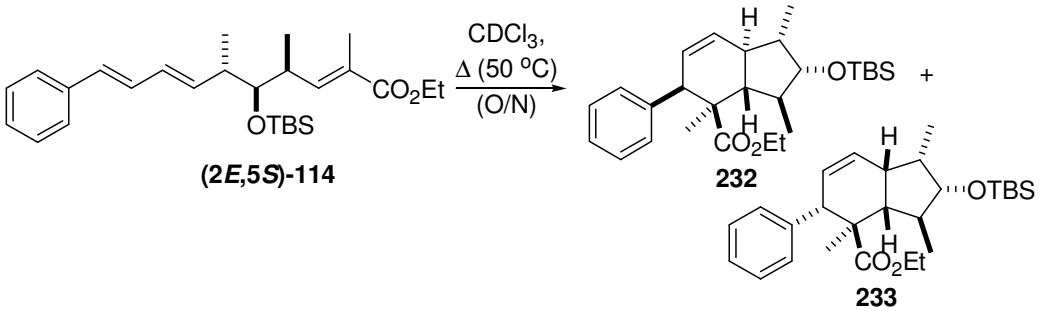
(1*S*, 2*S*, 3*S*, 3a*S*, 4*R*, 5*R*, 7a*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (232)



A solution of aldehyde **231** (96 mg, 0.27 mmol) and ylide **218** (116 mg, 0.32 mmol) in CH_2Cl_2 (1.8 mL) was heated under reflux for 6 days. TLC analysis of the reaction mixture failed to reveal anything about the reaction progress as the starting material and product had similar R_f values. The solvent was removed in *vacuo* and the product was triturated with mixed hexanes to remove the triphenylphosphine oxide. Purification by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.45) yielded 47 mg (40 %) the IMDA cycloadduct **232** and some recovered starting material.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.11 (5H, m, Ar*H*); 5.99 (1H, dt, *J* = 10.2, 1.8 Hz, PhCHCH=C*H*); 5.54 (1H, ddd, *J* = 10.2, 3.6, 3.0 Hz, PhCHC*H*); 3.70 (1H, dd, *J* = 6.6, 1.8 Hz, C*H*(OTBS)); 3.54 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.31 (1H, m, PhC*H*); 3.21(1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 2.04-1.99 (1H, m, CH=CHC*H*); 1.80 (1H, dd, *J* = 11.2, 10.2 Hz, $EtO_2CC(CH_3)CHCH(CH_3)$); 1.70 (1H, ddd, *J* = 12.0, 6.6, 6.6 Hz, $CH=CHCHCH(CH_3)$); 1.59-1.54 (1H, m, $Et_2OC(CH_3)CHCH(CH_3)$); 1.34 (3H, s, $Et_2OCC(CH_3)$); 1.03 (3H, d, *J* = 6.6 Hz, $CH=CHCHCH(CH_3)$); 0.88 (9H, s, $SiC(CH_3)_3$); 0.86 (3H, d, *J* = 7.2 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.69 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 0.03 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.02 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.3; 142.0; 129.6; 128.3; 128.0; 127.7; 126.7; 82.9; 59.7; 54.3; 49.6; 47.0; 44.3; 44.2; 40.4; 26.1; 25.9; 18.3; 18.2; 13.2; 12.5; -4.3; -4.6; **IR** (film, cm^{-1}) 3026; 2954; 2929; 2885; 2856; 1720; 1473; 1460; 1256; 1092; 1060; 1028; 834; 773; 701; 669; **HRMS (ESI)** $C_{27}H_{42}O_3SiH^+$ requires 443.2976, found 443.2979; **LREIMS** 385 (22 %); 310 (11 %); 285 (62 %); 237 (35 %); 235 (22 %) 206 (23 %); 195 (16 %); 181 (12 %); 157 (23 %); 129 (17 %); 125 (41 %); 116 (24 %); 105 (14 %); 91 (41 %); 75 (90 %); 73 (100 %); 57 (40 %).

(1*S*, 2*S*, 3*S*, 3a*S*, 4*R*, 5*R*, 7a*R*)- and (1*S*, 2*S*, 3*S*, 3a*S*, 4*R*, 5*S*, 7a*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (232 and 233)



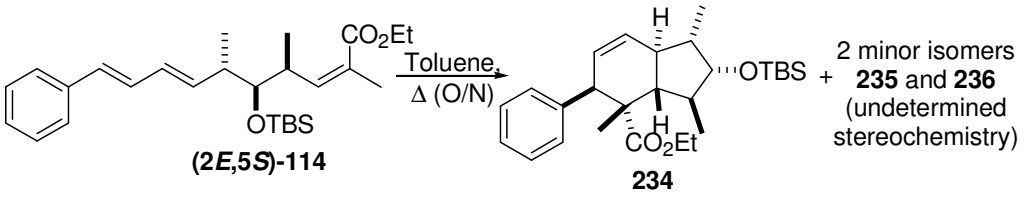
A solution of triene **(2*Z*,5*S*)-114** (120 mg, 0.28 mmol) in $CDCl_3$ (4 mL) was warmed to 50 °C overnight. After this time the product was concentrated in *vacuo* and the product purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.52 and 0.45) yielding two stereoisomers, cycloadduct **233** (5.1 mg, 4.3 % yield) and cycloadduct **232** (95 mg, 84 % yield, 94 % ds) as clear, colourless oils.

232 – *data is identical to the cycloadduct from the Wittig olefination reaction above.*

233 - **^{1}H NMR** (600 MHz, C_6D_6) δ 7.29-7.10 (5H, m, Ar*H*); 5.88 (1H, ddd, *J* = 9.9, 2.8, 2.8 Hz, =C*H*CHAr); 5.83 (1H, ddd, *J* = 9.9, 2.8, 2.1 Hz, PhCHCH=C*H*); 4.08-

4.07 (1H, m, C*H*Ph); 3.97 (1H, qd, *J* = 7.2, 6.8 Hz, OCH_AH$_B$CH$_3$); 3.94 (1H, dq, *J* = 10.8, 7.2 Hz, OCH$_A$$H_BCH_3$); 3.52 (1H, dd, *J* = 3.2, 3.2 Hz, CHOTBS); 2.77 (1H, dd, *J* = 10.3, 7.4 Hz, EtO$_2$CC(CH$_3$)C*H*CH(CH$_3$)); 2.64 (1H, ddddd, *J* = 10.3, 10.3, 3.2, 3.2, 3.2, CH=CHC*H*); 1.95 (1H, qdd, *J* = 7.0, 4.3, 3.2 Hz, Et$_2$OC(CH$_3$)CHC*H*(CH$_3$)); 1.50 (1H, dqd, *J* = 6.6, 6.6, 3.2 Hz, CH=CHCHC*H*(CH$_3$)); 1.13 (3H, s, Et$_2$OCC(C*H$_3$*)); 1.02 (3H, d, *J* = 7.0 Hz, CH=CHCHCH(C*H$_3$*)); 1.01 (9H, s, SiC(C*H$_3$*)$_3$); 0.96 (3H, d, *J* = 6.6 Hz, CH=CHCHCH(C*H$_3$*)); 0.92 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C*H$_3$*); 0.0349 (3H, s, Si(C*H$_3$*)$_A$(CH$_3$)$_B$); 0.0347 (3H, s, Si(CH$_3$)$_A$(C*H$_3$*)$_B$); **^{13}C NMR** (150 MHz, CDCl$_3$) δ 176.5; 142.5; 130.1; 129.8; 129.5; 128.3; 127.0; 79.7; 60.3; 50.9; 50.2; 48.8; 44.6; 43.7; 40.1; 26.3; 18.6; 16.1; 14.2; 13.4; 12.9; -3.8; -3.9; **IR** (film, cm^{-1}) 2956; 2928; 1712; 1462; 1257; 1160; 1096; 1061; 1028; 862; 834; 773; $[\alpha]_D^{20}$ = + 11 (*c* 0.45, CHCl$_3$).

(1*S*, 2*S*, 3*S*, 3a*S*, 4*S*, 5*R*, 7a*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (234-236)



(2*E*,5*S*)-114 **234**

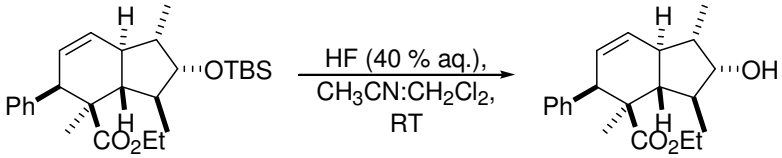
A solution of triene **(2*E*,5*S*)-114** (80.9 mg, 0.18 mmol) was heated under reflux in toluene (4 mL) overnight. The solvent was then removed in *vacuo* and the product purified by column chromatography (5 % Et$_2$O/mixed hexanes, R$_f$ = 0.31) yielding 70.7 mg (87 %, 85 % ds) of an inseparable mixture of three stereoisomers **234-236** (ratio 85:10:5) as a clear, colourless oil. Characterisation of the major isomer within the mixture was achieved.

234 – ^{1}H NMR (600 MHz, C$_6$D$_6$) δ 7.16-7.03 (5H, m, Ar*H*); 5.93 (1H, apt ddd, *J* = 9.6, 1.8, 1.8 Hz, PhCHCH=C*H*); 5.72 (1H, ddd, *J* = 9.6, 6.6, 2.4 Hz, PhCHC*H*); 4.27 (1H, apt qn, *J* = 1.8 Hz, PhC*H*); 4.06 (1H, dq, *J* = 10.8, 7.2 Hz, CO$_2$CH_AH$_B$); 3.99 (1H, dq, *J* = 10.8, 7.2 Hz, CO$_2$CH$_A$$H_B$); 3.52 (1H, dd, *J* = 5.4, 1.8 Hz, C*H*OTBS); 2.39 (1H, dqd, *J* = 9.6, 7.2, 1.8 Hz, Et$_2$OCCHC*H*(CH$_3$)CH(OTBS)); 2.24 (1H, ddddd, *J* = 11.4, 11.4, 1.8, 1.8, 1.8 Hz, CH=CHC*H*); 1.43 (1H, dq., *J* = 6.6, 6.6 Hz, CH=CHCHC*H*(CH$_3$)); 1.36 (1H, dd, *J* = 11.4, 9.6 Hz, Et$_2$OCC(CH$_3$)C*H*); 1.02 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C*H$_3$*); 1.01 (3H, d, *J* = 6.6 Hz, CH=CHCHCH(C*H$_3$*)); 0.95

(9H, s, $SiC(CH_3)_3$); 0.92 (3H, s, $Et_2OCC(CH_3)$); 0.87 (3H, d, J = 7.2 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.03 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.01 (3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (150 MHz, C_6D_6) δ 175.7; 141.7; 131.0; 130.7; 128.8; 128.1; 127.0; 84.5; 60.4; 52.8; 51.1; 49.1; 45.7; 43.9; 42.6; 26.2; 23.9; 21.2; 18.4; 14.4; 12.2; -4.0; -4.6; **IR** (film, cm^{-1}) 3018; 2956; 2928; 2886; 2856; 1724; 1463; 1452; 1251; 1207; 1102; 1089; 1021; 875; 773; 703; 674; $[\alpha]_D^{20}$ = + 55.6 (*c* 0.36, $CHCl_3$); **HRMS (ESI)** $C_{27}H_{42}NaO_3Si^+$ requires 465.2795, found 465.2796; **LREIMS** 385 (74 %); 339 (13 %); 310 (17 %); 285 (18 %); 237 (84 %); 221 (19 %); 195 (35 %); 181 (17 %); 157 (27 %); 129 (20 %); 115 (26 %); 103 (19 %); 91 (43 %); 86 (45 %); 84 (69 %); 75 (100 %); 73 (87 %); 57 (30 %).

235-236 (2 isomers) – **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.22-7.21 (Ar*H*); 5.88 (1H, ddd, J = 9.6, 2.4, 2.4 Hz); 5.83 (1H, m); 4.29 (1H, m); 3.89 (1H, dq, J = 10.8, 7.2 Hz); 2.67 (1H, dq); 2.15 (1H, apt sex, J = 7.2 Hz); 1.96 (1H, dd, J = 12.6, 9.0 Hz); 1.90 (m); 1.87 (m); 0.92 (9H,s) (Note: data incomplete due to overlap with major isomer obscuring some resonances). Minor isomers were not able to be identified in the ^{13}C NMR spectrum.

(1*S*, 2*S*, 3*S*, 3a*S*, 4*R*, 5*R*, 7a*R*)-2-hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (237)



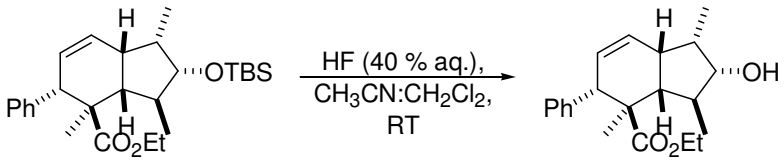
232 **237**

To a solution of the TBS ether **232** (47 mg, 0.106 mmol) in $CH_3CN:CH_2Cl_2$ (1:1, 2 mL) in a Teflon® screw cap jar was added aqueous HF (40 %, 200 μL) at room temperature. The resulting solution was stirred at room temperature and the reaction monitored by TLC. Successive additions of aqueous HF (200 μL) was performed over 3 hours until the starting material was consumed. The reaction was quenched by the addition of H_2O (30 mL) and the product was extracted with EtOAc (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.25), yielding 29 mg (84 %) of alcohol **237** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.23 (2H, m, Ar*H*); 7.21-7.18 (1H, m, Ar*H*); 7.13-7.12 (2H, m, Ar*H*); 5.99 (1H, ddd, J = 9.6, 1.8, 1.8 Hz, PhCHCH=C*H*); 5.59 (1H, ddd, J = 9.6, 3.6, 2.4 Hz, PhCHC*H*=CH); 3.80 (1H, dd, J = 7.8, 5.4 Hz,

C*H*(OH)); 3.57 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.34 (1H, apt qn, *J* = 2.4 Hz, C*H*(Ph)); 3.22 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 1.91 (1H, dq, *J* = 11.4, 1.8 Hz, CH=CHC*H*) 1.86 (1H, apt t, *J* = 11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 1.82-1.75 (1H, m $CH(CH_3)CHCH=CH$); 1.60-1.54 (2H, m, OH, $CCHCH(CH_3)$); 1.36 (3H, s, CH_3C); 1.13 (3H, d, *J* = 7.2 Hz, $CH(CH_3)CHCH=CH$); 0.92 (3H, d, *J* = 7.2 Hz, $CCHCH(CH_3)$); 0.69 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.1; 141.8; 129.5; 128.3; 127.7; 127.5; 126.8; 82.0; 59.7; 54.2; 49.1; 45.8; 44.8; 44.7; 39.9; 17.9; 17.6; 13.2; 11.7; **IR** (film, cm^{-1}) 3450; 3020; 2961; 2930; 2905; 2875; 1720; 1453; 1381; 1268; 1242; 1167; 1088; 1029; 760; 701; $[\alpha]_D^{20} = +120$ (*c* 0.3, $CHCl_3$).

(1*S*, 2*S*, 3*S*, 3a*S*, 4*R*, 5*S*, 7aS)-2-hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (238)

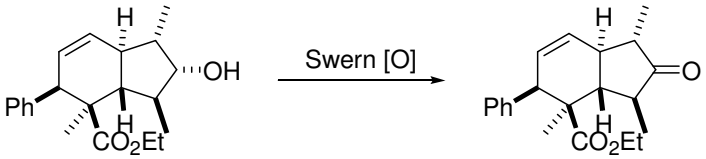


233 **238**

As per the procedure for **237** using TBS ether **233** (5.1 mg, 0.012 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.31) yielded 3.0 mg (76 %) of alcohol **238** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.24 (2H, m, Ar*H*); 7.24-7.21 (1H, m, Ar*H*); 7.17-7.16 (2H, m, Ar*H*); 5.98 (1H, ddd, *J* = 10.0, 3.0, 3.0 Hz, PhCHPhCH=C*H*); 5.83 (1H, ddd, *J* = 10.0, 2.8, 2.8 Hz, PhCHC*H*=CH); 4.07 (2H, q, *J* = 7.2 Hz, CO_2CH_2); 3.95 (1H, m, *J* = 2.4 Hz, PhC*H*Ph); 3.93 (1H, dd, *J* = 4.0, 4.0 Hz, C*H*(OH)); 2.66 (1H, dd, *J* = 10.3, 7.2 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 2.59 (1H, ddddd, *J* = 10.3, 10.3, 3.0, 3.0, 3.0 Hz, CH=CHC*H*); 2.11 (1H, dqd, *J* = 7.2, 7.2, 4.4 Hz, $CCHCH(CH_3)$); 1.79 (1H, dqd, *J* = 13.2; 6.7; 3.7 Hz, $CH(CH_3)CHCH=CH$); 1.24 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.12 (3H, d, *J* = 6.7 Hz, $CH(CH_3)CHCH=CH$); 0.98 (3H, d, *J* = 7.2 Hz, $CCHCH(CH_3)$); 0.95 (3H, s, CH_3C); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.8; 141.7; 129.5; 129.2; 129.2; 127.8; 126.6; 79.3; 60.8; 50.7; 49.7; 48.6; 43.8; 43.5; 39.0; 14.6; 14.2; 12.4; 12.2; **IR** (film, cm^{-1}) 3462; 2926; 1729; 1455; 1237; 672.

(1*S*, 3*S*, 3a*R*, 4*R*, 5*R*, 7a*R*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (239)

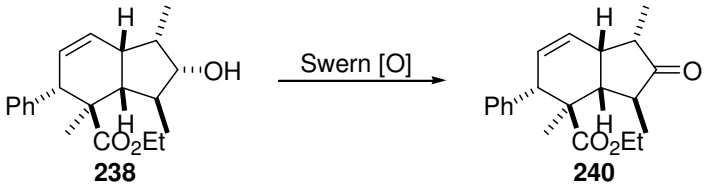


237 **239**

To a solution of DMSO (0.27 mmol, 21 mg, 19 μL) in CH_2Cl_2 (700 μL) at -78 ^oC was added a solution of oxalyl chloride in CH_2Cl_2 (2 M, 0.13 mol, 66 μL), dropwise. The solution was stirred at -78 ^oC for 30 minutes before addition of alcohol **237** (29 mg, 0.088 mmol) in CH_2Cl_2 *via* a cannula (200 μL, 200 μL, 100 μL). The resulting mixture was stirred at -78 ^oC for 45 minutes before addition of NEt_3 (0.53 mmol, 54 mg, 74 μL) over several minutes. The mixture was stirred at -78 ^oC for 30 minutes before warming to 0 ^oC and the stirring continued for 30 minutes. The reaction was quenched by the addition of NH_4Cl (sat. aq., 15 mL) and the product extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.42) yielding 29 mg (98 %) of ketone **239** a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.21 (3H, m, Ar*H*); 7.15 (2H, d, *J* = 7.2 Hz, Ar*H*); 6.11 (1H, d, *J* = 9.6 Hz, CH(Ph)CH=C*H*); 5.72 (1H, dt, *J* = 9.6, 3.6 Hz, CH(Ph)C*H*=CH); 3.58 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_BCH_3$); 3.43 (1H, m, C*H*(Ph)); 3.23 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_BCH_3$); 2.22 (1H, apt t, *J* = 11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 2.04 (1H, apt qn, *J* = 7.2 Hz, $CH(CH_3)CHCH=CH$); 2.00 – 1.92 (2H, m, $CCHCH(CH_3)$), $CH=CHCH$); 1.41 (3H, s, $C(CH_3)(CO_2Et)$); 1.25 (3H, d, *J* = 7.2 Hz, $CH(CH_3)CHCH=CH$); 0.93 (3H, d, *J* = 7.2 Hz, $CCHCH(CH_3)$); 0.69 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 219.8; 174.4; 141.0; 129.5; 129.0; 127.9; 127.1; 125.9; 60.1; 53.6; 48.9; 47.7; 46.3; 44.9; 43.0; 17.7; 13.5; 13.1; 12.5; **IR** (film, cm^{-1}) 3026; 2961; 2929; 2874; 1721; 1453; 1379; 1266; 1241; 1157; 701; 672; $[\alpha]_D^{20} = +191$ (*c* ,0.2 $CHCl_3$).

(1*S*, 3*S*, 3a*S*, 4*R*, 5*S*, 7a*S*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (240)

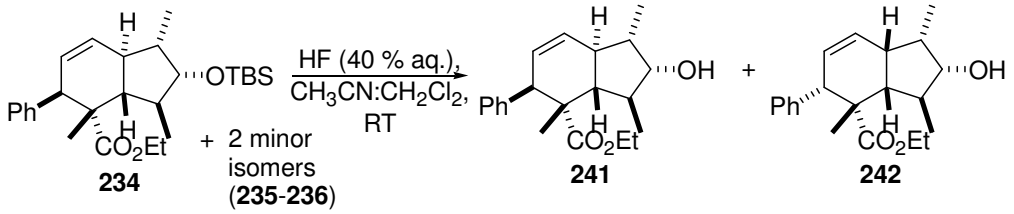


238 **240**

As per the procedure for **237** using alcohol **238** (3 mg, 0.009 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.40) yielded 1.5 mg (50 %) of ketone **240** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.25 (2H, m, Ar*H*); 7.24-7.21 (1H, m, Ar*H*); 7.11-7.09 (2H, m, Ar*H*); 6.09 (1H, ddd, *J* = 10.2, 3.6, 3.6 Hz, PhCHCH=C*H*); 5.90 (1H, ddd, *J* = 10.2, 2.4, 2.4 Hz, PhCHC*H*=CH); 4.10 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 4.07 (1H, m, C*H*(Ph)); 2.79 (1H, dd, *J* = 8.4, 1.8 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 2.58 (1H, ddddd, *J* = 8.4, 8.4, 3.0, 3.0, 3.0 Hz, CH=CHC*H*); 2.28 (1H, qdd, *J* = 7.8, 1.8, 1.8 Hz, $CCHCH(CH_3)$), 2.24 (1H, qdd, *J* = 6.6, 6.6, 1.8 Hz, $CH(CH_3)CHCH=CH$); 1.94 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.44 (3H, d, *J* = 7.2 Hz, $CCHCH(CH_3)$); 1.18 (3H, d, *J* = 7.2 Hz, $CH(CH_3)CHCH=CH$); 0.86 (3H, s, $C(CH_3)(CO_2Et)$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 222.0; 175.9; 141.1; 129.7; 129.1; 128.0; 127.4; 126.9; 60.8; 49.6; 49.2; 48.1; 47.5; 44.9; 41.7; 17.6; 14.7; 14.2; 12.8; **IR** (film, cm^{-1}) 3028; 2977; 2930; 2872; 1736; 1603; 1494; 1454; 1384; 1297; 12229; 1182; 1103; 1025; 947; 748; 705; $[\alpha]_D^{20}$ = - 44 (*c* 0.6 $CHCl_3$).

(1*S*, 2*S*, 3*S*, 3a*S*, 4*S*, 5*R*, 7a*R*)- and (1*S*, 2*S*, 3*S*, 3a*S*, 4*S*, 5*S*, 7a*S*)-2-hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (241-243)



234 **241** **242**

As per the procedure for **237** using TBS ethers **234-236** (0.37 g, 0.88 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f (**243**) = 0.46, R_f(**242**) = 0.45, R_f(**241**) = 33) yielded 0.29 g (44 %) of alcohol **241** and 0.011 g (5 %) of alcohol **242** and 0.004 g (3 %) of alcohol **234** (impure) as clear, colourless oils

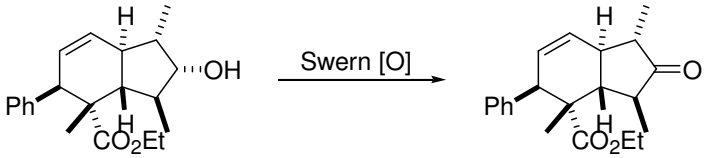
241 - ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.12 (5H, m, Ar*H*); 5.91 (1H, apt dt, *J* = 9.6, 1.8 Hz, CH(Ph)CH=C*H*); 5.58 (1H, ddd, *J* = 9.6, 4.2, 3.0 Hz, CH(Ph)C*H*=CH); 4.16 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 4.12 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.34 (1H, m, C*H*(Ph)); 3.62 (1H, dd, *J* = 6.0, 2.4 Hz, C*H*(OH)); 2.19 (1H, dqd, *J* = 9.6, 7.2, 2.4 Hz, CCHC*H*(CH_3)); 1.98 (1H, apt tq, *J* = 12.0, 2.4 Hz, CH=CHC*H*); 1.59 (1H, apt septet, *J* = 7.2 Hz, CH=CHCHC*H*(CH_3)); 1.51 (1H, br s, O*H*); 1.28 (1H, dd, *J* = 12.0, 9.6, CCHC*H*(CH_3)); 1.23 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.03 (3H, d, *J* = 7.2 Hz, CH(CH_3)CHCH=CH); 0.93 (3H, d, *J* = 7.2 Hz, CCHCH(CH_3)); 0.81 (3H, s, CH_3C); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.7; 140.8; 130.6; 130.1; 128.4; 127.8; 126.7; 83.7; 60.7; 51.7; 50.4; 48.7; 45.2; 43.5; 41.3; 23.4; 21.2; 14.3; 11.1; **IR** (film, cm^{-1}) 3501; 2969; 1722; 1452; 1377; 1209; 1139; 1101; 1023; 704; $[\alpha]_D^{20}$ = + 117.9 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** $C_{21}H_{28}NaO_3^+$ requires 351.1931, found 351.1936; **LREIMS** 310 (17 %); 237 (100 %); 221 (37 %); 195 (60 %); 181 (19 %); 171 (10 %); 133 (10 %); 125 (19 %); 115 (10 %); 91 (18 %).

242 - ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.21 (5H, m, Ar*H*); 6.00 (1H, ddd, *J* = 9.8, 1.7, 1.7 Hz, PhCHCH=C*H*); 5.66 (1H, ddd, *J* = 9.8, 4.1, 2.9 Hz, PhCHC*H*); 4.25 (1H, qd, *J* = 10.8, 7.1, $CO_2CH_AH_B$); 4.20 (1H, dq, *J* = 10.8, 7.1 Hz, $CO_2CH_AH_B$); 4.11-4.10 (1H, m, PhC*H*); 3.71 (1H, dd, *J* = 5.7, 2.3 Hz, C*H*OH); 2.28 (1H, dqd, *J* = 9.3, 7.0, 2.3 Hz, Et_2OCCHC*H*(CH_3)CH(OTBS)); 2.05 (1H, ddddd, *J* = 12.1, 9.3, 2.0, 2.0, 2.0, CH=CHC*H*); 1.68 (1H, dqd, *J* = 6.8, 6.8, 5.7 Hz, CH=CHCHC*H*(CH_3)); 1.61 (1H, br s, O*H*); 1.37 (1H, dd, *J* = 9.3, 5.1 Hz, Et_2OCC(CH_3)C*H*); 1.32 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); 1.11 (3H, d, *J* = 6.8 Hz, CH=CHCHCH(CH_3)); 1.01 (3H, d, *J* = 7.0 Hz, Et_2OC(CH_3)CHCH(CH_3)); 0.90 (3H, s, Et_2OCC(CH_3)); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.7; 140.8; 130.6; 130.1; 128.4; 127.7; 126.7; 83.6; 60.7; 51.7; 50.4; 48.7; 45.2; 43.6; 41.3; 23.5; 21.3; 14.3; 11.2; **IR** (film, cm^{-1}) 3452; 2965; 2929; 2286; 1722; 1491; 1451; 1378; 1232; 1206; 1101; 1024; 759; 704; $[\alpha]_D^{20}$ = + 57 (*c* 0.5, $CHCl_3$).

243 - ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.10 (5H, m, Ar*H*); 6.04 (1H, ddd, *J* = 10.0, 2.9, 2.9 Hz, PhCHCH=C*H*); 5.78 (1H, ddd, *J* = 7.3, 2.9, 2.2 Hz, PhCHC*H*); 4.23 (1H, dq, *J* = 11.1, 7.1, $CO_2CH_AH_B$); 4.17 (1H, dq, *J* = 11.1, 7.0 Hz, $CO_2CH_AH_B$); 3.89 (1H, dd, *J* = 4.5, 3.9 Hz, C*H*OH); 3.32 (1H, ddd, *J* = 3.1; 3.1; 2.3 Hz, PhC*H*); 2.57 (1H, ddddd, *J* = 12.5, 10.4, 3.1, 3.1, 3.1, CH=CHC*H*); 2.26(1H, dqd, *J* = 12.5, 6.7, 3.9 Hz, CH=CHCHC*H*(CH_3)); 2.08 (1H, dd, *J* = 10.4, 7.8 Hz,

$Et_2OCC(CH_3)CH$); 1.90 (1H, dqd, *J* = 7.8, 7.0, 4.5 Hz, $Et_2OCCHCH(CH_3)CH(OTBS)$); 1.24 (3H, s, $Et_2OCC(CH_3)$); 1.23 (3H, d, *J* = 7.0 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 1.23 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.12 (3H, d, *J* = 6.6 Hz, $CH=CHCHCH(CH_3)$).

(1*S*, 3*S*, 3a*R*, 4*S*, 5*R*, 7a*R*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (244)

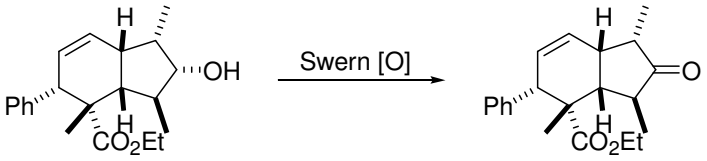


241 **244**

As per the procedure for **237** using alcohol **241** (26.8 mg, 0.082 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.42) yielded 19.2 mg (71 %) of ketone **244** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.21 (5H, m, Ar*H*); 6.06 (1H, d, *J* = 9.6 Hz, $CH(Ph)CH=CH$); 5.78 (1H, ddd, *J* = 9.6, 4.2, 2.4 Hz, $CH(Ph)CH=CH$); 4.21 (1H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 4.15 (1H, m, $CH(Ph)$); 2.63 (1H, dq, *J* = 12.0, 7.2 Hz, $CCHCH(CH_3)$); 2.02-1.93 (2H, m, $CH(CH_3)CHCH=CH$, $CH=CHCH$); 1.68 (1H, t, *J* = 11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 1.27 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.20 (3H, d, *J* = 6.0 Hz, $CH(CH_3)CHCH=CH$); 1.08 (3H, d, *J* = 7.2 Hz, $CCHCH(CH_3)$); 0.97 (3H, s, $C(CH_3)(CO_2Et)$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 220.7; 176.0; 139.9; 130.6 (2); 128.0; 127.0; 126.7; 60.9; 49.9; 48.5; 48.4; 48.2; 45.9; 44.3; 23.8; 16.2; 14.3; 12.2; **IR** (film, cm^{-1}) 3024; 2971; 2931; 2873; 1741; 1726; 1451; 1259; 1210; 1129; 1092; 705; $[\alpha]_D^{20}$ = + 175 (*c* 1.0, $CHCl_3$); **HRMS (ESI)** $C_{21}H_{26}NaO_3^+$ requires 349.1774, found 349.1771; **LREIMS** 326 (6.6 %); 308 (68 %); 253 (24 %); 235 (100 %); 225 (6.6 %); 207 (6.6 %); 195 (10 %); 181 (7.4 %); 169 (34 %); 157 (19 %); 141 (24 %); 129 (14 %); 113 (25 %); 105 (7.4 %); 91 (19 %).

(1*S*, 3*S*, 3a*R*, 4*S*, 5*S*, 7a*S*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (245)

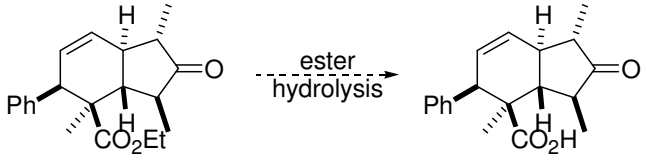


242 **245**

As per the procedure for **237** using alcohol **242** (11 mg, 0.0.335 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.36) yielded 10.5 mg (96 %) of ketone **245** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.27 (2H, m, Ar*H*); 7.30-7.27 (1H, m, Ar*H*); 7.24-7.22 (2H, m, Ar*H*); 6.08 (1H, ddd, *J* = 9.6, 1.2, 1.2 Hz, PhCHCH=C*H*); 5.79 (1H, ddd, *J* = 9.6, 4.2, 4.2 Hz, PhCHC*H*=CH); 4.22 (1H, q, *J* = 7.2 Hz, $CO_2CH_AH_BCH_3$); 4.16 (1H, m, C*H*(Ph)); 3.23 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_BCH_3$); 2.65 (1H, dq, *J* = 11.4, 7.2 Hz, CCHC*H*(CH_3)), 1.99 (1H, ddddd, *J* = 11.4, 11.4, 2.4, 2.4, 2.4, CH=CHC*H*); 1.98 (1H, dq, *J* = 6.6, 6.6 Hz, C*H*(CH_3)CHCH=CH); 1.69 (1H, dd, *J* = 11.4, 11.4 Hz, C(CH_3)(CO_2Et)C*H*CH(CH_3)); 1.28 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.22 (3H, d, *J* = 6.6 Hz, CH(C*H*$_3$)CHCH=CH); 1.10 (3H, d, *J* = 7.2 Hz, CCHCH(C*H*$_3$)); 0.98 (3H, s, C(C*H*$_3$)(CO_2Et)); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.8; 176.0; 139.9; 130.6; 130.6; 128.0; 127.0; 126.7; 60.9; 49.9; 48.5; 48.4; 48.2; 46.3; 44.3; 23.9; 16.2; 14.3; 12.3; **IR** (film, cm^{-1}) 2967; 2930; 1741; 1726; 1451; 1377; 1259; 1210; 1129; 1022; 762; 705; 672; $[\alpha]_D^{20}$ = + 227 (c 0.6, $CHCl_3$).

Attempts at Ester Hydrolysis



239

1. The ester **239** (3.9 mg, 0.012 mmol) was dissolved in a 50 % EtOH solution (0.4 mL) and KOH (2 M, 6 mL, 0.012 mmol) in H_2O was added at room temperature. The solution was stirred overnight, after which time no reaction was occurring so additional KOH was added and the reaction mixture heated to 50 ^oC overnight. Still no reaction was occurring so the starting material was extracted with Et_2O (15 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo*.

2. To a solution of the ester **239** (5-10 mg) in CH_2Cl_2 (0.5 mL) was added a few drops to CF_3COOH and the solution stirred at room temperature. After several hours no reaction was occurring so additional CF_3COOH was added and the solution left to stir overnight. TLC analysis suggested that still no reaction had occurred so the reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$).

3. To a solution of the ester **239** (4.5 mg, 0.014 mmol) in THF:H_2O (3:1, 0.4 mL) at 0 ^oC was added H_2O_2 (30 % aq., 5.6 μL, 0.055 mmol) and LiOH in H_2O (8.6 mL, 0.28mmol). The resulting solution was stirred at 0 ^oC for 1 hour, 15 minutes after which time TLC analysis indicated that no reaction was occurring. The solution was warmed to room temperature and still no reaction occurred so the reaction was quenched by addition of Na_2SO_3 (1.5 N, 1 mL). The THF was removed in *vacuo* and the starting material extracted into CH_2Cl_2 (3 x 8 mL), the combined extracts were dried (Na_2SO_4) and concentrated in *vacuo*.

4. To a solution of the ester **239** (4.5 mg, 0.014 mmol) in H_2O:MeOH (9:1, 1 mL) was added, at room temperature, a solution of $Ba(OH)_2$ (sat. aq., 200 μL) and the solution stirred overnight at room temperature. The solution was diluted with EtOAc (5 mL) and acidified to pH 1 with HCl (1 M, ~ 1mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined extracts were dried ($NaSO_4$) and concentrated in *vacuo*. Analysis by ^1H NMR revealed that the starting material had been recovered and no product was isolated.

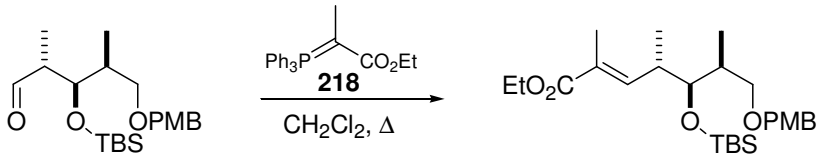
5. To a solution of the ester **239** (5.5 mg, 0.017 mmol) and NaI (7.6 mg, 0.051 mmol) in CH_3CN (200 μL) at room temperature, was added with stirring TMSCl (6.4 μL, 5.5 mg, 0.051 mmol). The resulting yellow solution was heated under reflux overnight before addition of H_2O (10 mL) to quench the silyl ether products. The solution was extracted with Et_2O (3 x 10 mL) and the combined extracts washed with H_2O (10 mL) and $Na_2S_2O_3$ (1 M, 10 mL). Any potential carboxylic acid products were extracted into $NaHCO_3$ (sat. aq., 2 x 10 mL), which was then acidified to pH 1 (1 M HCl) and extracted with

EtOAc (2 x 10 mL). The Et_2O extracts and the EtOAC extracts were dried (Na_2SO_4) separately and concentrated in *vacuo*. ^{1}H NMR analysis of the Et_2O extracts revealed recovered starting material while the EtOAc extracts contained no organic products.

6. To a stirred suspension of K^{t}BuO (16 mg, 0.15 mmol) in ether (300 μL) at 0 ^{o}C was added H_2O (67 μL) *via* a syringe. The resulting slurry was stirred for 5 minutes before addition of the ester **239** (5.5 mg, 0.017 mmol) *via* a cannula in Et_2O (3 x 200 μL). The solution was warmed to room temperature and stirred overnight. TLC analysis the following morning revealed no reaction had occurred so the reaction mixture was diluted with Et_2O (15 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo* to recover the starting material.

6.3.2 Model System Two

(2*E*, 4*S*, 5*S*, 6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-enoic acid ethyl ester ((2*E*)-250)



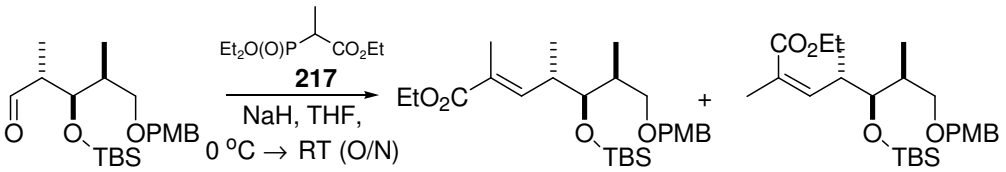
214 **(2*E*)-250**

A solution of aldehyde **214** (0.36 g, 0.94 mmol) and the ylide **218** (0.41 g, 1.13 mmol) in CH_2Cl_2 (6.3 mL) was heated under reflux for 5 days. (TLC analysis was ineffective because the starting material and product had similar R_f values). Solvent was removed in *vacuo* and the product triturated with mixed hexanes to remove the triphenylphosphine oxide. Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.35) yielded 0.44 g (100 %) of the *E*-alkene **(2*E*)-250** as a clear, colourless oil

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.78 (1H, dd, *J* = 9.9, 1.2 Hz, C*H*=C); 4.43 (1H, d, *J* = 11.4 Hz, OCH_AH$_B$Ar); 4.35 (1H, d, *J* = 11.4 Hz, OCH$_A$$H_B$Ar); 4.25 (1H, q, *J* = 6.9 Hz, CH_3CH_2O); 3.81 (3H, s, OCH_3); 3.71 (1H, dd, *J* = 5.4, 3.0 Hz, C*H*OTBS); 3.37 (1H, d, *J* = 9.0, 6.6 Hz, CH_AH$_B$OPMB); 3.16 (1H, d, *J* = 9.0, 6.9 Hz, CH$_A$$H_B$OPMB); 2.69-2.61 (1H, m, C=CHC*H*(CH_3)); 1.97-1.87 (1H, m, CH(OTBS)C*H*(CH_3)CH_2OPMB); 1.79 (3H, d, *J* = 1.2 Hz, EtO(O)C(CH_3)=CH); 1.28

(3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$O); 0.95 (3H, d, J = 7.2 Hz, =CHCH(C*H*$_3$)CH(OTBS)); 0.89 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(C*H*$_3$)CH$_2$OPMB); 0.86 (9H, s, SiC(C*H*$_3$)$_3$); 0.02 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 168.3; 159.1; 145.7; 130.6; 129.2; 126.7; 113.7; 76.1; 72.8; 72.5; 60.3; 55.3; 37.7; 37.6; 26.0; 18.3; 17.5; 14.2; 12.4; 11.8; -3.9; -4.0; **IR** (film, cm^{-1}) 2957; 2931; 2856; 1710; 1613; 1514; 1463; 1365; 1301; 1249; 1173; 1095; 1037; 837; 774; **HRMS (ESI)** found 487.2846, $C_{26}H_{44}O_5SiNa^+$ requires 487.28.50; **LREIMS** 323 (5.3 %); 285 (1.5 %); 187 (6.8 %); 137 (2.3 %); 121 (100 %); 89 (1.5 %); 73 (5.3 %).

(2*E/Z*, 4*S*, 5*S*, 6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-enoic acid ethyl ester ((2*E*)-250 and (2*Z*)-250)



214 **(2*E*)-250** **(2*Z*)-250**

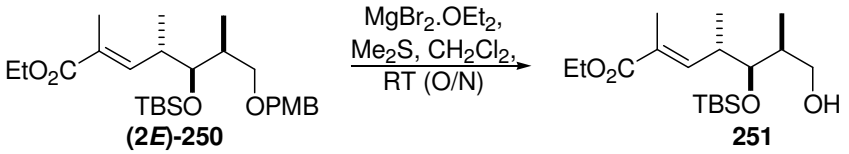
To a solution of NaH (37 mg, 1.54 mmol) (washed with mixed hexanes to remove oil and dried under N_2) in THF (0.23 mL) at 0 ^{o}C was added the phosphonate **217** (0.32 mL, 1.47 mmol) dropwise. The solution was stirred at room temperature for 1 hour before cooling to 0 ^{o}C and addition of aldehyde **214** (0.177g, 0.47 mmol). The solution was warmed slowly to room temperature and the reaction stirred overnight. TLC analysis the next morning was inconclusive so the reaction was quenched by addition of NH_4Cl (sat. aq., 20 mL) and the organics were extracted with Et_2O (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (10 % EtOAc/mixed hexanes, R_f (*Z*) = 0.27, R_f (*E*) = 0.30) yielded 0.945 g (44 %) of the *Z*-isomer **(2*Z*)-250** and 0.0275 g (12 %) of the *E*-isomer **(2*E*)-250** both as clear, colourless oils.

(2*Z*)-221- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, ArH); 6.87 (2H, d, *J* = 8.7 Hz, ArH); 5.94 (1H, d, *J* = 10.2 Hz, C=C*H*); 4.41 (1H, d, *J* = 11.7 Hz, OC*H*$_A$H$_B$Ar); 4.36 (1H, d, J = 11.7 Hz, OCH$_A$*H*$_B$Ar); 4.17 (2H, q, *J* = 7.2 Hz, CH$_3$C*H*$_2$O); 3.80 (3H, s, OC*H*$_3$); 3.64 (1H, apt t, *J* = 4.2 Hz, C*H*(OTBS)); 3.39 (1H, dd, *J* = 9.0, 4.8 Hz, C*H*$_A$H$_B$OPMB); 3.48-3.43 (1H, m, =CHC*H*(CH$_3$)); 3.16 (1H, dd, *J* = 9.0, 7.5 Hz, CH$_A$*H*$_B$OPMB); 1.98-1.87 (1H, m, C*H*(CH$_3$)CH$_2$OPMB); 1.87 (3H, d, *J* = 1.5 Hz, (C*H*$_3$)C=CH); 1.29 (3H, t, J = 7.2 Hz, C*H*$_3$CH$_2$O); 0.97 (3H, d, *J* = 6.6 Hz, =CHCH(C*H*$_3$)); 0.90-0.86 (12H, m, SiC(C*H*$_3$)$_3$, CH(OTBS)CH(C*H*$_3$)CH$_2$OPMB); 0.03 (6H, s, Si(CH$_3$)$_2$); **^{13}C NMR** (75.5 MHz,

$CDCl_3$) δ 168.0; 159.1; 145.6; 130.8; 129.2; 126.0; 113.7; 76.8; 72.8; 72.5; 60.0; 55.3; 38.3; 37.3; 26.1; 21.0; 18.6; 18.4; 14.3; 12.4; -3.9; -4.0

(2*E*)-221- *data as reported above for the Wittig olefination.*

(2*E*, 4*S*, 5*S*, 6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-hydroxy-2,4,6-trimethylhept-2-enoic acid ethyl ester (251)

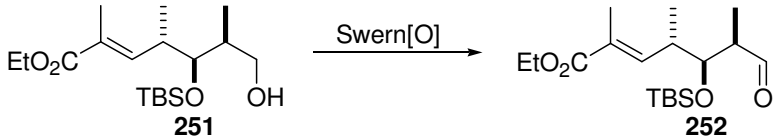


(2*E*)-250 **251**

To a solution of the PMB ether **(2*E*)-251** (126 mg, 0.27mmol) in dry CH_2Cl_2 (4.5 mL) at room temperature was added Me_2S (201 μL, 2.74 mmol) and powdered $MgBr_2.OEt_2$ (0.21 g, 0.81 mmol). The mixture was stirred for 24 - 48 hours at room temperature until TLC analysis showed consumption of the starting material. The reaction was quenched by addition of NH_4Cl (sat. aq., 30 mL) and the product was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (5 % Et_2O/CH_2Cl_2, R_f = 0.31) yielding 78 mg (84 %) of alcohol **251** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (1H, dd, *J* = 10.2, 1.5 Hz, C(CH_3)=C*H*); 4.23-4.14 (2H, m, OC$H_2$$CH_3$); 3.74 (1H, dd, *J* = 5.1, 3.0 Hz, C*H*(OTBS)); 3.59 (1H, dd, *J* = 10.5, 7.5 Hz, C$H_A$$H_B$OH); 3.42 (1H, dd, *J* = 10.5, 6.0 Hz, $CH_A$$H_B$OH); 2.89-2.69 (1H, m, C(CH_3)=CHC*H*(CH_3)); 1.94-1.84 (1H, m, CH(OTBS)C*H*(CH_3)CH_2OH); 1.85 (3H, d, *J* = 1.5 Hz, C(CH_3)=CH); 1.75 (1H, br s, O*H*); 1.28 (3H, t, *J* = 6.9 Hz, OCH_2CH_3); 0.99 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)CH(OTBS)); 0.92 (3H, d, *J* = 7.2 Hz, CH(OTBS)CH(CH_3)CH_2OH); 0.89 (9H, s, SiC(CH_3)$_3$); 0.08 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.06 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 168.2; 145.2; 126.8; 76.9; 65.5; 60.4; 40.1; 36.8; 26.0; 18.2; 17.8; 14.2; 12.5; 11.8; -4.05; -4.09; **IR** (film, cm^{-1}) 3450; 2959; 2932; 2885; 2858; 1710; 1473; 1463; 1388; 1367; 1295; 1251; 1097; 1034; 1006; 860; 837; 774; 751; 668; $[\alpha]_D^{20}$ = -12.8 (*c* 0.7, $CHCl_3$); **HRMS (ESI)** $C_{18}H_{36}NaO_4Si^+$ requires 367.2275, found 367.2273; **LREIMS** 285 (7 %); 257 (8.5 %); 241 (8.5 %); 213 (8.5 %); 203 (41 %); 145 (52 %); 121 (61 %); 105 (21 %); 84 (82 %); 83 (98 %); 75 (100 %); 57 (28 %).

(2*R*, 3*S*, 4*S*, 5*E*)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-7-oxo-hept-2-enoic acid ethyl ester (252)

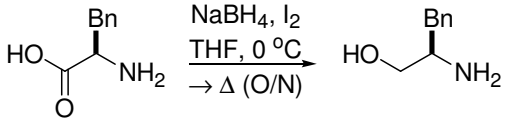


251 **252**

Oxalyl chloride (84 μL, 0.17 mol) was added dropwise to a solution of DMSO (24 μL, 0.33 mmol) in CH_2Cl_2 (500 μL) at -78 ^oC. The resulting solution was stirred at -78 ^oC for 30 minutes. A solution of the alcohol **251** (19 mg, 0.056 mmol) in CH_2Cl_2 (0.25 mL, 0.25 mL, 0.25 mL) was added *via* a cannula to the reaction mixture, dropwise. The resulting mixture was stirred for 45 minutes at -78 ^oC. Et_3N (93 μL, 0.67 mmol) was added dropwise over several minutes and stirred at -78 ^oC for 30 minutes before warming to 0 ^oC and stirring for 30 minutes. The reaction mixture was quenched by addition of NH_4Cl (sat. aq., 20 mL), and the product extracted with CH_2Cl_2 (3 x 20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.44) yielding 15.6 mg (82 %) of aldehyde **252** a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, apt s, C*H*O); 6.73 (1H, dd, *J* = 10.2, 1.5 Hz, C*H*=C(CH_3)CO_2Et); 4.25-4.12 (2H, m, OC$H_2$$CH_3$); 4.06 (1H, apt t, *J* = 4.8 Hz, C*H*(OTBS)); 2.78-2.64 (1H, m, CH(OTBS)C*H*(CH_3)CH=); 2.54-2.43 (1H, m, CH(=O)C*H*(CH_3)); 1.80 (3H, d, *J* = 1.5 Hz, CH=CH(CH_3)); 1.28 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); 1.09 (3H, d, *J* = 6.9 Hz, CH(=O)CH(CH_3)); 1.01 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)CH(OTBS)); 0.87 (9H, s, SiC(CH_3)$_3$); 0.07 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.02 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 204.1; 167.9; 143.2; 128.3; 75.6; 60.5; 51.3; 37.3; 25.8; 18.2; 17.6; 14.2; 12.6; 8.6; -4.0; -4.3; **IR** (film, cm^{-1}) 2956; 2929; 2884; 2856; 1720; 1472; 1462; 1449; 1253; 1099; 1030; 990; 837; 775; 749; 692; $[\alpha]_D^{20}$ = -33.3 (*c* 0.8, $CHCl_3$); **HRMS (ESI)** $C_{18}H_{34}NaO_4Si^+$ requires 365.2119, found 365.2113; **LREIMS** 342(3.4 %); 317 (3.4 %); 301 (3.4 %); 285 (3.4 %); 271 (3.4 %); 239 (3.4 %); 227 (5.1 %); 210 (5.1 %); 199 (8.5 %); 185 (8.5 %); 169 (8.5 %); 153 (14 %); 115 (31 %); 111 (25 %); 85 (16 %); 75 (100 %); 73 (70 %); 69 (37 %).

(2*R*)-2-amino-3-phenylpropan-1-ol (254)

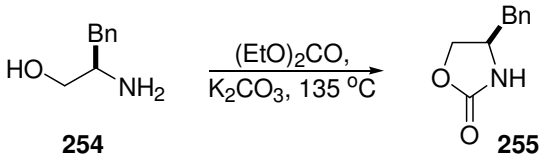


(*L*)-phenylalanine **254**

To a solution of $NaBH_4$ (5.5 g, 145 mmol) in THF (161 mL) was added (*L*)-phenylalanine (10 g, 61 mmol) in one portion. They system was flushed with nitrogen and cooled to 0 °C. A solution of I_2 (15.5 g, 61 mmol) in THF (40 mL) was added dropwise over 30 minutes, during which time H_2 was evolved. After complete addition of I_2 and H_2 evolution had ceased the solution was heated to reflux for 18 hours. The solution was cooled to room temperature and methanol added slowly until the solution became clear. The resulting solution was stirred for 30 minutes before concentrating in *vacuo*. The white paste was dissolved in KOH (20 % aq., 110 mL) and the solution stirred for 5 hours. The product was extracted with CH_2Cl_2 (3 x 110 mL) dried ($MgSO_4$) and concentrated in *vacuo*. Recrystallisation from toluene overnight in the freezer yielded 6.47 g (70 %) of the alcohol **254** as a white powder with spectroscopic data consistent with that reported.[81]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (5H, m, Ar*H*); 3.65 (1H, dd, *J* = 10.5, 3.9 Hz, CH_AH$_B$OH); 3.41 (1H, dd, *J* = 10.5, 7.2 Hz, CH$_A$$H_B$OH); 3.15 (1H, m, C*H*NH$_2$); 2.80 (1H, dd, *J* = 13.5, 5.7 Hz, CH_AH$_B$Ar); 2.57 (1H, dd, *J* = 13.5, 8.7 Hz, CH$_A$$H_B$Ar); 2.33 (3H, br s, N$H_2$, O*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 152.7; 138.4; 129.2; 128.6; 126.5; 65.9; 54.2; 40.5.

(4*R*)-4-benzyloxazolidin-2-one (255)



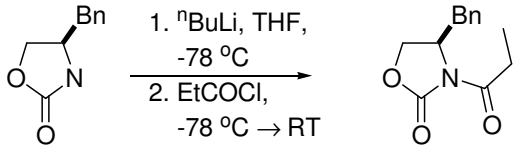
254 **255**

A mixture of alcohol **254** (7.00g, 46 mmol), anhydrous potassium carbonate (0.64 g, 4.6 mmol) and diethyl carbonate (11.6 mL, 95 mmol) was heated to 135 °C (oil bath) and the ethanol generated by the reaction as collected *via* distillation into a pre-cooled receiver flask. The solution was cooled to room temperature and diluted with CH_2Cl_2 (36 mL) and washed with H_2O (36 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Hot filtration of the white solid in EtOAc:mixed hexanes (2:1) and subsequent

cooling to allow precipitation yielded 6.08g (74 %) of oxazolodinone **255** as large, white plates with spectroscopic data consistent with that reported.[81]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (3H, m, Ar*H*); 7.17 (2H, d, *J* = 8.1 Hz, Ar*H*); 5.58 (1H, br s, N*H*); 4.45 (1H, t, *J* = 7.8 Hz, OCH_AH$_B$); 4.16 (1H, t, *J* = 7.8 Hz, OCH$_A$$H_B$); 4.11 (1H, tt, *J* = 6.9, 6.6 Hz, C*H*NH); 2.88 (2H, d, *J* = 6.6 Hz, CH_2Ar); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.2; 135.9; 129.01; 128.96; 127.3; 69.6; 53.7; 41.5.

(4*R*)-4-benzyl-3-propionyloxazolidin-2-one ((*R*)-41a)

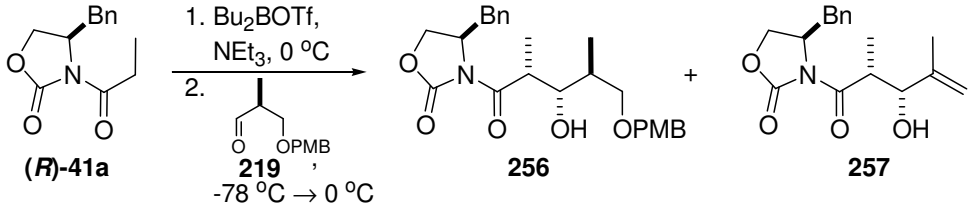


255 **(*R*)-41a**

To a cooled (-78 °C) solution of the oxazolidinone **255** (6.08 g, 34.3 mmol) in THF (104 mL) was added ^{n}BuLi (1.35 M in hexanes, 25.6 mL), dropwise. Freshly distilled propionyl chloride (3.28 mL, 3.50 g, 37.8 mmol) was added and the resulting solution stirred for 30 minutes at -78 °C before warming to room temperature and stirring for a further 30 minutes. Excess propionyl chloride was quenched by the addition of NH_4Cl (sat. aq., 20 mL) and the THF removed in *vacuo*. The resulting slurry was extracted with CH_2Cl_2 (2 x 150 mL) and the combined extracts washed with NaOH (1 M, 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The light yellow oil was placed in the fridge for two days to crystallise. The solid was then triturated with cold hexane and the resulting colourless crystals filtered and dried yielding 7.1 g (93 %) of the acylated oxazolidinone **(*R*)-41a** as colourless needles with spectroscopic data consistent with that reported.[83]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.18 (5H, m, Ar*H*); 4.67 (1H, m, NC*H*); 4.24-4.14 (2H, m, CH_2Ar); 3.30 (1H, dd, *J* = 13.2, 3.3 Hz, OCH_AH$_B$); 2.99 (1H, qd, *J* = 7.2, 6.3 Hz, C(=O)CH_AH$_B$); 2.93 (1H, qd, *J* = 7.2, 6.3 Hz, C(=O)CH$_A$$H_B$); 2.77 (1H, dd, *J* = 13.2, 9.6 Hz, OCH$_A$$H_B$); 1.20 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$).

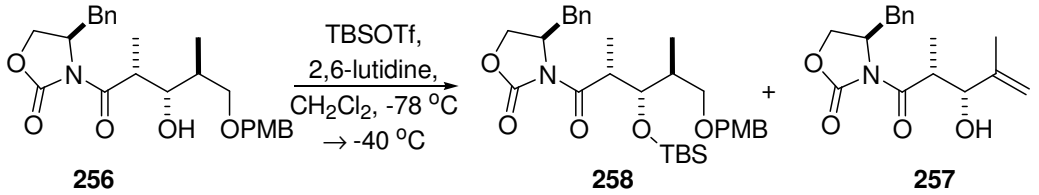
(4*R*)-3-[2*R*,3*S*,4*R*]-4-benzyl-3-[3-hydroxy-5-(4'-methoxybenzyloxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (256)



To a solution of the N-acylated oxazolidineone **(*R*)-41a** (1.15 g, 7.34 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added Bu_2BOTf (1 M in CH_2Cl_2, 8.8 mL) and the resulting dark orange solution stirred at 0 °C for 30 minutes. NEt_3 (1.33 mL, 9.54 mmol) was added dropwise and the solution turned pale yellow and was stirred for 30 mintes at 0 °C, before cooling to -78 °C. A solution of the aldehyde **219** in CH_2Cl_2 (3 mL, 2 mL, 1 mL) was added over 5 minutes and the yellow solution stirred at -78 °C for 30 minutes and then warmed to 0 °C. The solution was stirred at this temperature until TLC analysis showed no more consumption of the aldehyde. (~ 4 hours). The reaction was quenched by the addition of pH 7 buffer (15 mL), methanol (45 mL) and to this cloudy solution was added carefully at 0 °C a solution of methanol:H_2O_2 (30 % w/v) (45 mL) and the resulting solution stirred at room temperature for 1 hour, giving a homogeneous solution. The volatiles were removed in *vacuo* and the product extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with $NaHCO_3$ (sat. aq., 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (5 % Et_2O/CH_2Cl_2, R_f = 0.30) yielding 0.662 g of a mixture of the suspected alcohol **256**[306] (51 %, > 95 % ds) and the dehydrated adduct **257** as a clear, colourless oil.

256/257 - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.21 (m, Ar*H*); 6.92-6.86 (m, Ar*H*); 5.16 (br s, =CH_AH$_B$); 4.98 (br s, =CH$_A$$H_B$); 4.75-4.62 (1H, m); 4.62 (1H, s); 4.44 (2H, s); 4.24-4.15 (2H, m); 4.00-3.85 (2H, m); 3.82 (1H, s); 3.80 (3H, s); 3.60-3.45 (1H, m); 1.75 (1H, s); 1.26 (3H, d, *J* = 6.6Hz, CH_3); 1.22 (3H, t, *J* = 7.5 Hz, CH_3); 0.95 (3H, d, *J* = 6.9 Hz, CH_3).

(4*R*)-3-[2*R*,3*S*,4*S*]-4-benzyl-3-[3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (258)

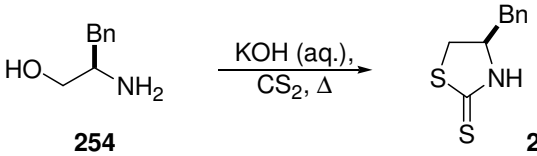


256 **258** **257**

To a solution of the alcohol **256** (0.66 g, 1.50 mmol) in CH_2Cl_2 (15 mL) at -78 °C was added 2,6-lutidine (0.349 mL, 0.321 g, 3.00 mmol) followed immediately by TBSOTf (0.508 mL, 0.594 g, 2.25 mmol). The solution was stirred at this temperature for 2 hours before warming to -40 °C to drive the reaction to completion by TLC analysis. The reaction was quenched by the addition of $NaHCO_3$ (sat. aq., 100 mL) and the reaction mixture was warmed to room temperature. The product was extracted with CH_2Cl_2 (3 x 100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.43) yielded 0.22 g (27 %) of the TBS ether **258**, while the alkene **257** was the dominant product.

258 - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.18 (7H, m, Ar*H*); 6.83 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.52-4.44 (1H, m, C*H*N); 4.38 (1H, d, *J* = 11.7 Hz, OCH_AH_BAr); 4.33 (1H, d, *J* = 11.7 Hz, OCH_AH_BAr); 4.06-3.97 (3H, m); 3.78 (1H, dd, *J* = 9.3, 6.9 Hz); 3.77 (3H, s, OCH_3); 3.54 (1H, dd, *J* = 9.3, 5.7 Hz); 3.24-3.14 (2H, m); 2.71 (1H, d, *J* = 13.9, 9.6 Hz); 2.02-1.92 (1H, m, $CH(CH_3)CH_2$); 1.24 (3H, d, *J* = 6.6 Hz, CH_3); 1.01 (3H, d, *J* = 6.9 Hz, CH_3); 0.90 (9H, s, $SiC(CH_3)_3$); 0.07 (6H, s, $Si(CH_3)_2$).

(4*R*)-4-benzylthiazolidine-2-thione (259)



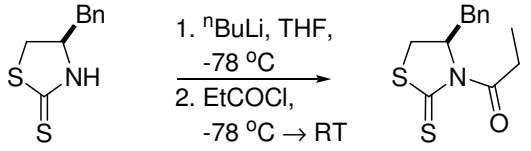
254 **259**

To a solution of the β-amino alcohol **254** in aqueous KOH (1M, 214 mL) was added CS_2 (12.9 mL, 16.3 g, 214 mmol). The reaction mixture was heated under reflux (110 °C oil bath) overnight. After cooling to room temperature the reaction mixture was extracted with CH_2Cl_2 (2 x 250 mL) and the combined extracts dried ($MgSO_4$) and concentrated in *vacuo*. The product was recrystallised from EtOH to give 5.83 g (65 %) of thiazolidinethione **259** as a fine white powder.[256]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (5H, m, Ar*H*); 4.47 (1H, apt qn, *J* = 7.2 Hz C*H*Bn); 3.61 (1H, dd, *J* = 11.1, 7.8 Hz, $CHCH_AH_BAr$); 3.34 (1H, dd, *J* = 11.1, 6.6

Hz, $CHCH_AH_BAr$); 3.02 (2H, qd, J = 7.8, 3.6 Hz, CH_2S); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 201.0; 135.9; 129.2; 129.0; 127.5; 65.0; 40.1; 38.3.

(4'*R*)-1-(4'-benzyl-2-thioxothiazolidin-3-yl)-propan-1-one ((*R*)-43a)

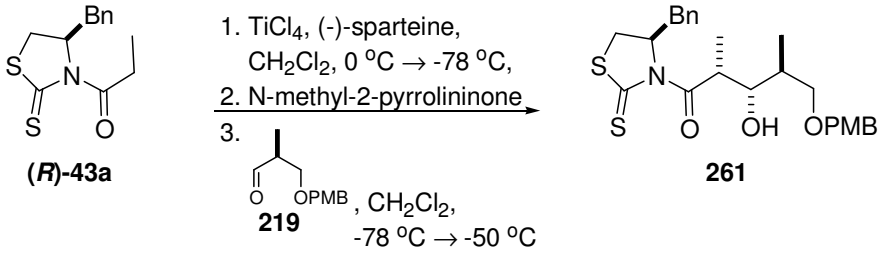


259 **(*R*)-43a**

To a solution of the thiazolidinethione **259** (5.83 g, 28 mmol) in THF (127 mL) at -78 °C was added dropwise ^{n}BuLi (1.6 M in hexanes, 18.4 mL, 28 mmol). The lithiated species was stirred for 15-20 minutes at -78 °C before dropwise addition of propionyl chloride (3.1 mL, 36 mmol). The solution was stirred at -78 °C for 15 minutes before warming to room temperature and stirring for 1.5 hours. TLC analysis indicated that the reaction was failing to proceed further after this time so the solution was cooled to –78 °C and additional propionyl chloride was added (1.6 mL, 16 mmol). The solution was stirred at – 78 °C for 30 minutes before warming to room temperature for 1 hour. Again TLC analysis indicated that the reaction had not proceeded further so the reaction was quenched by addition of K_2CO_3 (10 % aq.) until formation of a white semi-solid ceased. The solvent was removed in *vacuo* and the product extracted with CH_2Cl_2 (2 x 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was recrystallised from EtOAc yielding 5.54 g (75 %) of N-acylated thiazolidinethione **(*R*)-43a** as needle-like yellow crystals (m.p. 100-102 °C), with spectroscopic data consistent with that reported.[256]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m, Ar*H*); 5.40 (1H, apt ddd, J = 10.8, 7.2, 3.9 Hz, C*H*Bn); 3.50-3.37 (2H, m, C(=O)CH_AH_B, CH_AH_BAr); 3.26-3.02 (3H, m, SCH_2, C(=O)CH_AH_B); 2.90 (1H, d, J = 11.4 Hz, CH_AH_BAr); 1.21 (3H, t, J = 7.2 Hz, CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 201.1; 174.9; 136.6; 129.4; 128.9; 127.2; 68.6; 36.8; 32.3; 31.9; 8.8; **IR** (film, cm^{-1}) 2978; 1701; 1495; 1454; 1343; 1293; 1264; 1192; 1166; 1137; 1040; 812; 746; 702; $[\alpha]_D^{20}$ = + 217 (*c* 1.2, $CHCl_3$).

(1-(4'*R*)-2*R*,3*S*,4*S*)-1-(4'-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentan-1-one (261)



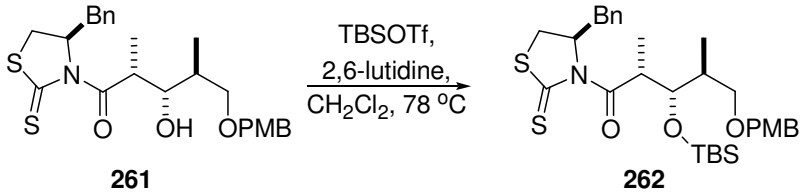
To a solution of the N-acylthiazolidinethione **(*R*)-43a** (2.29 g, 8.65 mmol) in CH_2Cl_2 (55 mL) at 0 °C was added $TiCl_4$ (9 mL, 9.07 mmol) dropwise. The solution was allowed to stir for 5 minutes at 0 °C before (-)-sparteine (2 mL, 2.03 g, 8.65 mmol) was added dropwise to the suspension. The dark red enolate was stirred for 20 minutes at 0 °C before cooling to -78 °C and addition of N-methyl-2-pyrrolininone (0.83 mL, 8.65 mmol) dropwise. The solution was stirred for 10 minutes. at -78 °C before addition of the aldehyde **219** (0.90 g, 4.32 mmol) in CH_2Cl_2 (3 mL, 1 mL x 2). The resulting mixture was stirred at -78 °C → -50 °C for 2.5 hours before placing overnight in the -80 °C freezer. The next morning the reaction was warmed to -50 °C for 3 hours however TLC analysis showed no further reaction. The reaction was quenched by addition of NH_4Cl (half sat. aq., 80 mL). The product was extracted with CH_2Cl_2 (2 x 100 mL) and the combined extracts washed with brine (80 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2 → 2.5 % Et_2O/CH_2Cl_2, R_f (2.5 % Et_2O/CH_2Cl_2) = 0.28 (iso 1), 0.17 (iso 2 & 3)) yielded 1.29 g (63 %) of isomer **261** (desired isomer) and 0.29 (14 %) of a mixture of two minor isomers as clear, yellow oils.

Major Isomer 231 - ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.23 (8H, m, Ar*H*); 6.87 (2H, d, *J* = 8.4 Hz, Ar*H*); 5.27 (1H, ddd, *J* = 10.5, 6.6, 3.3 Hz, C*H*Bn); 4.57 (1H, apt qn, *J* = 6.9 Hz, C(=O)C*H*(CH_3)); 4.44 (1H, d, *J* = 12.6 Hz, OC$H_A$$H_B$Ar); 4.39 (1H, d, *J* = 12.6 Hz, OC$H_A$$H_B$Ar); 3.97 (1H, dd, *J* = 6.3, 4.8 Hz, C*H*OTBS); 3.80 (3H, s, OCH_3); 3.44 (2H, m, CH_2OPMB); 3.35 (1H, dd, *J* = 11.4, 6.9 Hz, CHC$H_A$$H_B$Ar); 3.21 (1H, dd, *J* = 13.2, 3.9 Hz, SC$H_A$$H_B$); 3.03 (1H, dd, *J* = 13.2, 10.5 Hz, SC$H_A$$H_B$); 2.89 (1H, d, *J* = 11.4 Hz, CHC$H_A$$H_B$Ar); 1.79 (1H, m, C*H*($CH_3$)$CH_2$OPMB); 1.33 (3H, d, *J* = 6.9 Hz, C(=O)CH(CH_3)); 1.00 (3H, d, *J* = 7.2 Hz, CH(CH_3)CH_2OPMB); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 200.9; 177.9; 159.2; 136.4; 130.2; 129.4; 129.2; 129.0; 127.2; 113.8; 75.2; 73.9; 73.1; 68.7; 55.3; 41.9; 36.7; 36.4; 32.1; 13.1; 12.2; **IR** (film, cm^{-1}) 3483; 2932; 1684; 1653; 1612; 1558; 1513; 1456; 1341; 1299; 1249;

1165; 1135; 1031; 820; 702; $[\alpha]_D^{20}$ = +143.6 (c 1.5, $CHCl_3$); **HRMS (ESI)** $C_{25}H_{31}NNaO_4S_2^+$ requires 496.1587, found 496.1582; **LREIMS** 352 (7.1 %); 276 (12 %), 264 (56 %); 210 (100 %); 121 (71 %); 117 (14 %).

Minor Isomers - ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 -7.21 (7H, m, ArH); 6.86 (2H, d, *J* = 8.7 Hz, ArH); 5.25 (1H, ddd, *J* = 10.5, 6.6, 3.9 Hz, C*H*Bn); 4.76 (1H, qd, *J* = 6.6, 3.6 Hz, C(=O)C*H*(CH_3)), 4.44 (2H, s, OCH_2Ar); 3.90 (1H, dd, *J* = 8.1, 3.6 Hz, CH(OH)); 3.80 (3H, s, OCH_3); (3.59-3.29 (4H, m) & 3.05 (1H, dd, *J* = 12.9, 10.8 Hz) & 2.86 (1H, d, *J* = 11.4 Hz) CH_2OPMB, CH_2S, CHCH_2Ar)); 1.95-1.86 (1H, m, C*H*(CH_3)CH_2OPMB); 1.24 (3H, d, *J* = 6.6 Hz, C(=O)CH(CH_3)); 0.89 (3H, d, *J* = 6.9 Hz, CH(CH_3)CH_2OPMB); ^{13}**C NMR** (75.5 MHz, $CDCl_3$) 201.2; 201.1; 177.8; 177.4; 159.3; 159.2; 152.4; 136.6; 136.5; 130.1; 129.7; 129.4; 129.4; 129.3; 129.3; 128.9; 127.2; 127.1; 113.9; 113.8; 76.3; 74.9; 74.3; 74.2; 73.2; 73.1; 69.8; 69.1; 65.8; 55.2; 42.2; 41.7; 37.1; 36.6; 36.1; 36.0; 32.0; 31.7; 15.2; 13.9; 13.6; 10.6; 9.6.

(1(4'*R*), 2*R*, 3*S*, 4*S*)-1-(4'-benzyl-2-thioxothiazolidin-3-yl)-3-(*tert*-butyldimethylsilyloxy)-5-(4''-methoxybenzyloxy)-2,4-dimethylpentan-1-one (262)



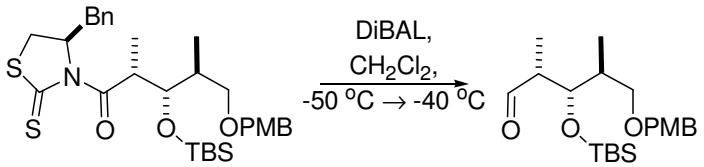
261 **262**

To a solution of the alcohol **261** (0.82 g, 1.74 mmol) in CH_2Cl_2 (17.4 mL) at -78 °C was added 2,6-lutidine (0.30 mL, 0.28 g, 2.61 mmol), followed immediately by TBSOTf (0.59 mL, 0.69 g, 2.61 mmol). The solution was stirred at -78 °C for 30 minutes, after which time TLC analysis indicated consumption of starting material. The reaction was quenched by the addition of $NaHCO_3$ (sat. aq., 20 mL) and was warmed to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % mixed hexanes/CH_2Cl_2, R_f = 0.49) yielding 0.99 g (98 %) of TBS ether **262** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (8H, m, Ar*H*); 6.86 (2H, d, *J* = 8.4 Hz, Ar*H*); 5.21 (1H, ddd, *J* = 10.2, 6.6, 3.9 Hz, C*H*Bn); 4.50 (1H, qd, *J* = 8.4, 6.9 Hz, C(=O)C*H*(CH_3)); 4.43 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ar); 4.38 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ar); 4.09 (1H, dd, *J* = 8.4, 2.1 Hz, C*H*(OTBS)); 3.78 (3H, s, OCH_3); 3.40

(1H, dd, J = 9.3, 6.6 Hz, CH_AH$_B$OPMB); 3.31 (1H, dd, *J* = 11.7, 7.2 Hz, CH_AH$_B$Ar); 3.25-3.17 (2H, m, CH$_A$$H_B$OPMB, SC$H_AH_B$); 3.03 (1H, dd, *J* = 13.2, 10.2, SCH$_A$$H_B$); 2.86 (1H. d, *J* = 11.7 Hz, CH$_A$$H_B$Ar); 1.82-1.75 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$OPMB); 1.26 (3H, d, *J* = 6.6 Hz C(=O)CH(CH_3)); 0.89-0.87 (12H, m, SiC(CH_3)$_3$, CH(CH_3)CH$_2$OPMB); 0.09 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$); 0.03 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 200.8; 177.3; 159.1; 136.6; 130.7; 129.5; 129.2; 128.9; 127.2; 113.7; 75.0; 72.8; 72.6; 69.0; 55.3; 43.1; 38.9; 36.6; 32.1; 26.1; 18.4; 15.5; 11.6; -3.7; -4.1; **IR** (film, cm^{-1}) 2930; 2856; 1693; 1613; 1513; 1462; 1362; 1341; 1250; 1062; 1109; 1032; 838; 775; $[\alpha]_D^{20}$ = +119.6 (*c* 0.9, $CHCl_3$); **HRMS (ESI)** $C_{31}H_{45}NO_4S_2SiNa^+$ requires 610.2456, found 610.2451; **LREIMS** 530 (21 %); 482 (21 %); 466 (22 %); 330 (39 %); 319 (20 %); 286 (16 %); 276 (33 %); 264 (90 %); 228 (44 %); 201 (14 %); 135 (15 %); 121 (100 %).

(2*R*, 3*S*, 4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentanal (253)



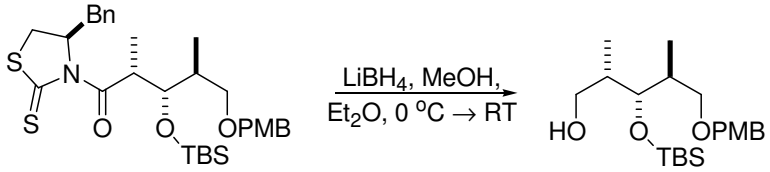
262 **253**

A solution of diisobutylaluminium hydride (1 M in toluene, 48 μL, 0.05 mmol) was added dropwise to a solution of the N-acylthiazolidinethione **262** (31 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at -50 °C → -40 °C. The reaction mixture was stirred for approx. 2 minutes when the yellow colour disappeared. The reaction was stirred for 15 minutes in total before the reaction was quenched by the addition of MeOH (several drops). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The product was purified by column chromatography (35 % EtOAC/mixed hexanes, R_f = 0.56) yielding 6.5 mg (33 %) of aldehyde **253** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, apt s, C*H*(=O)); 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (1H, d, *J* = 8.7 Hz, Ar*H*); 4.43 (1H, d, *J* = 11.4 Hz, OCH_AH$_B$Ar); 4.37 (1H, d, *J* = 11.4 Hz, OCH$_A$$H_B$Ar); 4.22 (1H, dd, *J* = 4.8, 3.6 Hz, C*H*(OTBS)); 3.80 (3H, s, OCH$_3$); 3.37 (1H, dd, *J* = 9.0, 7.2 Hz, CH_AH$_B$OPMB); 3.23 (1H, dd, *J* = 9.0, 5.7 Hz, CH$_A$$H_B$OPMB); 2.54 (1H, apt qn, *J* = 6.9 Hz, CH(=O)C*H*(CH$_3$)); 1.94 (1H,

m, C*H*(CH_3)CH_2OPMB); 1.04 (3H, d, *J* = 6.9 Hz, CH(=O)CH(C*H*$_3$)); 0.88 (9H, s, SiC(C*H*$_3$)$_3$); 0.85 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)CH_2OPMB); 0.06 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.04 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.3; 130.5; 129.2; 113.8; 72.64; 72.57; 72.4; 55.3; 51.4; 37.1; 25.9; 18.2; 12.2; 9.3; -4.0; -4.6 (one aromatic signal missing); **IR** (film, cm^{-1}) 2930; 2856; 1721; 1613; 1514; 1463; 1361; 1302; 1249; 1172; 1093; 1036; 836; 774; $[\alpha]_D^{20}$ = +36.5 (*c* 1.9, $CHCl_3$); **HRMS (ESI)** $C_{21}H_{36}NaO_4Si^+$ requires 403.2275, found 403.2276; **LREIMS** 143 (1.6 %); 137 (1.6 %); 132 (1.6 %); 121 (100 %); 115 (3.9 %); 112 (8.5 %); 97 (1.6 %); 91 (1.6 %); 78 (3.9 %); 75 (51 %); 67 (1.6 %); 59 (3.1 %); 55 (1.6 %); 47 (3.1 %).

(2*R*, 3*S*, 4*S*)-3-(*tert*-butyldimethylsilyloxy)-(4'-methoxybenzyloxy)-2,4-dimethylpentan-1-ol (263)



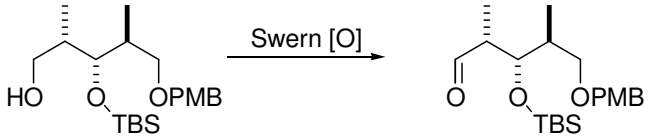
262 **263**

To a solution of the thione **262** (0.51g, 8.5 mmol) and methanol (45 μL, 36 mg, 1.1 mmol) in Et_2O (5 mL) was added a solution of $LiBH_4$ (2 M in THF, 0.56 mL, 1.1 mmol) at 0 °C. Evolution of H_2 was observed and after 15 minutes at 0 °C the solution was warmed to room temperature and the reaction progress monitored by TLC. After 15 minutes the starting material had been consumed and the reaction was quenched carefully with NaOH (5 M, 4 mL). The biphasic mixture was stirred for 30 minutes at room temperature to ensure complete hydrolysis of the borates. The layers were separated and the aqueous layer was back-extracted with Et_2O (20 mL). The organic layers were concentrated and the crude product filtered through a silica plug yielding 0.33 g (crude yield ~100 %) of the alcohol **263** as a clear, colourless oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.41 (2H, s, OC*H*$_2$Ar); 3.86 (1H, apt t, *J* = 3.6 Hz, C*H*(OTBS)); 3.80 (3H, s, OC*H*$_3$); 3.66 (1H, dd, *J* = 10.8, 8.1 Hz, C*H*$_A$H$_B$O); 3.48 (1H, dd, *J* = 10.8, 6.0 Hz, CH$_A$*H*$_B$O); 3.36 (1H, dd, *J* = 9.0, 7.2 Hz, C*H*$_A$H$_B$O); 3.23 (1H, dd, *J* = 9.0, 6.3 Hz, CH$_A$*H*$_B$O); 2.04-1.90 (3H, m, O*H*, C*H*(CH_3)CH_2(OH), C*H*(CH_3)CH_2OPMB); 0.94 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)); 0.89 (9H, s, SiC(C*H*$_3$)$_3$); 0.84 (3H, d, *J* = 7.2 Hz,

CH(C*H*$_3$)); 0.07 (3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$); 0.03 (3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.2; 130.7; 129.1; 113.8; 74.5; 73.5; 72.6; 66.3; 55.3; 40.3; 36.2; 26.0; 18.3; 12.9 (2); -4.2; -4.4; **IR** (film cm^{-1}) 3419; 2956; 2929; 2856; 1613; 1514; 1463; 1361; 1302; 1249; 1173; 1096; 1036; 837; 773; $[\alpha]_D^{20}$ = +1.6 (*c* 0.6, $CHCl_3$); **HRMS (ESI)** $C_{21}H_{38}NaO_4Si^+$ requires 405.2432, found 405.2430; **LREIMS** 203 (1.6 %); 187 (1.6 %); 145 (5.4 %); 137 (1.6 %); 121 (100 %); 115 (3.1 %); 89 (3.1 %); 75(16 %); 59 (1.6 %); 45 (1.6 %).

(2*R*, 3*S*, 4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentanal (253)

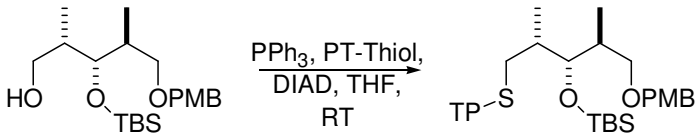


263 **253**

To a solution of DMSO (26 μL, 28 mg, 0.37 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C, was added a solution of oxalyl chloride (2 M in CH_2Cl_2, 92 μL, 0.18 mmol) and the resulting solution stirred at -78 °C for 30 min. A solution of the alcohol **263** (0.328 g, 8.59 mmol) in CH_2Cl_2 (3 x 0.3 mL) was added and the resulting solution stirred at -78 °C for 45 minutes. NEt_3 (102 μL, 74 mg, 0.73 mmol) was added and the solution stirred at -78 °C for 30 minutes before warming to 0 °C and stirring for a further 30 minutes. The reaction was quenched by addition of $NaHSO_4$ (1 M, 10 mL) and the product extracted with Et_2O (3 x 10 mL) and concentrated in *vacuo*. The product was taken up in Et_2O (20 mL), washed with $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (sat. aq., 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.45) yielding 0.27g (96 %) of the aldehyde **253** as a clear, colourless oil.

Data as reported above.

5-[2*R*,3*S*,4*S*]-5-[3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentylsulfanyl]-1-phenyl-1H-tetrazole (270)

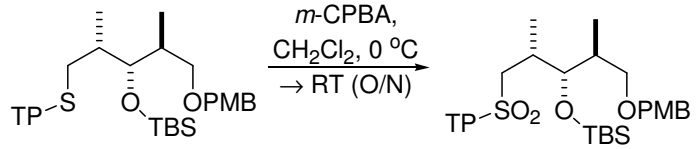


263 **270**

A solution of the alcohol **263** (0.021 g, 0.054 mmol) in THF (1 mL) at room temperature was added PPh_3 (21 mg, 0.080 mmol), 1-phenyl-1H-tetrazole-5-thiol (19 mg, 0.011 mmol) and DIAD (19 μL, 20 mg, 0.097 mmol). After 5 minutes TLC analysis indicated reaction completion and the reaction mixture was poured onto $NaHCO_3$ (sat. aq., 15mL) and the product was extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2CH_2, R_f = 0.45) yielding 22 mg (77 %) of the sulfide **270** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (5H, br s, Ar*H*); 7.21 (2H, d, *J* = 8.4 Hz, Ar*H*); 6.84 (2H, d, *J* = 8.4 Hz, Ar*H*); 4.37 (2H, s, OCH_2Ar); 3.82 (1H, dd, *J* = 3.9, 3.9 Hz, C*H*(OTBS)); 3.78 (3H, s, OCH_3); 3.51 (1H, dd, *J* = 12.9, 6.0 Hz, OC$H_A$$H_B$); 3.37 (1H, dd, *J* = 9.0, 6.6 Hz, OC$H_A$$H_B$); 3.26 (1H, dd, *J* = 12.9, 8.4 Hz, OCH_AH_B); 3.21 (1H, dd, *J* = 9.0, 8.1 Hz, OCH_AH_B); 2.18-2.07 (1H, m, C*H*(CH_3)); 2.02-1.93 (1H, m, C*H*(CH_3)); 1.02 (3H, d, *J* = 6.9 Hz, CH_3); 0.94 (3H, d, *J* = 6.9 Hz, CH_3); 0.89 (9H, s, SiC(CH_3)$_3$); 0.05 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.04 (3H, s, Si(CH_3)$_A$(CH_3)$_B$; **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.0; 154.5; 133.7; 130.6; 130.0; 129.7; 129.1; 123.9; 113.7; 74.6; 72.9; 72.5; 55.2; 53.4; 40.2; 38.0; 26.0; 18.4; 14.9; 13.2; -3.9; -4.1.

5-[2*R*,3S,4*S*]-5-[3-(*tert*-butyldimethylsilyloxy)-5-(4'-methoxybenzyloxy)-2,4-dimethylpentane-1-sulfonyl]-1-phenyl-1H-tetrazole (236)



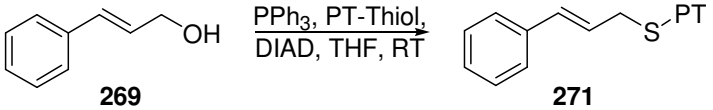
270 **266**

To a solution of the sulfide **270** (29 mg, 0.054 mmol) in CH_2Cl_2 (0.7 mL) was cooled to 0 ^oC and *m*-CPBA (77 %, 33 mg, 0.19 mmol) was added in small portions. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$ (sat. aq., 10

mL). The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined extracts were dried with ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.25) yielded 14 mg (46 %) of the sulfide **266** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.58 (5H, br s, Ar*H*); 7.23 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 4.38 (2H, s, OCH_2Ar); 4.09 (1H, dd, *J* = 14.1, 3.0 Hz, OCH_AH$_B$); 3.89 (1H, dd, *J* = 3.9, 3.9 Hz, C*H*(OTBS)); 3.80 (3H, s, OCH_3); 3.51); 3.61 (1H, dd, *J* = 1401, 9.6 Hz, OCH_AH_B); 3.32 (1H, dd, *J* = 9.0, 8.7 Hz, OCH_AH$_B$); 3.21 (1H, dd, *J* = 8.7, 5.7 Hz, OCH_AH_B); 2.64-2.52 (1H, m, C*H*(CH_3)); 2.04-1.90 (1H, m, C*H*(CH_3)); 1.12 (3H, d, *J* = 6.9 Hz, CH_3); 0.90 (9H, s, SiC(CH_3)$_3$); 0.88 (3H, d, *J* = 7.8 Hz, CH_3); 0.08 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.05 (3H, s, Si(CH_3)$_A$(CH_3)$_B$; **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 152.6; 131.4; 130.4; 129.6; 129.2; 125.1; 113.7; 74.3; 72.9; 72.6; 59.3; 55.3; 36.0, 33.2, 26.0; 18.2; 15.7; 12.8; -4.0; -4.4.

1-phenyl-5-(3-phenylallylsulfanyl)-1H-tetrazole (271)

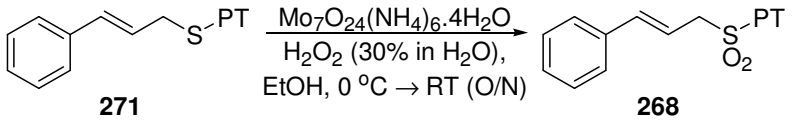


269 **271**

To a solution of the alcohol **269** (1.24g, 9.24 mmol) in THF (71 mL) at room temperature was added PPh_3 (3.64 g, 13.9 mmol), 1-phenyl-1H-tetrazole-5-thiol (3.29 g, 18.5 mmol) and DIAD (3.22 mL, 3.36 g, 16.6 mmol). After 5 minutes TLC analysis indicated complete conversion and the reaction mixture was poured onto $NaHCO_3$ (sat. aq., 100 mL) and the product was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % mixed hexanes/CH_2CH_2, R_f = 0.50) yielding 2.72 g (100 %) of the known sulfide **271** as a white powder.[307]

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63-7.23 (10H, m, ArH); 6.72 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.36 (1H, dt, *J* = 15.6, 7.6 Hz, ArCH=C*H*); 4.20 (2H, d, *J* = 7.6 Hz, CH_2S); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 136.0; 135.2; 131.0; 130.1; 129.7; 128.6; 128.1; 126.5; 124.4; 123.8; 122.4; 35.9.

1-phenyl-5-(3-phenylprop-2-ene-1-sulfonyl)-1H-tetrazole (268)

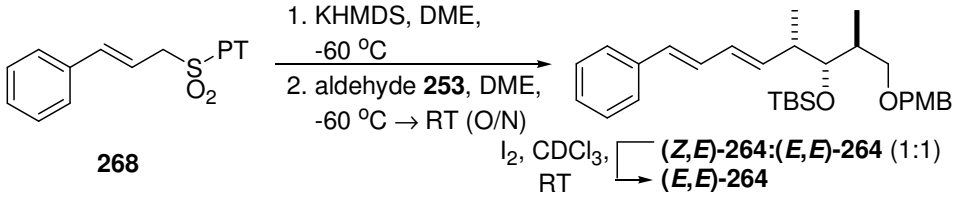


271 **268**

To a solution of the sulfide **271** (2.72 g, 9.24 mmol) in EtOH (185 mL) at 0°C was added a solution of $Mo_7O_{24}(NH_4)_6.4H_2O$ (1.14 g, 0.92 mmol) in H_2O_2 (30 % w/v in H_2O, 0.043 mol, 4.9 mL) and the resulting solution was warmed to room temperature slowly. The reaction mixture was stirred at room temperature overnight before removing the EtOH in *vacuo*, diluting with Et_2O (100 mL) and washing with H_2O (50 mL) and brine (50 mL). The aqueous layers were re-extracted with Et_2O (2 x 100 mL) and the combined organics dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, $R_f = 0.5$) yielding 1.45 g (48 %) of sulfone **268** as a white powder (m.p. 94-96 °C).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (5H, m, Ar*H*); 7.35-7.32 (5H, m, Ar*H*); 6.77 (1H, d, *J* = 15.9 Hz, ArC*H*); 6.16 (1H, dt, *J* = 15.9, 7.5 Hz, ArCH=C*H*); 4.58 (2H, d, *J* = 7.5 Hz, CH_2SO_2); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 152.5; 142.0; 135.1; 133.0; 131.4; 129.6; 129.1; 128.8; 126.9; 125.2; 111.9; 61.3; **HRMS (ESI)** found 349.0729, $C_{16}H_{14}N_4NaO_2S^+$ requires 349.0730; **LREIMS** 326 (7.3 %); 261 (36 %); 233 (27 %); 206 (39 %); 186 (12 %); 117 (100 %).

(2*R*, 3*R*, 4*S*, 5*E*, 7*E*)-3-(*tert*-butyldimethylsilyloxy)-1-(4'-methyoxybenzyloxy)-2,4-dimethyl-8-phenylocta-5,7-diene ((*E*,*E*)-234)



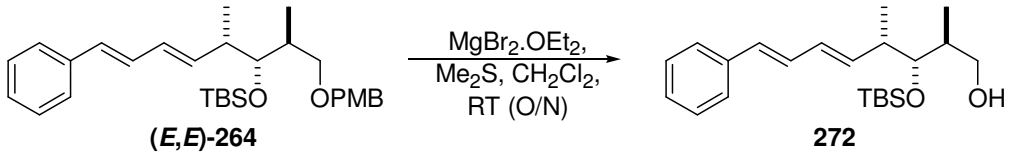
268

To a solution of sulfone **268** (0.99 g, 3.03 mmol) in anhydrous DME (7.6 mL) at -60 °C was added a solution of KHMDS in toluene (0.5 M, 5.4 mL, 2.72 mmol) dropwise. The solution turned deep red and was stirred at -60 °C for 30 minutes before addition of aldehyde **253** (0.576 g, 1.51 mmol) in DME (3 x 0.5 mL). The solution was stirred at -60 °C for 30 minutes before warming to room temperature and stirring overnight. The reaction was quenched by the addition of H_2O (30 mL) and diluted with Et_2O (50 mL). The layers were shaken well, separated and the organic layer dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by

column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.55) yielding 0.494 g (68 %) of a mixture of dienes **(*E*,*E*)-264** and **(*Z*,*E*)-264** as a pale yellow oil. The product was dissolved in $CDCl_3$ (1 mL) and few crystals of I_2 added. The isomerisation reaction was monitored by ^{1}H NMR and after 45 minutes isomerisation of the **(*Z*,*E*)-264** to **(*E*,*E*)-264** was complete. The solution was diluted with CH_2Cl_2 (50 mL) and washed with sodium metabisulfite solution (sat. aq., 20 mL) and H_2O (20 mL). The organics were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.55) yielded 0.464 g (94 %) of **(*E*,*E*)-264** as a single isomer.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.19 (7H, m, Ar*H*); 6.88 (2H, dt, *J* = 9.0, 2.4 Hz, Ar*H*); 6.73 (1H, dd, *J* = 15.6, 10.2 Hz, ArCH=C*H*); 6.43 (1H, d, *J* = 15.6, ArC*H*); 6.16 (1H, dd, *J* = 15.4, 10.2 Hz, ArCH=CHC*H*); 5.78 (1H, dd, *J* = 15.4, 8.0, ArCH=CHCH=C*H*); 4.44 (1H, d, *J* = 11.8 Hz, OCH_AH$_B$Ar); 4.36 (1H, d, *J* = 11.8 Hz, OCH$_A$$H_B$Ar); 3.80 (3H, s, OCH_3); 3.68 (1H, dd, *J* = 6.8 Hz, 2.4 Hz, C*H*(OTBS)); 3.36 (1H, dd, *J* = 9.2, 7.6 Hz, CH_AH$_B$OPMB); 3.19 (1H, dd, *J* = 9.2 6.6 Hz, CH$_A$$H_B$OPMB); 2.44 (1H, apt qn, *J* = 6.8 Hz, =CHC*H*(CH_3)); 1.98 (1H, apt qnd, *J* = 6.6, 2.4 Hz, C*H*(CH_3)CH_2OPMB); 1.04 (3H, d, *J* = 6.8 Hz, =CHCH(CH_3)); 0.91 (9H, s, SiC(CH_3)$_3$); 0.85 (3H, d, *J* = 6.6 Hz, CH(CH_3)CH_2OPMB); 0.06 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.03 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 138.9; 137.6; 130.8; 130.2; 129.6; 129.5; 129.2; 128.5; 127.1; 126.1; 113.7; 75.8; 73.4; 72.5; 55.3; 41.9; 36.8; 26.9; 18.4; 17.2; 11.2; -3.6; -4.1 (note: 2 coincident signals in vinyl region); $[\alpha]_D^{20}$ = 0 (*c* 0.4, $CHCl_3$); **IR** (film, cm^{-1}) 2956; 2928; 2855; 1731; 1612; 1513; 1462; 1385; 1248; 1173; 1111; 1038; 990; 837; 773; 747; 693; **HRMS** (ESI) $C_{30}H_{44}NaO_3Si^+$ requires 503.2952, found 503.2944; **LREIMS** 323 (57 %); 277 (41 %); 251 (31 %); 229 (20 %); 199 (21 %); 187 (100 %); 131 (16 %); 121 (41 %).

(2*R*, 3*R*, 4*S*, 5*E*, 7*E*)-2,4-dimethyl-8-phenylocta-5,7-dien-1-ol (272)



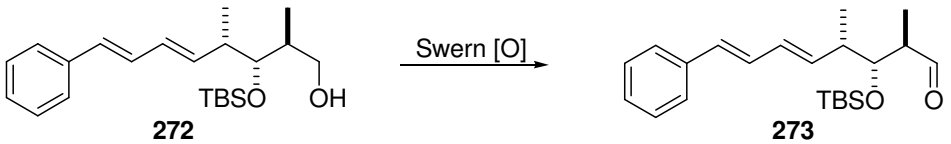
(*E*,*E*)-264 **272**

To a solution of PMB ether **(*E*,*E*)-264** (0.464 g, 0.96 mmol) in dry CH_2Cl_2 (16 mL) at room temperature was added Me_2S (0.72 mL, 9.74 mmol) and powered $MgBr_2.OEt_2$ (0.747 g, 2.89 mmol). The mixture was stirred at room temperature

overnight after which time TLC analysis showed consumption of starting material. The reaction was quenched by the addition of NH_4Cl (sat. aq., 40 mL) and the product extracted with CH_2Cl_2 (3 x 40 mL). The combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (20 % mixed hexanes/CH_2Cl_2, R_f = 0.35) yielded 0.292 g (84 %) of alcohol **272** as a clear, colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-7.10 (5H, m, Ar*H*); 6.65 (1H, dd, *J* = 15.8, 10.2 Hz, ArCH=C*H*); 6.37 (1H, d, *J* = 15.8 Hz, ArC*H*); 6.10 (1H, dd, *J* = 15.4, 10.4 Hz, ArCH=CHC*H*); 5.68 (1H, dd, *J* = 15.4, 8.2 Hz, ArCH=CHCH=C*H*); 3.60 (1H dd, *J* = 7.2, 2.6 Hz, C*H*(OTBS)); 3.52 (1H, dd, *J* = 10.4, 8.4 Hz, CH_AH_BOH); 3.38 (1H, dd, *J* = 10.5, 5.7, CH_AH_BOH); 2.42 (1H, apt sex., *J* = 6.8 Hz, =CHC*H*(CH_3)); 1.87-1..62 (1H, m, C*H*(CH_3)CH_2OH); 1.00 (3H, d, *J* = 6.8 Hz, =CHCH(C*H*$_3$)); 0.84 (9H, s, SiC(C*H*$_3$)$_3$); 0.76 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CH_2(OH)); 0.00 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.6; 137.5; 130.5; 129.6; 129.4; 128.5; 127.2; 126.1; 76.7; 66.1; 41.3; 39.6; 26.1; 18.3; 17.4; 11.5; -3.8; -4.2; **IR** (film, cm^{-1}) 3362; 2957; 2929; 2883; 2856; 1472; 1459; 1252; 1095; 1025; 988; 859; 837; 773; 746; 690; 669; $[\alpha]_D^{20}$ = +39.4 (*c* 2.9, $CHCl_3$).

(2*R*, 3*R*, 4*S*, 5*E*, 7*E*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-8-phenylocta-5,7-dienal (273)



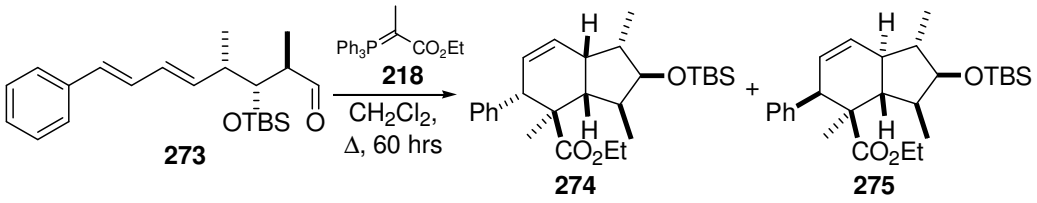
272 **273**

A solution of oxalyl chloride in CH_2Cl_2 (2 M, 0.61 mL, 1.21 mmol) was added dropwise to a solution of DMSO (0.172 mL, 2.43 mmol) in CH_2Cl_2 (3.5 mL) at -78 ^{o}C. The resulting solution was stirred at -78 ^{o}C for 30 min. A solution of alcohol **272** (0.292 g, 0.81 mmol) in CH_2Cl_2 (0.5 mL, 0.25 mL x 2) was added *via* a cannula to the reaction mixture, dropwise. The resulting mixture was stirred for 45 minutes at -78 ^{o}C. Et_3N (0.67 mL, 4.86 mmol) was added dropwise over several minutes and stirred at -78 ^{o}C for 30 minutes before warming to 0 ^{o}C and stirring for 30 minutes. The reaction mixture was quenched by addition of $NaHSO_4$ (1 M, 30 mL), and the product extracted with Et_2O (3 x 30 mL). The combined extracts were concentrated in *vacuo*. The product was taken up in Et_2O (50 mL) and washed with $NaHSO_4$ (1 M, 20 mL), H_2O (20 mL), $NaHCO_3$ (sat. aq., 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography

(100 % CH_2Cl_2, R_f = 0.41) yielding 0.243 g (84 %) of aldehyde **273** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (1H, s, C*H*O); 7.41-7.22 (5H, m, Ar*H*); 6.75 (1H, dd, *J* = 15.6, 10.5 Hz, ArCH=C*H*); 6.50 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.23 (1H, dd, *J* = 15.3, 10.5 Hz, ArCH=CHC*H*); 5.75 (1H, dd, *J* = 15.3, 8.4 Hz, ArCH=CHCH=C*H*); 4.09 (1H, dd, *J* = 7.2, 2.7 Hz, C*H*(OTBS)); 2.60-2.42 (2H, m, =CHC*H*(CH_3), C*H*(CH_3)C(=O)); 1.14 (3H, d, *J* = 7.2 Hz, C(=O)CH(C*H*$_3$) or CH(C*H*$_3$)CH=); 1.10 (3H, d, *J* = 6.9 Hz, C(=O)CH(C*H*$_3$) or CH(C*H*$_3$)CH=); 0.91 (9H, s, SiC(C*H*$_3$)$_3$); 0.11 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.01 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 Hz, $CDCl_3$) δ 205.2; 137.3; 137.2; 131.3; 130.7; 128.9; 128.6; 127.3; 126.2; 75.0; 50.8; 41.9; 26.0; 18.3; 16.9; 7.8; -4.1 (2C); **IR** (film, cm^{-1}) 3024; 2956; 2930; 2884; 2857; 1725; 1491; 1462; 1447; 1253; 1104; 1028; 990; 837; 775; 747; 691; 672; $[\alpha]_D^{20} = +135$ (*c* 1.1, $CHCl_3$).

(1*S*, 2*R*, 3*S*, 3a*S*, 4*R*, 5*S*, 7a*S*)- and (1*S*, 2*R*, 3*S*, 3a*S*, 4*R*, 5*R*, 7a*R*)-2-(*tert*-butyldimethylsilyloxy)-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (274 and 275)



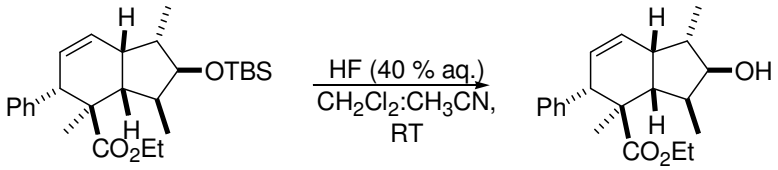
To a solution of the aldehyde **273** (0.243 g, 0.678 mmol) in CH_2Cl_2 (5 mL) at room temperature was added the ylide **218** (1.23 g, 3.39 mmol), carefully with stirring and the resulting yellow solution, heated under reflux for 60 hours. The solvent was removed in *vacuo* and the product triturated with mixed hexanes. The residue was a mixture of two cycloadducts **274** and **275**, separable by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f (**274**) = 0.5 , R_f (**275**) = 0.36) yielded 0.187 g (65 %) of adduct **274** and 0.049 g (17 %) of adduct **275** (overall yield 82 %).

274 - ^{1}H NMR (600 MHz, C_6D_6) δ 7.24-7.07 (5H, m, Ar*H*); 5.80 (2H, ABq, *J* = 11.4 Hz, PhCHC*H*=C*H*); 4.12 (1H, m, PhC*H*); 3.89 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 3.12 (1H, dd, *J* = 9.0, 7.8 Hz, C*H*(OTBS)); 2.56 (1H, dd, *J* = 10.2, 6.6 Hz, $EtO_2CC(CH_3)CHCH(CH_3)$); 2.05 (1H, apt br sex, *J* = 6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 1.95 (1H, m, CH=CHC*H*); 1.76 (1H, ddq, *J* = 12.6, 9.0, 6.6 Hz, CH=CHCHC*H*(CH_3)); 1.19 (3H, s, $Et_2OCC(CH_3)$); 1.13 (3H, d, *J* = 6.6 Hz,

CH=CHCHCH(C*H*$_3$)); 1.03 (3H, d, *J* = 6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.99 (9H, s, $SiC(CH_3)_3$); 0.87 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 0.11 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.09(3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.4; 142.4; 129.0; 128.4; 130.0; 128.3; 127.0; 88.2; 60.4; 50.1; 50.5; 49.2; 45.8; 42.8; 42.3; 26.2; 20.0; 18.3; 16.4; 13.5; 14.2; -3.5; -3.6; **IR** (film, cm^{-1}) 2956; 2929; 2856; 1717; 1463; 1386; 1255; 1111; 892; 835; 774; 752; 704; $[\alpha]_D^{20}$ = -6.0 (c 0.8, $CHCl_3$).

275 - ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.11 (5H, m, Ar*H*); 5.91 (1H, dt, *J* = 10.2, 1.8 Hz, PhCHCH=C*H*); 5.59 (1H, ddd, *J* = 9.6, 4.2, 3.0, PhCHC*H*=CH); 3.57 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.35 (1H, dd, *J* = 6.6, 1.8 Hz, C*H*(OTBS)); 3.29 (1H, m, PhC*H*); 3.23 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 2.53 (1H, ddddd, *J* = 10.8, 7.8, 4.8, 3.0, 1.8 Hz, CH=CHC*H*CH(CH_3)); 2.04 (1H, dqd, 7.8, 7.8, 1.8 Hz, CH=CHCHC*H*(CH_3)); 2.02 (1H, apt t, *J* = 12.0 Hz, $Et_2OCC(CH_3)CH$); 1.57 (1H, ddq, *J* = 13.2, 6.6, 6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 1.36 (3H, s, $Et_2OCC(CH_3)$); 1.07 (3H, d, *J* = 7.8 Hz, CH=CHCHCH(C*H*$_3$)); 0.89 (9H, s, $SiC(CH_3)_3$); 0.79 (3H, d, *J* = 6.6 Hz, $Et_2OC(CH_3)CHCH(CH_3)$); 0.69 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 0.07 (3H, s, $Si(CH_3)_A(CH_3)_B$); 0.05(3H, s, $Si(CH_3)_A(CH_3)_B$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.2; 141.9; 129.5; 128.5; 127.7; 127.5; 126.7; 89.1; 59.7; 53.6; 49.0; 45.1; 41.3; 41.2; 41.1; 25.9; 18.0; 17.6; 16.9; 16.0; 13.2; -4.2; -4.5; **IR** (film, cm^{-1}) 2956; 2928; 2856; 1721; 1456; 1377; 1258; 1204; 1105; 1074; 866; 836; 774; 700; $[\alpha]_D^{20}$ = + 143 (*c* 0.4, $CHCl_3$).

(1*S*, 2*R*, 3*S*, 3a*S*, 4*R*, 5*S*, 7a*S*)-2-hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (276)



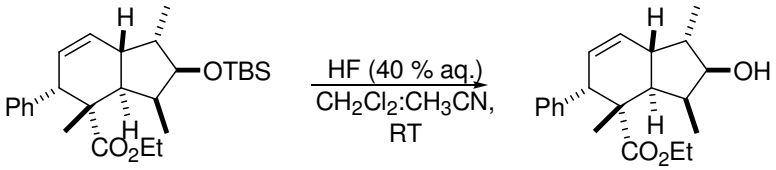
274 **276**

To a solution of the TBS ether **274** (232 g, 0.548 mmol) in CH_3CN:CH_2Cl_2 (1:1, 4 mL) in a Teflon® screw cap jar was added aqueous HF (40 %, 400 μL) at room temperature. The resulting solution was stirred at room temperature and the reaction monitored by TLC. Successive additions of aqueous HF (400 μL) over 3 hours resulted in consumption of the starting material. The reaction was quenched by the addition of H_2O (50 mL) and the product was extracted with EtOAc (3 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product

was purified by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.25) yielding 94 mg (65 %) of alcohol **276** as a white solid (m.p. 147-149 ^oC).

^{1}H NMR (600 MHz, C_6D_6) δ 7.20-7.17 (2H, m, Ar*H*); 7.15-7.12 (1H, m, Ar*H*); 7.07-7.06 (2H, m, Ar*H*); 5.87 (1H, ddd, *J* = 9.6, 3.0, 3.0 Hz, PhCHCH=C*H*); 5.74 (1H, ddd, *J* = 9.6, 2.4, 2.4 Hz, PhCHC*H*=CH); 3.99 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.96 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.86 (1H, m, C*H*(Ph)); 3.10 (1H, dd, *J* = 9.0, 9.0 Hz, C*H*(OH)); 2.42 (1H, dd, *J* = 9.6, 6.0 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 2.08 (1H, ddddd, *J* = 9.6, 9.6, 3.0, 3.0, 3.0 Hz, CH=CHC*H*); 1.71 (1H, ddq, *J* = 6.6, 6.6, 6.6, $CCHCH(CH_3)$); 1.62 (1H, br s, O*H*); 1.56 (1H, ddq, *J* = 9.6, 9.0, 6.0, $CH(CH_3)CHCH=CH$); 1.12 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); 1.02 (3H, d, *J* = 6.0 Hz, $CH(CH_3)CHCH=CH$); 0.97 (3H, d, *J* = 6.6 Hz, $CCHCH(CH_3)$); 0.92 (3H, s, CH_3C); **^{13}C NMR** (150 MHz, C_6D_6) δ 176.6; 141.7; 129.4; 129.4; 127.9; 127.8; 126.7; 87.1; 60.4; 49.7; 49.4; 48.7; 45.0; 42.7; 41.5; 19.3; 15.7; 14.2; 13.0; **IR** (film, cm^{-1}) 3311; 3028; 2956; 2925; 2869; 1716; 1495; 1454; 1381; 1237; 1171; 1098; 1032; 754; 742; 705; $[\alpha]_D^{20}$ = + 5.19 (*c* 1.2, $CHCl_3$).

(1*S*, 2*R*, 3*S*, 3a*R*, 4*S*, 5*S*, 7a*S*)-2-hydroxy-1,3,4-trimethyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (277)



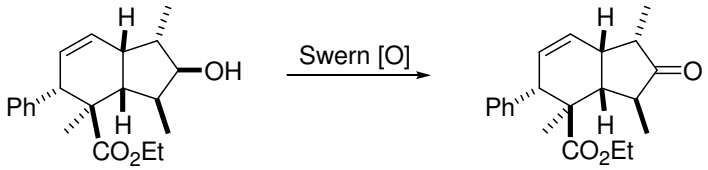
275 **277**

As per the procedure for **276** using TBS ether **275** (49 mg, 0.116 mmol), purification by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.25) yielded 28 mg (73 %) of alcohol **277** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.23 (2H, m, Ar*H*); 7.21-7.18 (1H, m, Ar*H*); 7.12-7.11 (2H, m, Ar*H*); 5.92 (1H, ddd, *J* = 10.2, 1.8, 1.8 Hz, PhCHCH=C*H*); 5.61 (1H, ddd, *J* = 10.2, 4.2, 3.0 Hz, PhCHC*H*=CH); 3.58 (1H, dq, *J* = 10.8, 7.2 Hz, $CO_2CH_AH_B$); 3.41 (1H, dd, *J* = 6.0, 1.8 Hz, C*H*(OH)); 3.29 (1H, m, C*H*(Ph)); 3.23 (1H, dq, *J* = 11.4, 7.8 Hz, $CO_2CH_AH_B$); 2.53 (1H, ddddd, *J* = 11.4, 7.8, 2.4, 2.4, 2.4 Hz, CH=CHC*H*); 2.10 (1H, ddq, *J* = 7.8, 7.8, 2.4, $CH(CH_3)CHCH=CH$); 2.09 (1H, dd, *J* = 11.4, 11.4 Hz, $C(CH_3)(CO_2Et)CHCH(CH_3)$); 1.55 (1H, ddq, J = 11.4, 6.6, 6.6, $CCHCH(CH_3)$); 1.25 (1H, br s, O*H*); 1.37 (3H, s, CH_3C); 1.10 (3H, d, *J* = 7.2 Hz, $CH(CH_3)CHCH=CH$); 0.86 (3H, d, *J* = 6.6 Hz, $CCHCH(CH_3)$); 0.70 (3H, t, *J* =

7.2 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.0; 141.7; 129.5; 128.7; 127.8; 127.1; 126.8; 88.9; 59.7; 53.6; 48.2; 44.9; 41.7; 41.2; 41.1; 17.5; 16.9; 16.2; 13.2; **IR** (film, cm^{-1}) 3412; 3023; 2956; 2927; 2872; 1719; 1493; 1453; 1380; 1269; 1231; 1205, 1138; 1102; 1031; 764; 701; $[\alpha]_D^{20}$ = + 220 (*c* 1.4, $CHCl_3$).

(1*S*, 3*S*, 3a*R*, 4*R*, 5*S*, 7a*R*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (240)

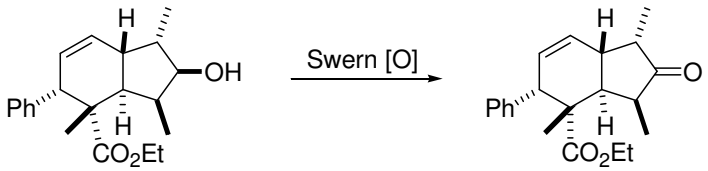


276 **240**

To a solution of DMSO (0.64 mmol, 50 mg, 45 µL) in CH_2Cl_2 (900 µL) at -78 ^oC was added a solution of oxalyl chloride in CH_2Cl_2 (2 M, 0.32 mol, 160 µL), dropwise. The solution was stirred at -78 ^oC for 30 minutes before addition of alcohol **274** (70.1 mg, 0.213 mmol) in CH_2Cl_2 *via* a cannula (200 µL, 200 µL, 100 µL). The resulting mixture was stirred at -78 ^oC for 45 minutes before addition of NEt_3 (1.28 mmol, 129 mg, 178µL) over several minutes. The mixture was stirred at -78 ^oC for 30 minutes before warming to 0 ^oC and the stirring continued for 30 minutes. The reaction was quenched by the addition of NH_4Cl (sat. aq., 20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.65) yielding 68.3 mg (98 %) of ketone **240** as a clear, colourless oil.

*Data as per that reported for oxidation of cycloadduct **233**.*

(1*S*, 3*S*, 3a*S*, 4*S*, 5*S*, 7a*R*)-1,3,4-trimethyl-2-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carboxylic acid ethyl ester (278)



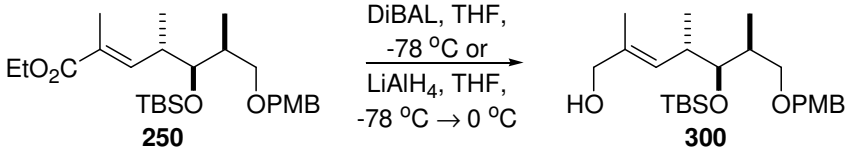
277 **278**

As per the procedure for **240** using alcohol **277** (28 mg, 0.085 mmol), purification by column chromatography (100 % CH_2Cl_2, R_f = 0.39) yielded 19 mg (69 %) of ketone **278** as a clear, colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.27 (2H, m, Ar*H*); 7.26-7.23 (1H, m, Ar*H*); 7.15-7.13 (2H, m, Ar*H*); 6.04 (1H, ddd, *J* = 10.1, 1.8, 1.8 Hz, PhCHCH=C*H*); 5.74 (1H, ddd, *J* = 10.1, 4.2, 2.4 Hz, PhCHC*H*=CH); 3.60 (1H, dq, *J* = 10.1, 7.2 Hz, $CO_2CH_AH_BCH_3$); 3.42 (1H, m, PhC*H*); 3.60 (1H, dq, *J* = 10.7, 7.2 Hz, $CO_2CH_AH_BCH_3$); 2.65 (1H, qdd, *J* = 7.6, 7.6, 0.66 Hz, C*H*(CH_3)CHCH=CH); 2.59 (1H, ddddd, *J* = 12.1, 12.1, 2.6, 2.6, 2.6 Hz, CH=CHC*H*); 2.42 (1H, dd, *J* = 12.1, 12.1 Hz, C(CH_3)(CO_2Et)C*H*CH(CH_3)); 2.08 (1H, qdd, *J* = 12.1, 6.9, 6.9 Hz, CCHC*H*(CH_3)); 1.45 (3H, s, C(C*H*$_3$)(CO_2Et)); 1.18 (3H, d, *J* = 7.6 Hz, CH(C*H*$_3$)CHCH=CH); 0.89 (3H, d, *J* = 6.9 Hz, CCHCH(C*H*$_3$)); 0.69 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 220.7; 174.3; 141.0; 129.6; 129.4; 128.0; 127.1; 125.3; 60.0; 53.3; 48.9; 47.1; 43.3; 41.9; 39.1; 17.3; 13.2; 13.1; 11.7; **IR** (film, cm^{-1}) 3026; 2972; 2934; 2875; 1740; 1720; 1453; 1381; 1265; 1244; 1226; 1134; 1098; 1030; 762; $[\alpha]_D^{20} = +239$ (*c* 1.0 $CHCl_3$).

6.4 Experimental Procedures for Chapter 5

(2*E*, 4*S*, 5*S*, 6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-en-1-ol (300)



Procedure using DiBAL

To a solution of the ester **250** (33 mg, 0.072 mmol) in CH_2Cl_2 (0.4 mL) at -78 °C was added, dropwise a solution of DiBAL (1 M in THF, 0.25 mL, 0.25 mmol). The solution was stirred at -78 °C and the reaction monitored by TLC for 2.5 hrs. After this time no change was occurring so the reaction was quenched by addition of MeOH (50 μL) and NH_4Cl (sat. aq., 25 μL). The mixture was diluted with Et_2O (20 mL) and passed through a silica gel plug. ^{1}H NMR analysis indicated that a mixture of starting material and product were present.

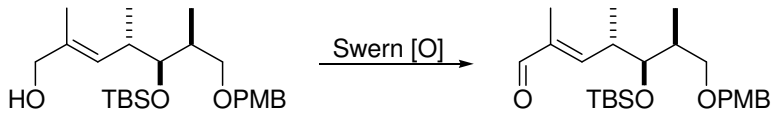
Procedure using $LiAlH_4$

To a cooled (-78 °C) suspension of $LiAlH_4$ (0.043 g, 1.13 mmol) in THF (3 mL) was added (*via* a syringe) a solution of the ester **250** (0.44 g, 0.94 mmol) in THF (3 x 0.5 mL). The solution was warmed to 0 °C. After 10 minutes TLC analysis showed that

the starting material had been consumed. The reaction was quenched by addition of H_2O (100μL), NaOH (5 M, 100 μL) and H_2O (100 μL), dried ($MgSO_4$), filtered at the water pump and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.42) yielding 0.33 g (84 %) of alcohol **300** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 5.36 (1H, d, *J* = 9.6 Hz, C=C(*H*)); 4.43 (1H, d, *J* = 11.7 Hz, OCH_AH$_B$Ar); 4.35 (1H, d, OCH$_A$$H_B$Ar); 3.95 (2H, br s, C$H_2$(OH)); 3.80 (3H, s, OC$H_3$); 3.63 (1H, dd, *J* = 4.8, 3.3 Hz, C*H*(OTBS)); 3.35 (1H, dd, *J* = 9.0, 6.6 Hz, CH_AH$_B$(OPMB); 3.16 (1H, dd, *J* = 9.0, 7.2 Hz, CH$_A$$H_B$OPMB); 2.59-2.52 (1H, m, C*H*(CH$_3$)CH(OTBS)); 1.97-1.89 (1H, m, CH(OTBS)C*H*(CH$_3$)CH$_2$OPMB); 1.62 (3H, d, *J* = 1.2 Hz, (CH_3)C=C); 1.49 (1H, br s, OH); 0.92 (3H, d, *J* = 6.6 Hz, CH(CH_3)CH(OTBS)); 0.90 (3H, d, *J* = 6.9 Hz, CH(OTBS)CH(CH_3)CH$_2$OPMB); 0.87 (9H, s, SiC(CH_3)$_3$); 0.01 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 133.6; 130.8; 129.8; 129.2; 113.7; 76.2; 73.2; 72.5; 69.2; 55.3; 37.5; 36.6; 26.1; 18.4; 18.2; 13.8; 12.3; -3.9; -4.1; **IR** (film, cm^{-1}) 3423; 2959; 2931; 2858; 1614; 1516; 1472; 1463; 1388; 1362; 1303; 1250; 1173; 1107; 1093; 1039; 1007; 866; 836; 774; 674; 666; $[\alpha]_D^{20}$ = -2.9 (*c* 0.6, $CHCl_3$); **HRMS (ESI)** found 445.2739 $C_{24}H_{42}O_4Si$ requires 445.2745; **LREIMS** 323 (2.9 %); 187 (5.9 %); 145 (8.9 %); 137 (3.7 %); 121 (100 %); 89 (2.2 %); 73 (6.7 %).

(2*E*, 4*S*, 5*R*, 6*S*)-5-(*tert*-butyldimethylsilyl)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-enal (295)



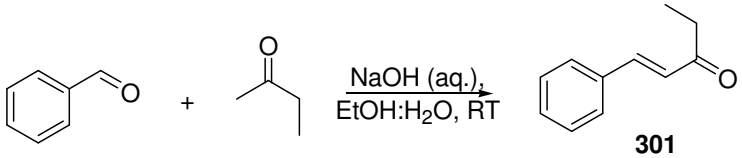
300 **295**

Oxalyl chloride (2 M, 42 μL, 0.08 mmol) was added dropwise to a solution of DMSO (12 μL, 0.17 mmol) in CH_2Cl_2 (0.3 mL) at -78 ^{o}C. The resulting solution was stirred at -78 ^{o}C for 30 minutes. A solution of the alcohol **300** (12 mg, 0.028 mmol) in CH_2Cl_2 (3 x 0.1 mL) was added *via* a cannula. The resulting mixture was stirred for 45 minutes at -78 ^{o}C. NEt_3 (46 μL, 0.33 mmol) was added dropwise over several minutes and was the solution was stirred at -78 ^{o}C for 30 minutes before warming to 0 ^{o}C and the stirring continued for a further 30 minutes. The reaction was quenched by the addition of $NaHSO_4$ (1 M, 10 mL) and the product was extracted with Et_2O (3 x 15 mL). The volatiles were removed in *vacuo* and the product taken up in Et_2O (30

mL). The organics were washed with $NaHSO_4$ (1 M, 10 mL), H_2O (10 mL), $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2, R_f = 0.55) yielding 11 mg (92 %) of the aldehyde **295** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (1H, s, C*H*(=O)); 7.22 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*); 6.55 (1H, dd, *J* = 9.9, 1.2 Hz, C(CH_3)=C*H*); 4.42 (1H, d, *J* = 11.7 Hz, C$H_A$$H_B$Ar); 4.34 (1H, d, *J* = 11.7 Hz, C$H_A$$H_B$Ar); 3.81 (3H, s, OC$H_3$); 3.78 (1H, dd, *J* = 8.1, 4.5 Hz, C*H*OTBS); 3.35 (1H, dd, *J* = 9.0, 6.6 Hz, C$H_A$$H_B$OPMB); 3.12 (1H, dd, *J* = 9.0, 6.6 Hz, C$H_A$$H_B$OPMB); 2.91-2.97 (1H, m, =CHC*H*(CH_3)); 1.95-1.87 (1H, m, C*H*(CH_3)CH_2OPMB); 1.69 (3H, d, *J* = 1.2 Hz, C(CH_3)=C*H*); 1.02 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)); 0.90 (3H, d, *J* = 6.9 Hz, CH(CH_3)CH_2OPMB); 0.88 (9H, s, SiC(CH_3)$_3$); 0.05 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.03 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 195.6; 159.2; 157.7; 138.0; 130.5; 129.3; 113.8; 76.2; 72.6; 72.3; 55.3; 38.5; 37.8; 26.0; 18.3; 17.8; 12.5; 9.3; -3.7; -4.0; **HRMS (ESI)** $C_{24}H_{40}NaO_4Si^+$ requires 443.2588, found 443.2586; **LREIMS** 323 (3.0 %); 241 (2.2 %); 187 (3.7 %); 137 (2.2 %); 121 (100 %); 73 (5.2 %).

1-phenylpent-1-en-3-one (301)



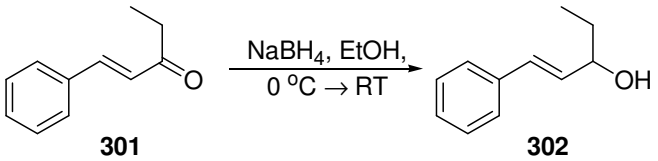
301

A solution of benzaldehyde (0.95 mL, 1g, 9.4 mmol), methyl ethyl ketone (0.84 mL, 0.73 g, 9.4 mmol), ethanol (9.6 mL), H_2O (7.85 mL) and NaOH (1 M, 9.42 mL) were stirred at room temperature for 4 hours, 20 minutes. TLC analysis showed some benzaldehyde still remained however the reaction wasn't proceeding so the EtOH was removed in *vacuo* and the product was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The product was purified by column chromatography (10 % mixed hexanes/CH_2Cl_2 → 100 % CH_2Cl_2, R_f = 0.35) yielding 0.70 g (46 %) of ketone **301** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.38 (6H, m, Ar*H*, ArC*H*); 6.75 (1H, d, *J* = 16.2 Hz, ArCH=C*H*); 2.70 (2H, q, *J* = 7.2 Hz, C$H_2$$CH_3$); 1.17 (3H, t, *J* = 7.2 Hz,

CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 200.9; 142.2; 134.6; 130.3; 128.9; 128.2; 126.0; 34.0; 8.2.

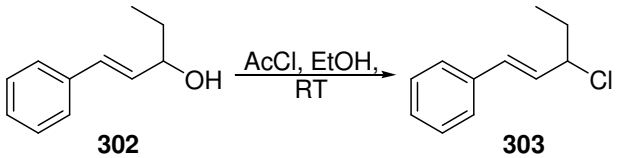
1-phenylpent-1-en-3-ol (302)



301 **302**

To a solution of the ketone **301** (0.68 g, 4.27 mmol) in ethanol (6.9 mL) at 0 °C, was added with stirring $NaBH_4$ (177 mg, 4.68 mmol). The solution was stirred at 0 °C for 20 minutes and then warmed slowly to room temperature for 20 minutes. The reaction was quenched by addition of HCl (1 M) dropwise until fizzing stopped. The ethanol was removed in *vacuo* and the product extracted with EtOAc (3 x 50 mL). The combined extracts were washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (10 % Et_2O/CH_2Cl_2, R_f = 0.5) yielding 0.66 g (95 %) of the alcohol **302** as a clear, colourless oil with spectroscopic data consistent with that reported.[308] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.22 (5H, m, Ar*H*); 6.58 (1H, d, *J* = 15.9 Hz, ArC*H*); 6.22 (1H, dd, *J* = 15.9, 6.6 Hz, ArCH=C*H*); 4.22 (1H, q, *J* = 6.6 Hz, C*H*OH); 1.72-1.60 (3H, m, O*H*, CH(OH)CH_2); 0.98 (3H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 136.8; 132.2; 130.4; 128.6; 127.6; 126.4; 74.4; 30.2; 9.7; **IR** (film, cm^{-1}) 3337; 3026; 2964; 2931; 2875; 1493; 1450; 965; 747; 693; **HRMS (ESI)** $C_{11}H_{14}NaO^+$ requires 185.0937, found 185.0938; **LREIMS** 162 (34 %); 144 (5.2 %); 133 (100 %); 129 (16 %); 115 (39 %); 105 (51 %); 91 (33 %); 77 (23 %); 55 (26 %); 51 (6.7 %).

(3-chloropent-1-enyl)-benzene (303)



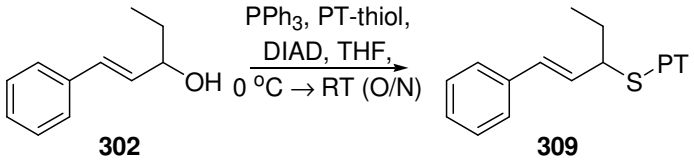
302 **303**

AcCl (3.07 mL, 3.39 g, 43 mmol) was added dropwise to a solution of the alcohol **302** (0.88 g, 5.39 mmol) in ethanol (2.5 mL). The solution was stirred at room temperature for 30 minutes before removal of the volatiles in *vacuo*. The product was taken up in EtOAc (100 mL), washed with brine (40 mL) and extracted again with EtOAc (2 x 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated in

vacuo. The chloride **303** (0.94 g, 96 %) was isolated as a clear oil and was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.23 (5H, m, Ar*H*); 6.60 (1H, d, *J* = 15.6 Hz, =C*H*Ar); 6.24 (1H, dd, *J* = 15.6, 8.6 Hz, C*H*=CHAr); 4.49 (1H, dq, *J* = 8.6, 6.8 Hz, C*H*Cl); 2.11-1.82 (2H, m, CH_2CH$_3$); 1.06 (3H, t, *J* = 7.4 Hz, CH$_2$CH_3); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 136.0; 129.7; 128.9; 128.3; 126.9; 126.4; 65.2; 32.0; 11.0.

5-(1-phenylpent-1-ene-3-sulfanyl)-1-phenyl-1H-tetrazole (309)

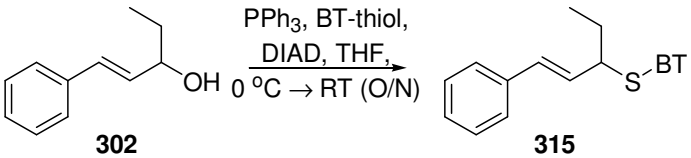


302 **309**

To a cooled (0 ^{o}C) solution of the alcohol **302** (0.46 g, 2.8 mmol), PPh_3 (0.81 g, 3.09 mmol) and the 1-phenyl-1H-tetrazole-5-thiol (0.55 mg, 3.09 mmol) in THF (33 mL) was added DIAD (0.60 mL, 0.62 g, 3.09 mmol) dropwise very slowly. The solution was warmed to room temperature and was left to stir overnight at room temperature. The solvent was removed in *vacuo* and pentane:EtOAc (9:1, 20 mL) added and the suspension filtered through Celite and the filtrate concentrated in *vacuo*. The crude oil was purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.34) yielding 0.82 g (91 %) of the desired sulfide **309**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (4H, br s, Ar*H*); 7.39-7.19 (5H, m, Ar*H*); 6.66 (1H, d, *J* = 15.8 Hz, ArC*H*=); 6.09 (1H, ddd, *J* = 15.8, 9.4, 1.0 Hz, ArCH=C*H*); 4.58 (1H, dt, *J* = 8.8, 8.8 Hz, C*H*S); 2.10-1.93 (2H, m, CH_2CH$_3$); 1.07 (3H, t, *J* = 6.6 Hz, CH$_2$CH_3); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 136.3; 133.5; 130.3; 129.9; 129.0; 128.8; 128.2; 128.1; 127.7; 126.8; 124.4; 53.9; 28.2; 12.0; **IR** (film, cm^{-1}) 3060; 3027; 2966; 2931; 2873; 1597; 1499; 1453; 1385; 1278; 1289; 1089; 1074; 1015; 965; 912; 854; 759; 694; **HRMS (ESI)** found 345.1141, $C_{18}H_{18}N_4NaS^+$ requires 345.1150; **LREIMS** 279 (11 %); 265 (74 %); 145 (100 %); 129 (17 %); 117 (80 %); 91 (9.2 %).

2-(1-phenylpent-1ene-3-sulfanyl)-benzothiazole (315)



302 **315**

As per the procedure for sulfide **309** using alcohol **302** (0.62 g, 3.83 mmol), and benzothiazole (0.70 g, 4.21 mmol), purification by column chromatography (80 % CH_2Cl_2/mixed hexanes, R_f = 0.66) yielded 0.83 mg (70 %) of the desired sulfide **315**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 8.1 Hz, Ar*H*); 7.75 (1H, d, *J* = 8.1 Hz, Ar*H*); 7.51-7.21 (7H, m, Ar*H*); 6.69 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.24 (1H, dd, *J* = 15.6, 9.0 Hz, ArCH=C*H*); 4.52 (1H, td, *J* = 8.1 Hz, 6.6 Hz, C*H*S); 2.09-1.90 (2H, m, CH(S)CH_2); 1.13 (3H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 165.5; 153.2; 136.5; 135.5; 132.6; 128.7; 128.5; 127.7; 136.5; 126.0; 124.3; 121.7; 120.9; 53.1; 28.0; 11.8; **IR** (film, cm^{-1}) 3059; 3026; 2965; 2930; 1457; 1425; 1310; 1260; 991; 963; 755; 726; 692; **HRMS (ESI)** $C_{18}H_{17}NNaS_2^+$ requires 334.0695, found 334.0697; **LREIMS** 294 (100 %); 262 (9.4 %); 215 (5.5 %); 183 (66 %); 152 (7.9 %); 139 (13 %); 107 (7.1 %); 77 (4.7 %); 6.3 (4.7 %); 51 (4.7 %).

Attempts at Oxidation of Sulfides 309 and 315 to the corresponding Sulfones 307 and 314;

General Procedure for H_2O_2/$Mn_7O_{24}(NH_4)_6.4H_2O$ Oxidation

To a solution of the sulfide (1 eq.) in EtOH or ^{i}PrOH (0.01-0.2 M) at 0^{o}C, was added a solution of $Mo_7O_{24}(NH_4)_6.4H_2O$ (0.04 → 0.5 eq.) in H_2O_2 (30 % w/v in H_2O, 2.9 → 4.7 eq.) and the resulting solution was either warmed to room temperature slowly or maintained at 0 ^{o}C. The reaction mixture was stirred at room temperature overnight or, in the case of the 0 ^{o}C conditions, stored in the freezer (-20 ^{o}C) overnight. The EtOH was removed in *vacuo* and the reaction mixture was diluted with Et_2O and washed with H_2O and brine. The aqueous layers were re-extracted with Et_2O (x 2) and the combined organics dried ($MgSO_4$) and concentrated in *vacuo*.

General Procedure for Oxone Oxidation

To a solution of the sulfide (1 eq.) in MeOH:H_2O:THF (1:1:2) or acetone:H_2O (1:1) was added a suspension of oxone (4-10 eq.) in the same solvent. The solution was

stirred at room temperature, 50 °C or 100 °C overnight. The solvent was removed in *vacuo* and the product extracted with Et_2O (x 3), washed with brine, dried ($MgSO_4$) and concentrated in *vacuo*.

General Procedure for Oxone Oxidation with a Solid Support

To silica gel or alumina, was added H_2O (5 g silica/mL) and the mixture stirred gently at atmospheric pressure on the rotary evaporator. To a solution of the sulfide (1 eq.) in CH_2Cl_2 (0.2 M sulfide) at room temperature was added the silica gel or alumina and oxone (1.5 eq.) to make a dry slurry. The slurry was stirred overnight at room temperature before filtering the adsorbent off and washing with EtOAc. Crude ^{1}H NMR analysis confirmed that no reaction had occurred and starting material had been recovered.

Procedure for $NaIO_4$ Oxidation

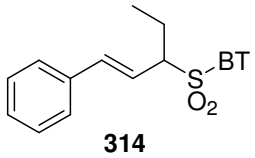
To a solution of $NaIO_4$ (28 mg, .013 mmol) in H_2O (0.3 mL) at 0 °C was added the sulfide (17 mg, 0.053 mmol) in MeOH:THF (0.3 mL, 0.1 mL, 0.1 mL) and the reaction stirred at 0 °C for 30 minutes before warming to room temperature and stirring overnight. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combine extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Decomposition of starting material was suggested from the ^{1}H NMR spectrum which revealed no vinyl proton signals.

Procedures for $NaBO_3.4H_2O$ Oxidation

1. To a solution of $NaBO_3.4H_2O$ in MeOH:THF was added the sulfide in MeOH:THF (3 x 0.2 mL) and the solution heated to 50 °C for 2 days. The solution was filtered through a silica plug to remove the inorganic salts and was washed through with EtOAc. Crude ^{1}H NMR analysis revealed that starting material was recovered and no reaction occurred.

2. To a solution of $NaBO_3.4H_2O$ (38 mg, 0.25 mmol) in acetic acid (0.4 mL) was added the sulfide (16 mg, 0.050 mmol) in acetic acid (3 x 0.2 mL) and the solution heated to 50 °C for 2 hours. The solution was filtered through a silica plug to remove the inorganic salts and was washed through with EtOAc. Crude ^{1}H NMR analysis revealed that cleavage of the thioester had occurred.

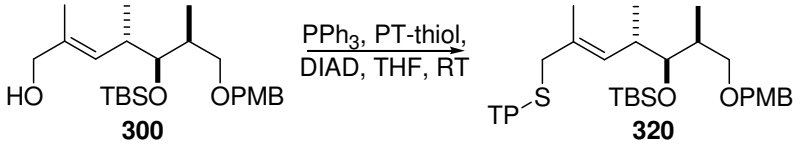
2-(1-phenylpent-1-ene-3-sulfonyl)-benzothiazole (314)



314

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 7.8 Hz, Ar*H*); 7.94 (1H, d, *J* = 8.1 Hz, Ar*H*) 7.64 (1H, t, *J* = 8.1 Hz, Ar*H*); 7.58 (1H, t, *J* = 7.8 Hz, Ar*H*); 7.40-7.16 (5H, m, Ar*H*); 6.49 (1H, d, *J* = 15.6 Hz, ArC*H*); 6.04 (1H, dd, *J* = 15.6, 9.6 Hz, ArCH=C*H*); 4.23 (1H, td, *J* = 7.5, 3.6 Hz, C*H*SO_2), 2.40-2.32 (1H, m, C$H_A$$H_B$$CH_3$); 2.06-1.95 (1H, m, $CH_A$$H_B$$CH_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 165.5; 152.7; 139.6; 137.0; 135.6; 128.6 (2C); 127.9; 127.5; 126.7; 125.4; 122.2; 119.5; 70.3; 20.7; 11.2; **IR** (film, cm^{-1}) 2969; 2932; 1494; 1470; 1324; 1146; 1085; 1022; 969; 762; 729; 691; 630; **HRMS (ESI)** $C_{18}H_{17}NNaO_2S_2^+$ requires 366.0593, found 366.0594; **LREIMS** 343 (2.7 %); 279 (7.1 %); 264 (2.7 %); 250 (8.9 %); 225 (13 %); 145 (100 %); 129 (7.1 %); 117 (50 %).

5-[(2*E*, 4*S*, 5*R*, 6*S*)-5-[5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-enylsulfanyl]-1-phenyl-1H-tetrazole (320)



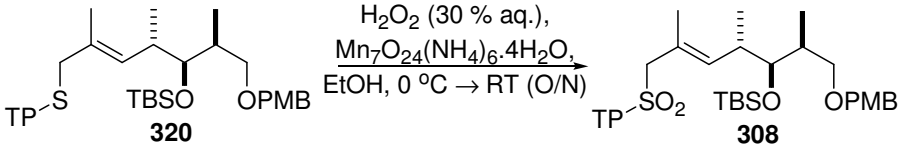
300 **320**

To a solution of the alcohol (28.4 mg, 0.067 mmol) in THF (0.6 mL) at room temperature, was added PPh_3 (36 mg, 0.10 mmol), 1-phenyl-1H-tetrazole-5-thiol (24 mg, 0.13 mmol) and DIAD (23 μL, 24 mg, 0.12 mmol). After 5 minutes TLC analysis indicated complete conversion of starting material and the reaction mixture was poured onto $NaHCO_3$ (sat. aq., 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (100 % CH_2Cl_2 R_f = 0.45) yielding 33 mg (83 %) of sulfide **320** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (5H, m, Ar*H*); 7.21 (2H, d, *J* = 7.5 Hz, Ar*H*); 6.86 (2H, d, *J* = 7.5 Hz, Ar*H*); 5.54 (1H, d, *J* = 9.6 Hz, C(CH_3)CH); 4.39 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ar); 4.32 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ar); 4.06 (1H, d, *J* = 12.6 Hz, C$H_A$$H_B$S); 3.99 (1H, d, *J* = 12.6 Hz, C$H_A$$H_B$S); 3.79 (3H, s, OC*H*$_3$); 3.61 (1H, br s, C*H*(OTBS)); 3.34 (1H, dd, *J* = 7.5, 7.2 Hz, C$H_A$$H_B$OPMB); 3.12 (1H, dd, *J* = 7.2, 7.2 Hz, C$H_A$$H_B$OPMB); 2.50 (1H, br m, =CHC*H*(CH_3)); 1.85 (1H, br m,

C*H*(CH_3)CH_2OPMB); 1.69 (3H, s, C(C*H*$_3$)=CH); 1.42 (3H, d, *J* = 6.9 Hz, =CHCH(C*H*$_3$)); 0.86 (12H, br s, Si(C*H*$_3$)$_3$, CH(C*H*$_3$)CH_2OPMB); 0.00 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 154.2; 135.0; 133.7; 130.7; 130.0; 127.9; 129.2; 127.2; 123.8; 113.7; 76.2; 72.9; 72.5; 55.3; 43.1; 37.9; 37.0; 26.1; 21.6; 18.3; 15.5; 12.5; -3.8; -4.1.

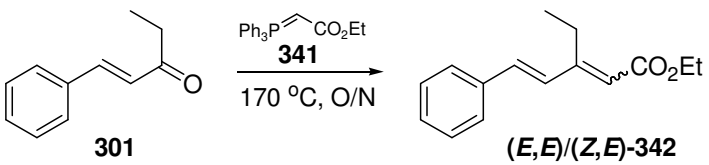
5-[(2*E*, 4*S*, 5*R*, 6*S*)-5-[5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-2,4,6-trimethylhept-2-ene-1-sulfonyl]-1-phenyl-1H-tetrazole (308)



To a solution of the sulfide **320** (33 mg, 0.056 mmol) in EtOH (5.5 mL) at 0 °C, under N_2, was added a solution of $Mo_7O_{24}(NH_4)_6.4H_2O$ (35 mg, 0.0028 mmol) in H_2O_2 (30 %, 63 μL, 0.56 mmol) and the mixture warmed to room temperature slowly and stirred for 21 hours. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL) and brine (10 mL). The aqueous phase was further extracted with Et_2O (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (10 % mixed hexanes/CH_2Cl_2, R_f = 0.46) yielding 9 mg (26 %) of sulfone **308** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.52 (5H, m, Ar*H*); 7.22 (2H, d, *J* = 8.4 Hz, Ar*H*); 6.86 (1H, d, *J* = 8.4 Hz, Ar*H*); 5.64 (1H, d, *J* = 11.1 Hz, C(CH_3)=C*H*); 4.41 (4H, m, OC*H*$_2$Ar, C*H*$_2$$SO_2$); 3.80 (3H, s, OC*H*$_3$); 3.61 (1H, br m, C*H*(OTBS)); 3.32 (1H, m, C*H*$_A$$H_B$OPMB); 3.13 (1H, m, CH_A*H*$_B$OPMB); 2.56 (1H, br m, =CHC*H*(CH_3)); 1.56 (3H, s, C(C*H*$_3$)=CH); 1.25 (1H, br m, C*H*(CH_3)CH_2OPMB); 0.87-0.85 (15 H, m, Si(C*H*$_3$)$_3$, =CHCH(C*H*$_3$), CH(C*H*$_3$)CH_2OPMB); 0.01 (3H, s, Si(C*H*$_3$)$_A$(CH_3)$_B$); 0.00 (3H, s, Si(CH_3)$_A$(C*H*$_3$)$_B$.

(2*E*/*Z*)-3-ethyl-5-phenylpenta-2,4-dienoic acid ethyl ester ((*E*,*E*)/(*Z*,*E*)-342)



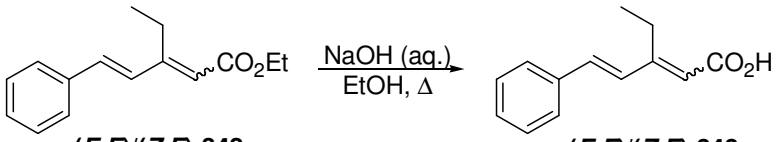
The ketone **301** (0.20 g, 1.50 mmol) and ylide **341** (0.52 g, 1.50 mmol) were heated to 170 °C and maintained at this temperature overnight. After this time the reaction

was cooled to room temperature and the product purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.34) yielding 89 mg (26 %) of the desired ester as a mixture of **(*E,E*)-342** and **(*Z,E*)-342** (ratio 0.5:1.0) isomers, which were partially separated.

(*Z,E*)-342: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.28 (1H, d, *J* = 16.5, C*H*=); 7.48-7.45 (2H, m, Ar*H*); 7.29-7.17 (3H, d, Ar*H*); 6.86 (1H, d, *J* = 16.5, C*H*=); 5.67 (1H, s, =C*H*CO_2Et); 4.12 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$); 2.43 (2H, q, *J* = 7.5 Hz, C$H_2$$CH_3$); 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); 1.12 (3H, t, *J* = 7.5 Hz, CH_2CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 166.7; 156.3; 136.9; 134.3; 128.6; 128.5; 127.3; 125.1; 116.1; 59.7; 26.8; 14.3; 13.6; **IR** (film, cm^{-1}) 2974; 1705; 1622; 1600; 1448; 1382; 1276; 1227; 1204; 1153; 1037; 974; 860; 755; 691; **HREIMS** $C_{15}H_{17}O_2$ requires 230.1307, found 230.1302.

(*E,E*)-342: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (2H, m, Ar*H*); 7.35-7.26 (3H, m, Ar*H*); 6.96 (1H, d, *J* = 16.2 Hz, C*H*=); 6.72 (1H, d, *J* = 16.2 Hz, C*H*=); 5.85 (1H, s, C=C*H*(CO_2Et)); 4.20 (2H, q, *J* = 6.9 Hz, OCH_2); 2.93 (2H, q, *J* = 7.2 Hz, C$H_2$$CH_3$); 1.31 (3H, t, *J* = 6.9 Hz CH_2CH_3); 1.19 (3H, t, *J* = 7.2 Hz, CH_2CH_3).

(2*E/Z*, 4*E*)-3-ethyl-5-phenylpenta-2,4-dienoic acid ((*E,E*)/(*Z,E*)-343)



(*E,E*)/(*Z,E*)-342 **(*E,E*)/(*Z,E*)-343**

A solution of the ethyl esters **(*E,E*)-342** and **(*E,Z*)-342** (35 mg, 0.15 mmol) in ethanol (0.5 mL) and aqueous NaOH (1 M, 200 μL) was heated under reflux for 4 hours. The ethanol was removed in *vacuo* and the aqueous layer extracted acidified and extracted with Et_2O (3 x 10 mL), The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo* yielding 30 mg (100 %) of a mixture of acids **(*E,E*)-343** and **(*E,Z*)-343** (ratio 0.5:1.0).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (0.5H, d, *J* = 16.5 Hz, C*H*=); 7.56-7.27 (7.5 H, m, Ar*H*); 7.01 (1H, *J* = 15.9 Hz, C*H*=); 7.00 (0.5H, d, *J* = 16.5 Hz, C*H*=); 6.76 (1H, d, *J* = 15.9 Hz, C*H*=); 5.88 (1H, s, =CH(CO_2*H*)); 5.79 (1H, s, =C*H*(CO_2H)); 2.95 (2H, q, *J* = 7.5 Hz, C$H_2$$CH_3$); 2.56 (1H, q, *J* = 7.5 Hz, C$H_2$$CH_3$); 1.27-1.17 (5.5H, m, CH_2CH_3, CH_2CH_3).

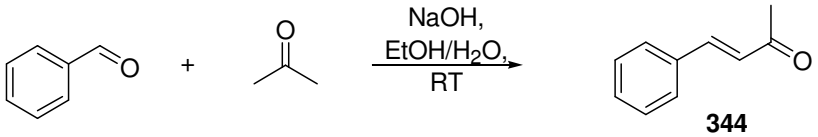
[(1*E*/*Z*,3*E*)-3-iodomethylenepent-1-enyl]-benzene ((*E*,*E*)/(*E*,*Z*)-338)

(*E*,*E*)/(*Z*,*E*)-343 **(*E*,*E*)/(*Z*,*E*)-338**

To a solution of TBATFA (11 mg, 0.030 mmol) in DCE (0.5 mL) was added a solution of the carboxylic acids **(*E*,*E*)-343** and **(*Z*,*E*)-343** (30 mg, 0.015 mmol) in DCE (3 x 100 μL) *via* a cannula. The solution was stirred at room temperature for 5 minutes, before addition of NIS (37 mg, 0.17 mmol) in DCE (300 μL) dropwise. The reaction progress was monitored by TLC and after 3 hours no change was occurring so the solvent was removed in *vacuo* and the product purified by column chromatography (100 % mixed hexanes, R_f = 0.36) yielding 24 mg (58 %) of the iodide as a mixture of inseparable **(*E*,*E*)-338** an **(*E*,*Z*)-338** isomers (ratio 0.5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.26 (7.5H, m, Ar*H*); 7.12 (1H, d, *J* = 16.2 Hz, C*H*=); 6.77 (0.5H, d, *J* = 16.8 Hz, C*H*=); 6.72 (0.5H, d, *J* = 16.8 Hz, C*H*=); 6.66 (1H, d, *J* = 16.2 Hz, C*H*=); 6.43 (1H, s, =C*H*(I)); 6.27 (0.5H, s, =C*H*(I)); 2.56 (2H, q, *J* = 7.5 Hz, CH_2CH$_3$); 2.52 (1H, qd, *J* = 7.5, 0.9 Hz, CH_2CH$_3$); 1.78 (1.5H, t, *J* = 7.5 Hz, CH$_2$CH_3); 1.12 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3).

4-phenylbut-3-en-2-one (344)

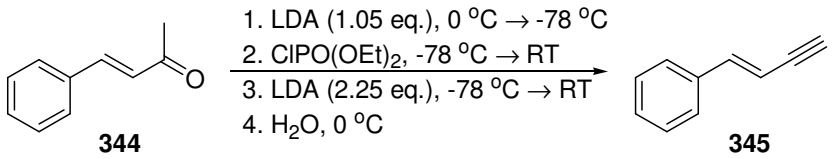


344

As per the procedure for ketone **301** using benzaldehyde (0.95 mL, 1.0 g, 9.42 mmol) and acetone (6.9 mL, 5.47 g, 94.2 mmol). Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.35) yielded 1.15 g (83 %) of the ketone **344** as a white solid with spectroscopic data consistent with the commercially available (Sigma-Aldrich) ketone.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.49 (3H, m, Ar*H*, C*H*=); 7.42-7.39 (3H, m, Ar*H*); 6.72 (1H, d, *J* = 16.8 Hz, C*H*=); 2.39 (3H, s, CH_3); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 198.3; 143.4; 130.5; 129.0; 128.2; 127.2; 27.5; **IR** (film, cm^{-1}) 3028; 1690; 1668; 1609; 1576; 1495; 1450; 1358; 1328; 1256; 1204; 1175; 975; 749; 680; **HREIMS** $C_{10}H_{10}O$ requires 146.0732, found 146.0732.

(1*E*)-but-1-en-3-ynylbenzene (345)



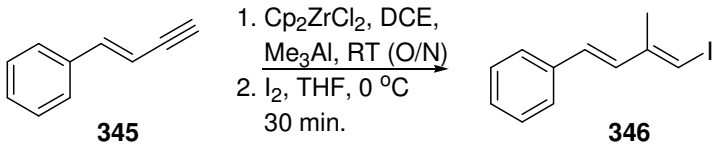
344 **345**

To a flask charge with THF (1 mL) at 0 °C was added diisopropyl amine (151 µL, 109 mg, 1.08 mmol) and ^{n}BuLi in hexane (1.37 M, 788 µL, 1.08 mmol). The solution was stirred for 30 minutes at 0 °C before cooling to -78 °C. The ketone **344** (150 mg, 1.03 mmol) was added in THF (500 µL, 300 µL, 200 µL) dropwise and the bright yellow mixture stirred for 1 hour at -78 °C. Diethylchlorophosphate (155 µL, 186 mg, 1.08 mmol) is added and the solution allowed to warm to room temperature over 2-3 hours, during which time the bright yellow colour faded.

In a separate flask isopropyl amine (325 µL, 235 mg, 2.32 mmol) and ^{n}BuLi (1.37 M, 1.69 mL, 2.32 mmol) were stirred in THF (1 mL) at 0 °C for 30 minutes before cooling to -78 °C. To this solution was added the above solution *via* a cannula over 45 minutes. The resulting mixture was allowed to warm to room temperature over 2-3 hours before quenching with H_2O (2-3 mL) at 0 °C. The organic layer was separated and the aqueous layer extracted with pentane (3 x 10 mL). The combined organics were washed with ice-cold HCl (1 M, 10 mL), water (2 x 10 mL) and $NaHCO_3$ (sat. aq.) until pH > 8. The combined organics were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % CH_2Cl_2/mixed hexanes, R_f = 0.6) yielding 29 mg (22 %) of the desired alkyne **345**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (5H, m, Ar*H*); 7.05 (1H, d, *J* = 16.2 Hz, ArC*H*=); 6.14 (1H, dd, *J* = 16.2, 2.4 Hz, ArCH=C*H*); 3.06 (1H, d, *J* = 2.4 Hz, =CHCC*H*); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 143.1; 135.9; 128.9; 128.7; 126.3; 107.0; 82.9; 79.2; **IR** (film, cm^{-1}) 3291; 3032; 1491; 955; 748; 690.

(1*E*, 3*E*)-(4-iodo-3-methylbuta-1,3-dienyl)-benzene (346)



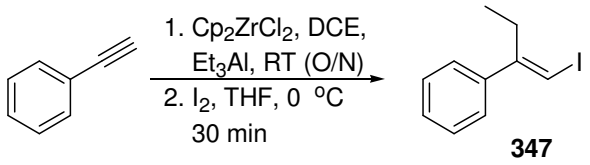
345 **346**

To a suspension of Cp_2ZrCl_2 (19 mg, 0.065 mmol) in DCE (0.2 mL) at room temperature under nitrogen, was added a solution of Me_3Al in toluene (2 M, 65 µL, 0.13 mmol) dropwise. The resulting clear yellow solution was stirred in the dark for

10 minutes before addition of the alkyne **345** (8.3 mg, 0.065 mmol) in DCE (3 x 100 µL) dropwise. The resulting solution was stirred for 20 hours before cooling to 0 ^{o}C and adding a solution of I_2 (20 mg, 0.078 mmol) in THF (3 x 100 µL). The dark brown/red solution was stirred at 0 ^{o}C for 30 minutes until no further colour change occurred. The reaction was quenched by the addition of H_2O (5 mL) followed by addition of Et_2O (15 mL). The layers were separated and the organic layer dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (100 % mixed hexanes, R_f = 0.45) yielded 3 mg (17 %) of **(*E*,*E*)-346** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.26 (2H, m, Ar*H*); 7.41-7.32 (3H, m, Ar*H*); 7.17 (1H, s, =C*H*(I)); 7.08 (1H, d, *J* = 15.0 Hz, C*H*=); 6.63 (1H, d, *J* = 15.0 Hz, C*H*=); 1.55 (3H, s, CH_3).

(1*E*)-(1-iodomethylenepropyl)-benzene (347)

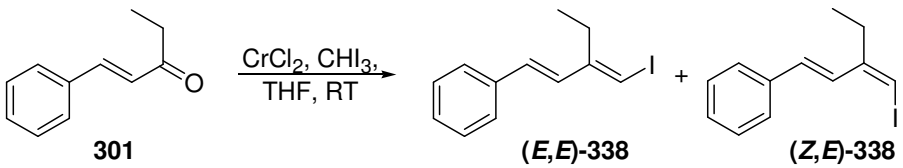


347

As per the procedure for iodide **346** using phenylacetylene (29 mg, 0.225 mol) and Et_3Al in toluene (1.1 M, 1.78 mL, 1.96 mmol), purification by column chromatography (100 % mixed hexanes, R_f = 0.5) yielded 140 mg (55 %) of the *E*-iodide **347**with spectroscopic data consistent with that reported.[309]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.27 (5H, m, Ar*H*); 6.39 (1H, s, =C*H*(I)); 2.73 (2H, q, *J* = 7.5 Hz, CH_2CH$_3$); 1.03 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3); **^{13}C NMR** (75.5 Hz, $CDCl_3$) δ 152.6; 140.5; 128.4; 127.8; 126.6; 77.9; 31.1; 12.0.

(1*E*/*Z*, 3*E*)-(3-iodomethylenepent-1-enyl)-benzene ((*E*,*E*)-338 and (*Z*,*E*)-338)



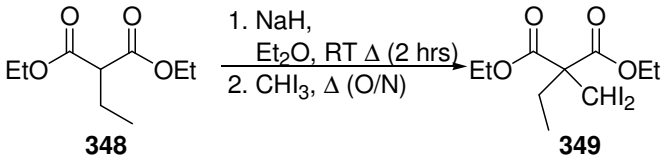
301 **(*E*,*E*)-338** **(*Z*,*E*)-338**

$CrCl_2$ (300 mg, 2.45 mmol) was dried under nitrogen with a heat gun and was cooled and suspended in THF at room temperature. To this green slurry was added a solution of the ketone **301** (56 mg, 0.35 mmol) and CHI_3 (289 mg, 0.74 mmol) in THF (2.3 mL) *via* a cannula. The resulting solution was stirred at room temperature in the dark for 4.5 hours. The reaction was quenched by the addition of H_2O (10 mL)

and the product was extracted with EtOAc (3 x 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in *vacuo*. Purification by column chromatography (100 % CH_2Cl_2, R_f = 0.75) yielded 0.60 g (86 %) of the iodo alkenes as an inseperable mixture of **(*E*,*E*)-338** and **(*Z*,*E*)-338** (1:1).

NMR data as per that reported above.

2-diiodomethyl-2-ethyl-malonic acid diethyl ester (349)

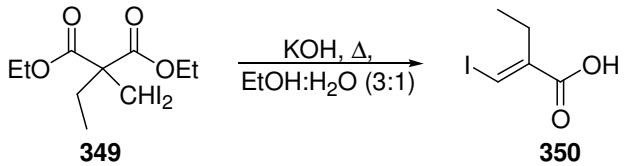


348 **349**

To a suspension of sodium hydride (60 % dispersion in mineral oil – washed with mixed hexanes and dried under N_2, 0.448 g, 19 mmol) in Et_2O (13 mL) was added diethylethylmalonate (**348**) (1.99 mL, 2 g, 11 mmol) dropwise with vigorous stirring. The resulting cloudy mixture was heated under reflux for 2.5 hours. Iodoform (1.18 mL, 4.72 g, 12 mmol) was added in one portion and the mixture heated under reflux for 20 hours. After cooling the solution to 0 ^oC, HCl (10 %, 4 mL) was added slowly and the mixture stirred for 10 minutes. The layers were separated and the organic phase dried ($MgSO_4$) and concentrated in *vacuo*. The residue was diluted with mixed hexanes (4 mL) and the precipitated iodoform removed by vacuum filtration. The filtrate was concentrated in *vacuo* and the residue distilled (130 ^oC at 2 mm Hg) yielding 3.24 g (68 %) of the diiodide **349** as a clear yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (1H, s, C*H*I_2); 4.37 - 4.21 (4H, m, OC*H*$_2$CH$_3$); 2.07 (2H, q, *J* = 7.5 Hz, CH_2Cl_3); 1.34 (6H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); 1.04 (3H, t, *J* = 7.5 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.7; 166.9; 64.0; 62.1; 30.1; 14.1; 9.4.

(2'*E*)-2-iodomethylenebutyric acid (350)



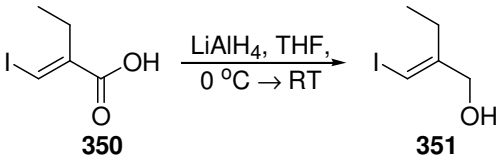
349 **350**

A solution of the malonate **349** (0.86 g, 1.90 mmol) and KOH (0.32 g, 5.71 mmol) in EtOH:H_2O (3:1, 2.6 mL) was heated under reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed in *vacuo*. The residue was dissolved in K_2CO_3 (10 % aq., 20 mL) and washed with CH_2Cl_2 (2 x 10 mL). The

basic solution was acidified with HCl (12 M) to pH 1 and the product extracted with CH_2Cl_2 (7 x 10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Further purification of the acid **350** was not required and 0.35 g (80 %) of the acid was isolated.

^{1}H NMR (200 MHz, $CDCl_3$) δ 11.3 (1H, br s, O*H*); 7.97 (1H, s, =C*H*(I)); 2.52 (2H, q, *J* = 7.4 Hz, CH_2CH$_3$); 1.06 (3H, t, *J* = 7.4 Hz, CH$_2$CH_3).

(2'*E*)-2-iodomethylene-butan-1-ol (351)



350 **351**

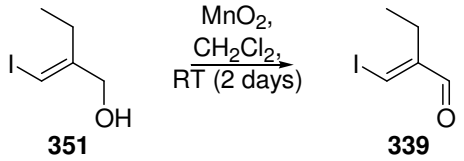
To a cooled (0 °C) solution of the acid **350** in THF (3 mL) was added $LiAlH_4$ (70 mg, 1.86 mmol) carefully over 10 minutes. The suspension was stirred at room temperature for 3 hours. The reaction mixture was re-cooled to 0 °C and quenched by the slow addition of Na_2SO_4 (sat. aq., 10 mL). The reaction mixture was diluted with Et_2O (20 mL) and the mixture poured onto H_2SO_4 (2 M, 20 mL). The organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (2 x 15 mL). The combined extracts were concentrated in *vacuo* and the residue taken up in CH_2Cl_2 (20 mL) and washed with K_2CO_3 (10 % aq., 15 mL). The basic aqueous phase was re-extracted with CH_2Cl_2 (2 x 15 mL) and then the combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The isolated alcohol **351** (0.276 g, 70 %) was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.24 (1H, s, =C*H*(I)); 4.17 (2H, s, CH_2OH); 2.25 (2H, q, *J* = 7.4 Hz, CH_2CH$_3$); 1.04 (3H, t, *J* = 7.4 Hz, CH$_2$CH_3).

Preparation of activated MnO_2

Over a period of 1 hour, solutions of $MnSO_4.4H_2O$ (22.3 g, 0.1 mol) in H_2O (30 mL) and NaOH (40 % aq., 24 mL) were added simultaneously to a hot stirred solution of $KMnO_4$ (19 g, 0.12 mol) in H_2O (120 mL). Stirring was continued for a further hour and the brown precipitate (MnO_2) was collected by vacuum filtration in a very large funnel. The precipitate was washed thoroughly with H_2O until the washings were colourless. The product was dried in an oven at 100-120 °C and ground prior to use.

(2'*E*)-2-iodomethylenebutyraldehyde (339)

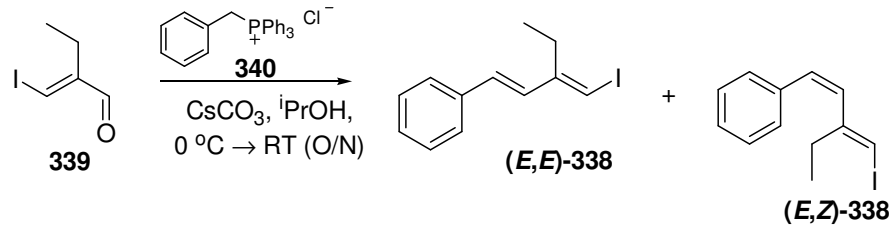


351 **339**

To a solution of the alcohol **351** (0.214 g, 1.0 mmol) in CH_2Cl_2 (4 mL) at room temperature under nitrogen was added activated MnO_2 (0.55 g, 6.36 mmol) in one portion. The resulting suspension was stirred over the weekend at room temperature. The manganese salts were removed by filtration through a silica gel plug and rinsed through with CH_2Cl_2 (30 mL). The solvent was concentrated in *vacuo* yielding 0.129 g (66 %) of aldehyde **339**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (1H, s, C*H*(=O)); 7.73 (1H, s, C*H*(I)); 2.41 (2H, q, *J* = 7.6 Hz, CH_2CH$_3$); 1.00 (3H, t, *J* = 7.6 Hz, CH$_2$CH_3).

(1*E*, 3*E*)/(1*E*, 3*Z*)-(3-iodomethylenepent-1-enyl)-benzene ((*E*,*E*)/(*E*,*Z*)-338)



339 **(*E*,*E*)-338** **(*E*,*Z*)-338**

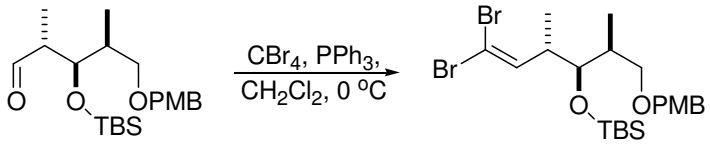
To a mixture of Cs_2CO_3 (0.50 g, 1.52 mmol) and the phosphonate salt **340** (0.53 g, 1.37 mmol) in ^{i}PrOH (3.5 mL) was stirred at 0 ^{o}C for 10 minute. To this suspension was added a solution of the aldehyde in ^{i}PrOH (1.73 mL) at 0 ^{o}C. The mixture was stirred for 1 hour at 0 ^{o}C before warming to room temperature and stirring overnight. The reaction was quenched by addition of HCl (5 % aq.) until the fizzing stoped and the solvent was evaporated in *vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The crude ^{1}H NMR spectrum revealed a mixture of **(*E*,*E*)-338** and **(*E*,*Z*)-338** however upon purification by column chromatography (100 % mixed hexanes, R_f = 0.29) yielded only 0.26g (60 %) the **(*E*,*E*)-338** isomer while the **(*E*,*Z*)-338** isomer did not elute from the column.

(*E*,*E*)-338 - **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.55 - 7.26 (5H, m, Ar*H*); 6.79 (1H, d, *J* = 16.2 Hz, C*H*=); 6.68 (1H, d, *J* = 16.2 Hz, C*H*=); 6.44 (1H, s, C*H*I); 2.57 (2H, q, *J* = 7.5 Hz, CH_2CH$_3$); 1.13 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3).

(*E*,*Z*)-338 - **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.42-7.18 (5H, m, Ar*H*); 6.42 (1H, d, *J* = 12.0 Hz, ArC*H*=); 6.14 (1H, d, *J* = 2.4 Hz, =C*H*(I)); 5.97 (1H, dd, *J* = 12.0, 2.4 Hz, ArCH=C*H*); 2.35 (2H, q, *J* = 7.6 Hz, CH_2CH_3); 1.05 (3H, t, *J* = 7.6 Hz, CH_2CH_3).

(*E*,*Z*)-338 and **(*E*,*E*)-338** - **^{13}C NMR** (50 MHz, $CDCl_3$) δ 150.5; 147.5; 136.9; 132.1; 129.7; 128.7; 128.6; 128.2; 128.1; 127.8; 126.8; 126.5; 82.9; 80.4; 27.8; 27.0; 13.3; 12.3.

4-(*tert*-butyldimethylsilyloxy)-6-(4'-methoxybenzyloxy)-3,5-dimethylhex-1-ene (353)



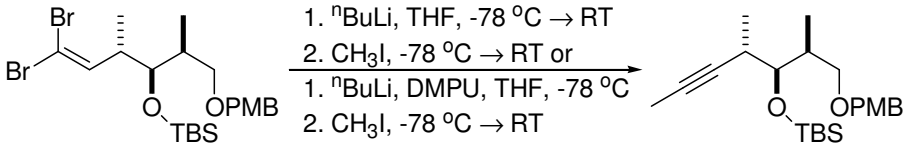
214 **353**

To a suspension of triphenylphosphine (0.422 g, 1.61 mmol) and CBr_4 (0.27 g,0.84 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added the aldehyde **214** (0.153 g, 0.40 mmol) in CH_2Cl_2 (0.5 mL, 2 x 0.25 mL). The solution was stirred at 0 °C for 5 minutes after which time TLC analysis (30 % mixed hexanes/CH_2Cl_2) revealed consumption of the starting material. The reaction was warmed to room temperature and diluted with Et_2O (30 mL). The solution was filtered at the H_2O pump and mixed hexanes added to the filtrate to further precipitate out the triphenylphosphine oxide. The solution was again filtered at the H_2O pump and the filtrate concentrated in *vacuo*. Purification by column chromatography (30 % mixed hexanes/CH_2Cl_2, R_f = 0.54) yielding 0.204 g (95 %) of the dibromoalkene **353** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.4 Hz, Ar*H*); 6.89 (2H, d, *J* = 8.4 Hz, Ar*H*); 6.38 (1H, d, *J* = 9.6 Hz, C*H*=C); 4.44 (1H, d, *J* = 11.7, OC$H_A$$H_B$Ar); 4.38 (1H, d, *J* = 11.7 Hz, OC$H_A$$H_B$Ar); 3.81 (3H, 3H, s, OC$H_3$); 3.67 (1H, apt t, *J* = 4.2 Hz, C*H*(OTBS)); 3.38 (1H, dd, *J* = 9.3, 6.3 Hz, C$H_A$$H_B$OPMB); 3.19 (1H, dd, *J* = 9.3, 7.2 Hz, C$H_A$$H_B$OPMB); 2.65-2.58 (1H, m, =CHC*H*(CH_3)); 1.95-1.85 (1H, m CH(OTBS)C*H*(CH_3)CH_2OPMB); 0.98 (3H, d, *J* = 6.9 Hz, =CHCH(CH_3)); 0.91 (3H, d, *J* = 6.3 Hz, CH(OTBS)CH(CH_3)CH_2OPMB); 0.89 (9H, s, SiC(CH_3)$_3$); 0.06 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); 0.03 (3H, s, Si(CH_3)$_A$(CH_3)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 141.6; 130.6; 129.3; 113.7; 87.9; 75.7; 72.6; 72.3; 55.3; 42.5; 38.4; 26.1; 18.3; 17.2; 12.6; -3.9; -4.0; **IR** (film, cm^{-1}) 2956; 2932; 2850; 1609; 1514; 1463; 1251; 1091; 1037; 839; 778; $[\alpha]_D^{20}$ = 0 (*c* 0.9, $CHCl_3$); **HRMS (ESI)** $C_{22}H_{36}Br_2NaO_3Si^+$

requires 557.0693, found 557.0698; **LREIMS** 357 (20 %); 324 (24 %); 323 (100 %); 251 (13 %); 187 (86 %); 145 (29 %); 137 (42 %).

5-(*tert*-butyldimethylsilyloxy)-7-(4'-methoxybenzyloxy)-4,6-dimethylhept-2-yne (352)



353 **352**

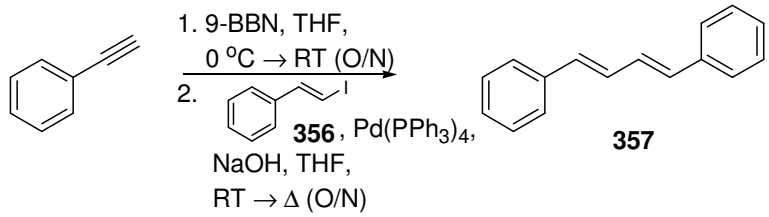
Procedure 1: To a stirred solution of the dibromoalkene **353** (64 mg, 0.12 mmol) in THF (0.5 mL) at -78 °C was added dropwise a solution of ^{n}BuLi in hexanes (1.6 M, 154 μL, 0.25 mmol). The mixture was allowed to warm to room temperature over two hours before cooling back to -78 °C. CH_3I (22 μL, 51 mg, 0.36 mmol) was added dropwise and the mixture was allowed to reach room temperature and was stirred for 20 hours. The reaction was quenched with NH_4Cl (sat. aq., 10 mL) and the product extracted with Et_2O (2 x 15 mL). The combined extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (20 % mixed hexanes/CH_2Cl_2, R_f = 0.33) yielding 37 mg (79 %) of the alkyne **352** as a clear, colourless oil.

Procedure 2: To a -78 °C solution of the dibromoalkene **353** (20 mg, 0.037 mmol) in THF (0.5 mL) was added ^{n}BuLi (1.38 M, 60 μL, 0.083 mmol). After stirring at -78 °C for 1 hour, DMPU was added and the solution stirred for 15 minutes. CH_3I (12 μL, 26 mg, 0.19 mmol) was added dropwise and the solution stirred for 30 minutes at -78 °C. The solution was warmed to room temperature and stirred for a further 30 minutes, during this time the solution turned brown. The reaction was quenched by the addition of H_2O (5 mL) and the product partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The product was purified by column chromatography (50 % mixed hexanes/CH_2Cl_2, R_f = 0.27) yielding 15 mg (100 %) of the alkyne **352** as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.24 (2H, m, Ar*H*); 6.90-6.86 (2H, m, Ar*H*); 4.42 (2H, br s, OCH_2Ar); 3.81 (3H, s, OCH_3); 3.77 (1H, dd, *J* = 5.1, 3.3 Hz, C*H*(OTBS)); 3.44 (1H, dd, *J* = 9.0, 6.6 Hz, C$H_A$$H_B$OPMB); 3.28 (1H, dd, *J* = 9.0, 6.6

Hz, CH_AH_BOPMB); 2.62 (1H, ddd, *J* = 7.2, 5.1, 2.4 Hz, C-C*H*(CH_3)); 2.14-2.06 (1H, m, C*H*(CH_3)CH_2); 2.03 (3H, d, *J* = 2.4 Hz, C*H*$_3$C); 1.18 (3H, d, *J* = 7.2 Hz, CCH(C*H*$_3$)); 0.92 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)CH_2); 0.90 (9H, s, SiC(C*H*$_3$)$_3$); 0.09 (3H, s, Si$(CH_3)_A(CH_3)_B$); 0.04 (3H, s, Si$(CH_3)_A$(C*H*$_3$)$_B$); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 159.1; 130.8; 129.2; 113.7; 87.4; 74.5; 73.1; 72.42; 72.37; 70.0; 55.3; 36.9; 31.7; 26.1; 18.4; 17.4; 12.1; -3.9; -4.2; **IR** (film, cm^{-1}) 3311; 2956; 2930; 2856; 16.13; 15.14; 1463; 1249; 1085; 1056; 1039; 836; 774; $[\alpha]_D^{20} = 0$ (*c* 0.2, $CHCl_3$); **HRMS (ESI)** $C_{23}H_{38}NaO_3Si^+$ requires 413.2482, found 413.2478; **LREIMS** 323 (28 %); 251 (2 %); 211 (3 %); 187 (17 %); 145 (4 %); 137 (10 %); 121 (100 %); 97 (8 %); 89 (6 %); 73 (22 %); 59 (3 %).

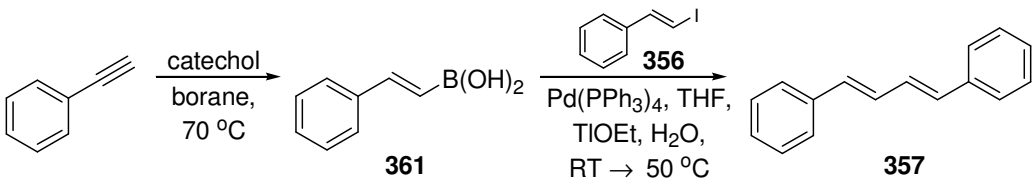
(1*E*, 3*E*)-1,4-diphenylbutyl-1,3-diene (357)



To a solution of phenylacetlyene (54 mL, 50mg, 0.49 mmol) in THF (2 mL) at 0 °C was added a solution of 9-BBN in THF (0.5 M, 2.1 mL, 1.03 mmol). The solution was warmed to room temperature and stirred for 15 hours. This solution was added at room temperature to a stirring suspension of $Pd(PPh_3)_4$ (57 mg, 0.49 mmol), iodide **356** (90 mg, 0.39 mmol) and NaOH (1 M, 0.98 mL, 0.98 mmol) in THF (1.96 mL). The reaction mixture was heated under reflux overnight before cooling to room temperature and then further cooling in an ice bath. H_2O_2 (30 %, 1 mL) was added slowly and the solution stirred for 30 minutes. The reaction mixture was poured onto mixed hexanes and washed with HCl (1 M, 10 mL), $NaHCO_3$ (sat. aq., 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography (20 % CH_2Cl_2/mixed hexanes, R_f = 0.36) yielded 47 mg (59 %) of the diene **357** as a white powder with ^{1}H NMR data consistent with the commercially available sample from Sigma-Aldrich.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.23 (10H, m, Ar*H*); 6.99 (2H, dd, *J* = 12.0, 3.0 Hz, C*H*=, C*H*=); 6.70 (2H, dd, *J* = 11.7, 3.0 Hz, C*H*=, C*H*=).

1,4-diphenylbutyl-1,3-diene (324)

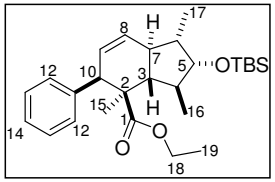


A mixture of phenylacetylene (54 μL, 50 mg, 0.49 mmol) and catecholborane (0.31 g, 2.54 mmol) was heated to 70 °C for 2 hours. To the mixture was added MeOH (1 mL) and H_2O (1 mL). The product was extracted with Et_2O (3 x 15 mL), the combined extracts were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Assuming complete conversion to the borane **361**, the product was immediately used in a Suzuki cross-coupling reaction without further purification. To a mixture of the borane **361**, $Pd(PPh_3)_4$ (57 mg, 0.49 mmol) and iodide **356** (56 mg, 0.25 mmol) in THF (0.6 mL) was added a solution of TlOEt (17 μL, 61 mg, 0.25 mmol) in H_2O (0.6 mL). The solution was heated to 50 °C for 1 hour before diluting with Et_2O (20 mL). The reaction mixture was dried ($MgSO_4$) and the suspension, containing $MgSO_4$, was filtered through a Celite plug and rinsed with Et_2O before concentrating the filtrate in *vacuo*. Purification by column chromatography (30 % CH_2Cl_2/mixed hexanes, R_f = 0.45) yielded <10 mg (5 %) of the diene **357**.

NMR data consistent with that reported above.

CHAPTER 7 APPENDICES

Appendix 1 Table of NMR data for Cycloadduct 232.

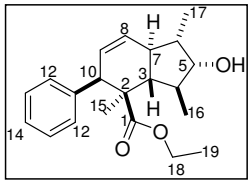


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175.3	-	H15	-	-
2	49.6	-	H3,H15, ArH	-	-
3	47	1.80 (dd) 11.2, 10.2	H15, H16	H4, H7	H4, H7, H16, ArH
4	44.3 or 44.2	1.59-1.54 (m)	H3, H5, H6, H17	H3, H5, H16	H3, H15, H16
5	82.9	3.70 (dd) 6.6, 1.8	H16, H17	H4, H6	H6, H16
6	40.4	1.70 (dq) 12.0, 6.6	H17	H5, H7, H17	H5, H7, H17
7	44.3 or 44.2	2.02 (ddddd) 11.2, 11.2, 2.4, 2.4, 2.4	H3, H5, H6, H17	H3, H6	H3, H6, H15, H17
8	128	5.99 (ddd) 10.2, 1.8, 1.8	ArH	H9	H9, H17
9	128.3	5.54 (ddd) 10.2, 3.6, 3.0	ArH	H8, H10	H8, H10, H17 (wk)
10	54.3	3.31 (m)	H9, H15, ArH	H7, H8, H9	H9, H15, ArH
11	142	-	ArH	-	-
12, 13, 14	129.6; 127.7; 126.7	7.24-7.11 (m)	ArH	ArH	H3, H10
15	26.1	1.34 (m)	-	-	H4, H7, H10
16	18.3 or 18.2	0.86 (d) 7.2	H5, H6	H4	H3, H4, H5
17	12.5	1.03 (d) 6.6	H6	H6	H6, H7, H8, H9 (w)
18	59.7	3.54 (dq) 10.8, 7.2 and 3.21 (dq) 10.8, 7.2	H19	H19	H18, H19
19	13.2	0.69 (t) 7.2	-	H18	H18, H19
SiC(**CH_3**)$_3$	25.9	0.88 (s)	$Si(CH_3)_3$	-	$Si(CH_3)_2$
Si**C**$(CH_3)_3$	18.3 or 18.2	-	$Si(CH_3)_2$, $SiC(CH_3)_3$	-	-
$Si(CH_3)_A$	-4.3	0.03 (s)	$Si(CH_3)_2$	-	$SiC(CH_3)_3$
$Si(CH_3)_B$	-4.6	0.02 (s)	$Si(CH_3)_2$	-	$SiC(CH_3)_3$

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 2 Table of NMR data for Alcohol 237.

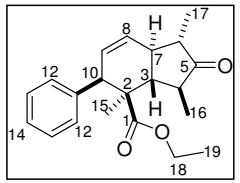


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175.1	-	H15	-	-
2	49.1	-	H3, H10	-	-
3	45.8	1.86 (dd) 11.4, 11.4	H8 (w), H15, H16	H4, H7	H4/OH, H5, H16, ArH
4	44.7	1.60-1.54 (m)	H16	H3, H5, H16	H3, H15, H16
5	82	3.80 (dd) 7.8, 5.4	H4/OH, H16, H17	H4, H6	H3, H7(w), H16, H17(w)
6	39.9	1.82-1.75 (m)	H17	H5, H7, H17	H5, H7, H16, H17
7	44.8	1.91 (ddddd) 11.4, 11.4, 1.8, 1.8, 1.8	H3, H5, H17	H3, H6, H9(w), H10 (w)	H5, H6, H8, H15, H17
8	127.5	5.99 (ddd) 9.6, 1.8, 1.8	H6, ArH	H9	H7(w), H9, H17
9	128.3	5.59 (ddd) 9.6, 3.6, 2.4	H10	H7 (w), H8, H10	H8, H10, ArH
10	54.2	3.34 (ddd) 2.4, 2.4, 2.4	H8 (w), H15, ArH	H7 (w), H9	H9, H15, ArH(w)
11	141.8	-	H15 (w)	-	-
12, 13, 14	129.5, 127.7, 126.8	7.25-7.12 (m)	H10, ArH	ArH	H3, H9(w), H10
15	17.6	1.36 (s)	-	-	H4/OH, H7, H10
16	17.9	0.92 (d) 7.2	H3, H5	H4	H3, H4/OH, H5, H6
17	11.7	1.13 (d) 7.2	H6	H6	H5, H6, H7, H8
18	59.7	3.57 (dq) 10.8, 7.2 and 3.22 (dq) 10.8, 7.2	H19	H18, H19	H18, H19
19	13.2	0.69 (t) 7.2	H18	H18, H19	H18, H19
OH		1.60-1.54 (m)			H3, H15, H16

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 3 Table of NMR data for Ketone 239.

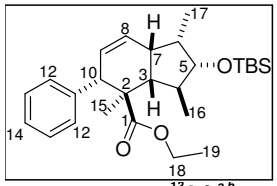


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	174.4	-	H15	-	-
2	48.9	-	H3, H15	-	-
3	44.9	2.22 (dd) 11.4, 11.4	H2, H6, H8 (wk), H15, H16	H4, H7	H4, H7, H16, ArH
4	46.3	2.03 (dq) 11.4, 7.2	H3, H5, H16	H3, H16	H3, H15, H16
5	219.8	-	H4, H6, H16, H17	-	-
6	47.7	2.04 (dq) 7.2, 7.2	H3 (wk), H5, H17	H7, H17	H7, H17
7	43.0	1.94 (ddddd) 11.4, 11.4, 1.8, 1.8, 1.8	H3, H16	H3, H6, H9, H10	H3, H6, H15, H17
8	125.9	6.11 (d) 9.6	H3, H7 (wk), H10	H9	H9
9	129	5.72 (ddd) 9.6, 3.6, 3.6	-	H7, H8, H10	H8, H10
10	53.6	3.43 (m)	H8, H15, ArH	H7, H9	H9, H15, ArH
11	141.0	-	ArH	-	-
12, 13, 14	129.5, 127.9, 127.1	7.28-7.21 (m) and 7.15 (d) 7.2	H10, ArH	ArH	H3, H10
15	17.7	1.41 (s)	-	-	H4, H7, H10
16	13.1	0.93 (d) 7.2	H3, H4, H5	H4	H3, H4
17	12.5	1.25 (d) 7.2	H5, H6, H7	H6	H6, H7
18	60.1	3.58 (dq) 10.8, 7.2 and 3.23 (dq) 10.8, 7.2	H19	H18, H19	H18, H19
19	13.5	0.69 (t) 7.2	H18	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 4 Table of NMR data for Cycloadduct 233.

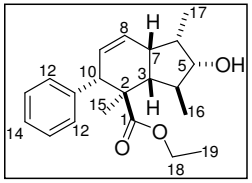


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H NOESY [a]
1	176.5	-	-	-
2	50.2	-	-	-
3	50.9	2.77 (dd) 10.3, 7.4	H4, H7	H6 (wk), H7, H10, H15 (v. wk), H16
4	40.1	1.95 (qdd) 7.0, 4.3, 3.2	H3, H5,H16	H5, H15, H16
5	79.7	3.52 (dd) 3.2, 3.2	H4, H6	H4, H6, H16, H17, $SiC(CH_3)_2$
6	44.6	1.50 (dqd) 6.6, 6.6, 3.2	H5, H7, H17	H3 (wk), H5, H15 (v. wk), H16 (wk), H17
7	43.7	2.64 (ddddd) 10.3, 10.3, 3.2, 3.2, 3.2	H3, H6, H8, H9, H10	H3, H8, H9, H10, H16 (wk), H17 (wk)
8	129.8	5.83 (ddd, 9.9, 2.8, 2.1	H7, H9, H10	H7, H9, H10, H17, ArH
9	129.5	5.88 (ddd) 9.9, 2.8, 2.8	H7, H8	H7, H8, H10, ArH
10	48.8	4.08-4.07 (m)	H7, H8, H9	H3, H7, H8, H9, H15 (wk), ArH (st)
11	142.5	-	-	-
12, 13, 14	130.1, 128.3, 127.0	7.29-7.10 (m)	ArH	H8, H9, H10, H15 (st)
15	12.9	1.13 (s)	-	H3 (v. wk), H4, H6 (v. wk), H10 (wk), ArH(st)
16	16.1	1.02 (d) 7.0	H4	H3, H4, H5, H6 (wk)
17	14.2	0.96 (d) 6.6	H6	H4, H5, H6, H7 (wk)
18	60.3	3.97 (qd) 7.2, 6.8 and 3.94 (dq) 10.8, 7.2	H19	H19
19	13.4	0.92 (t) 7.2	H18	H18
$SiC(\mathbf{CH_3})_3$	26.3	1.01 (s)	-	$Si(CH_3)_2$
$Si\mathbf{C}(CH_3)_3$	18.6	-	-	-
$Si(CH_3)_A$	-3.8	0.0349	-	H5, $SiC(CH_3)_3$
$Si(CH_3)_B$	-3.9	0.0347	-	H5, $SiC(CH_3)_3$

[a] NMR spectrometer (600 MHz, C_6D_6). Assignments assisted by ^{1}H-^{13}C HMBC,, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY

[b] Chemical shifts in ppm referenced to C_6D_6 at 7.16 ppm and to C_6D_6 at 128 ppm

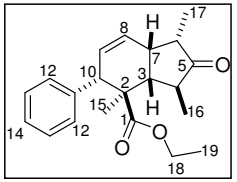
Appendix 5 Table of NMR data for Alcohol 238.



carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H NOESY [a]
1	176.8	-	-	-
2	48.6	-	-	-
3	50.7	2.66 (dd) 10.3, 7.2	H4, H7	H4, H5, H7, H10(wk), H15 (wk), H16
4	39	2.11 (dqd) 7.2, 7.2, 4.4	H3, H5,H16	H3, H15, H16
5	79.3	3.93 (dd) 4.0	H4, H6	H4, H6, H16 (wk), H17 (wk)
6	43.8	1.79 (dqd) 13.2, 6.7, 3.7	H5, H7, H17	H15 (wk), H17
7	43.5	2.59 (ddddd) 10.3, 10.3, 3.0, 3.0, 3.0	H3, H6, H8, H9, H10	H4, H8, H10, H16 (wk)
8	129.2	5.98 (ddd) 10.0, 3.0, 3.0	H7, H9 (wk), H10	H7, H9, H10,
9	129.2	5.83 (ddd) 10.0, 2.8, 2.8	H7, H8, H10 (wk)	H8, H10, ArH(12)
10	49.7	3.95 (m)	H7, H8, H9 (wk)	H3 (wk), H4 (wk), H7, H8, H9, ArH(12)
11	141.7	-	-	-
12	129.5	7.17-7.16 (m)	H10	H9, H10, H15
13	127.8	7.29-7.24 (m)	H10	ArH
14	126.6	7.24-7.21 (m)	H10	ArH
15	12.4	0.95 (s)	-	H3 (wk), H4, H6 (wk), ArH(12)
16	14.6	0.98 (d) 7.2	H4	H3, H4, H5 (wk), H7 (wk)
17	12.2	1.12 (d) 6.7	H6	H5 (wk), H6, H7 (wk)
18	60.8	4.07 (q) 7.2	H19	H19
19	14.2	1.24 (t) 7.2	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY
[b] NMR spectrometer (75 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMQC
[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 6 Table of NMR data for Ketone 240.

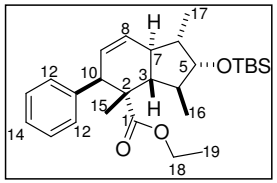


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175.9	-	H3, H15, H18	-	-
2	49.6	-	H3, H10, H15, ArH	-	-
3	48.1	2.79 (dd) 8.4, 1.8	H4, H15, H16	H7	H7, H10, H16
4	44.9	2.28 (qdd) 7.8, 1.8, 1.8	H3, H16	H16	H15, H16
5	222	-	-	-	-
6	47.5	2.24 (qdd) 6.6, 6.6, 1.8	H3, H8, H17	H7, H17	H7, H15, H17
7	41.7	2.58 (ddddd) 8.4, 8.4, 3.0, 3.0, 3.0	H3, H6, H8, H9, H17	H3, H6, H8, H9 (wk), H10 (wk)	H3, H6, H17
8	127.4	6.09 (ddd) 10.2, 3.6, 3.6	H6, H9, Ar	H7, H9, H10	H9, ArH(12)
9	129.7	5.90 (ddd)10.2, 2.4, 2.4	H8, ArH	H7 (wk), H8, H10	H8, H10, ArH(12)
10	49.2	4.07 (m)	H3, H4, H8, H9, H15, ArH	H7 (wk)	H3, H9, H15, ArH
11	141.1	-	H3 (wk), H9, H10, ArH	-	-
12	129.1	7.11-7.09 (m)	H10, ArH	ArH	H8, H9, H10, H15, ArH
13	128	7.29-7.25 (m)	H10, ArH	ArH	ArH
14	126.9	7.24-7.21 (m)	H10, ArH	ArH	ArH
15	12.8	0.86 (s)	H3	-	H4, H6, ArH(12)
16	17.6	1.44 (d) 7.8	H3, H4	H4	H3, H4
17	14.2	1.18 (d) 6.6	H6	H6	H6, H7
18	60.8	4.10 (q) 7.2	H19	H19	H19
19	14.7	1.94 (t) 7.2	H18	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 7 Table of NMR data for Cycloadduct 234.

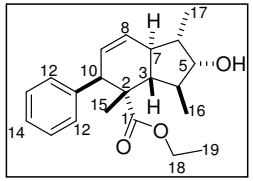


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175.7	-	H3, H10, H15, H18	-	-
2	49.1	-	H3, H4, H10, H15	-	-
3	52.8	1.36 (dd) 11.4, 9.6	H4, H5, H8, H10, H15, H16	H4, H7	H7, H15, H16, ArH
4	43.9	2.39 (dqd) 9.6, 7.2, 1.8	H3, H16	H3, H16	H16
5	84.5	3.52 (dd) 6.6, 1.8	H4, H16, H17	H6	H6, H16
6	42.6	1.43 (ddq) 6.6, 6.6, 6.6	H3, H8, H17	H5, H7, H17	H5, H17
7	45.7	2.24 (ddddd) 11.4, 11.4, 2.4, 2.4, 2.4	H3, H5, H6, H8, H9 H17	H3, H6	H3, H17
8	128.8	5.93 (ddd) 9.6, 1.8, 1.8	H3, H10, ArH		H9
9	130.7	5.72 (ddd) 9.6, 4.2, 1.8	H10, ArH	H10	H8, H10
10	51.1	4.27 (dddd) 1.8, 1.8, 1.8, 1.8	H3, H8, H9 (v wk), H15,	H9, H7 (w), H8 (w)	H9, ArH
11	141.7	-	H10, ArH	-	-
12, 13, 14	131.0, 128.0,127.0	7.16-7.03 (m)	ArH	ArH	H3, H10, H15
15	23.9	0.92 (s)	-	-	H3, ArH
16	21.2	0.87 (d) 7.2	H3, H4, H5	H4	H3, H4, H5
17	12.2	1.01 (d) 6.6	H6,	H6	H6, H7, H8
18	60.4	3.99 (dq) 10.8, 7.2 and 4.06 (dq) 10.8, 7.2	H15, H19	H19	-
19	14.4	1.02 (t) 7.2	H18	H18	-
$SiC(\mathbf{CH_3})_3$	26.2	0.95 (s)	$SiC(CH_3)_3$	-	$Si(CH_3)_2$
$Si\mathbf{C}(CH_3)_3$	18.4	-	$Si(CH_3)_2$, H5	-	-
$Si(CH_3)_A$	-4.0	0.03 (s)	$Si(CH_3)_2$	-	$SiC(CH_3)_3$
$Si(CH_3)_B$	-4.6	0.01 (s)	$Si(CH_3)_2$	-	$SiC(CH_3)_3$

[a] NMR spectrometer (600 MHz, C_6D_6). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to C_6D_6 at 7.16 ppm and to C_6D_6 at 128 ppm

Appendix 8 Table of NMR data for Alcohol 241.

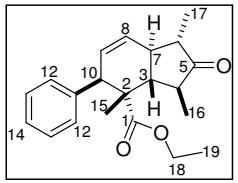


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	176.7	-	H10, H15, H18, H19	-	-
2	48.7	-	H3, H4(wk), H9(wk), H10(wk), H15	-	-
3	51.7	1.28 (dd) 12.0, 9.6	H4, H5, H6, H8, H10(wk), H15, H16	H4, H7	H4, H6, H7(w), H15, H16, ArH
4	43.5	2.19 (dqd) 9.6, 7.2, 2.4	H3, H16	H3, H5, H16	H3, H5, H7, H15, H16
5	83.7	3.62 (dd) 7.2, 2.4	H4, H6, H16, H17	H4, H6	H4, H6, H16, H17(w)
6	41.3	1.59 (ddq) 7.2, 7.2, 7.2	H8, H17	H5, H7, H17	H3, H5, H7, H17
7	45.2	1.98 (ddddd) 12.0, 12.0, 2.4, 2.4, 2.4	H3, H5, H6,H8, H17	H3, H6, H9, H10	H3(w), H4(w), H6, H8, H17
8	128.4	5.91 (ddd) 9.6, 1.8, 1.8	H3, H6, H7, H10, H11	H9, H10	H7, H9, H17
9	130.1	5.58 (ddd) 9.6, 4.2, 3.0	H2(w), H7 H10	H7, H8, H10	H8, H10, ArH
10	50.4	4.02 (m)	H3, H8, H9, H15, ArH	H7, H9	H9, H15, ArH
11	140.8	-	H8, H10, ArH	-	-
12, 13, 14	130.6, 127.8, 126.7	7.23-7.12 (m)	H10	-	H3, H9(w), H10, H15
15	23.4	0.81 (s)	H3, H16	-	H3, H4, H9, H10, H16, ArH,
16	21.2	0.93 (d) 7.2	H3, H4, H5, H15	H4	H3, H4, H5, H15
17	11.1	1.03 (d) 7.2	H6, H16	H6	H5(w), H6, H7, H8
18	60.7	4.16 (dq) 10.8, 7.2 and 4.12 (dq) 10.8, 7.2	H19	H18, H19	H19
19	14.3	1.23 (t) 7.2	H10, H18	H18	H18
OH					

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 9 Table of NMR data for Ketone 244.

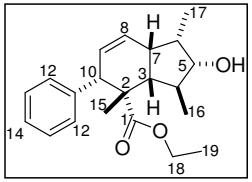


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	176	-	H3, H15, H18	-	-
2	48.2	-	H3, H10, H15	-	-
3	48.4	1.68 (dd) 11.4, 11.4	H4, H16	H4, H7	H4, H6, H7, H15, H16
4	45.9	2.63 (dq) 12.0, 7.2	H3, H16	H3, H16	H3, H16
5	220.7	-	H3, H6, H16, H17	-	-
6	48.5	2.00 (dq) 6.0, 6.0	H8, H17	H17	H3, H17
7	44.3	1.97 (ddddd)11.4, 11.4, 2.4, 2.4, 2.4	H3, H6, H8 (w), H17	H3	H3
8	126.7	6.06 (d) 9.6	H3, H6/H7, H10	H9	H9, H17 (w)
9	130.6	5.78 (ddd) 9.6, 4.2, 2.4	H10, ArH	H8, H10	H8, H10
10	49.9	4.15 (m)	H3 (w), H8, H15, ArH	H9	H9, H15, ArH
11	139.9	-	H10, ArH	-	-
12, 13, 14	130.6, 128.0, 127.0	7.32-7.21 (m)	ArH	ArH	H3, H10, H15
15	23.8	0.97 (s)	H16 (w)	-	H3, H10, ArH
16	16.2	1.08 (d) 7.2	H3, H4, H17(w)	H4	H3, H4
17	12.2	1.20 (d) 6.0	H6	H6	H6, H8 (w)
18	60.9	4.21 (q) 7.2	H19	H19	H19
19	14.3	1.27 (t) 7.2	H18	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 10 Table of NMR data for Alcohol 242.



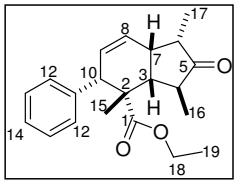
carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H NOESY [a]
1	176.6	-	-	-
2	48.7	-	-	-
3	51.7	1.37 (dd) 9.3, 5.1	H4, H7	H4, H6 (wk), H7, H15, H16, ArH
4	43.5	2.28 (dqd) 9.3, 7.0, 2.3	H3, H5,H16	H3, H5 (wk), H15 (wk), H16
5	83.6	3.71 (dd) 5.7, 2.3	H4, H6	H4 (wk), H6, H16, H17 (wk), OH
6	41.3	1.68 (dqd) 6.8, 6.8, 5.7	H5, H7, H17	H3 (wk), H5, H7, H16 (wk), H17
7	45.2	2.05 (ddddd) 12.1, 9.3, 2.0, 2.0, 2.0	H3, H6, H8, H9, H10	H3, H6, H8, H9, H10 (wk), H17 (wk)
8	130.1	6.00 (ddd) 9.8, 1.7, 1.7	H7, H9, H10, ArH	H7, H9, H10, H17 (wk)
9	128.4	5.66 (ddd) 9.8, 4.1, 2.9	H7, H8, H10, ArH	H7, H8, H10
10	50.4	4.11-4.10 (m)	H7, H8, H9, ArH	H7 (wk), H8, H9, H15, ArH
11	140.8	-	-	-
12, 13, 14	130.6, 127.7, 126.7	7.33-7.21 (m)	H10 (wk), ArH	H3, H10, H15
15	23.5	0.90 (s)	-	H3, H4 (wk), H10, ArH
16	21.3	1.01 (d) 7.0	H4	H3, H4, H5, H6 (wk)
17	11.2	1.11 (d) 6.8	H6	H5 (wk), H6, H7 (wk), H8 (wk)
18	60.7	4.25 (qd) 10.8, 7.1 and 4.20 (dq) 10.8, 7.1	H19	H19
19	14.3	1.32 (t) 7.1	H18	H18
OH	-	1.61 (br s)	-	-

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY

[b] NMR spectrometer (75 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMQC

[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 11 Table of NMR data for Ketone 245.



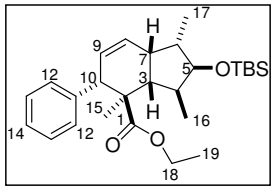
carbon no.	^{13}C δ [b,c]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H NOESY [a]
1	176	-	-	-
2	48.2	-	-	-
3	48.4	1.69 (dd) 11.4, 11.4	H4, H7	H6/7, H15, H16, H17 (wk), ArH(12)
4	46.3	2.65 (dq) 11.4, 7.2	H3, H16	H16
5	220.8	-	-	-
6	48.5	1.98 (dq) 6.6, 6.6	H7, H17	H3, H17
7	44.3	1.99 (ddddd) 11.4, 11.4, 2.4, 2.4, 2.4	H3, H6, H10	H3, H8, H17
8	126.7	6.08 (ddd) 9.6, 1.2, 1.2	H9, H10	H7, H9, H10 (wk), H15
9	130.6	5.79 (ddd) 9.6, 4.2, 2.4	H7, H8, H10	H8, H10
10	49.9	4.16 (m)	H7 (wk), H8,H9	H8 (wk), H9, H15, ArH
11	139.9	-	-	-
12	130.6	7.24-7.22 (m)	ArH	H3, H10, H15
13	128.0	7.34-7.31 (m)	ArH	ArH
14	127.0	7.30-7.27 (m)	ArH	ArH
15	23.9	0.98 (s)	-	H3, H8, H10, ArH(12)
16	16.2	1.10 (d) 7.2	H4	H3, H4
17	12.2	1.22 (d) 6.6	H6	H3 (wk), H6/7, H8 (wk)
18	60.9	4.22 (q) 7.2 and 3.23 (dq) 10.8, 7.2	H18, H19	H18, H19
19	14.3	1.28 (t) 7.2	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY

[b] NMR spectrometer (75 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMQC

[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 12 Table of NMR data for Cycloadduct 274.

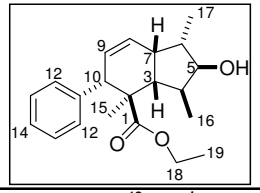


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	176.4	-	H3, H10(w), H15, H18	-	-
2	49.2	-	H3, H4, H15	-	-
3	50.5	2.56 (dd) 10.2, 6.6	H4, H10, H16	H4, H7	H7, H10, H16
4	42.3	2.05 (ddq) 6.6, 6.6, 6.6	H3, H16	H3, H5, H16	H15, H16
5	88.2	3.12 (dd) 9.0, 7.8	H4, H6, H16, H17	H4, H6	H16 (wk), H17
6	45.8	1.76 (ddq) 12.6, 9.0, 6.6	H3, H17	H4, H5, H7, H17	H7, H15, H16, H17
7	42.8	1.95 (m)	H3, H8/9, H17	H3, H6, H10	H3, H6, H8/9, H17
8	128.4/129.0	5.80 (ABq) 11.4	H7, H8/9	H10	H7, H10, H17, ArH
9	128.4/129.0	5.80 (ABq) 11.4	H8/9	H10	H7, H10, H17, ArH
10	50.1	4.12 (m)	H3, H4, H8/9, H15, ArH	H7, H8, H9	H3, H8/9, ArH(12)
11	142.4	-	H8/9, ArH	-	-
12	130.0	7.24-7.22 (m)	ArH	ArH	H8/9, H10, H15, ArH
13	128.3	7.16-7.13 (m)	H10, ArH	ArH	H8, H9,ArH
14	127	7.10-7.07 (m)	ArH	ArH	H8, H9,ArH
15	13.5	1.19 (s)	H3, H10	-	H4, H6, ArH(12)
16	20	1.03 (d) 6.6	H3, H4, H5	H4	H3, H4, H5 (wk), H6
17	16.4	1.13 (d) 6.6	H5	H6	H5, H6, H7, H8/H9
18	60.4	3.89 (q) 7.2 Hz	H19	H19	H19
19	14.2	0.87 (t) 7.2	H18	H18	H18
$SiC(\mathbf{CH_3})_3$	26.2	0.99 (s)	$Si\mathbf{C}(CH_3)_3$	-	$SiC(CH_3)_2$
$Si\mathbf{C}(CH_3)_3$	18.3	-	$SiC(C\mathbf{H_3})_3$	-	
$Si(CH_3)_A$	-3.5	0.11	-	-	$SiC(CH_3)_3$
$Si(CH_3)_B$	-3.6	0.09	-	-	$SiC(CH_3)_3$

[a] NMR spectrometer (600 MHz, C_6D_6). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to C_6D_6 at 7.16 ppm and to C_6D_6 at 128 ppm

Appendix 13 Table of NMR data for Alcohol 276.

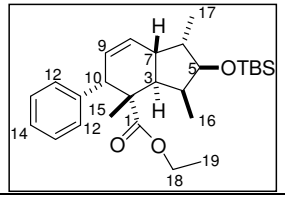


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	176.6	-	H3, H15, H18	-	-
2	48.7	-	H3, H4, H15, H16 (wk)	-	-
3	49.7	2.42 (dd) 9.6, 6.0	H4, H5 (wk), H16	H4, H7	H7, H10, H16
4	41.5	1.71 (ddq) 6.6, 6.6, 6.6	H3, H5 (wk), H16	H3, H5, H16	H5 (wk), H15, H16
5	87.1	3.10 (dd) 9.0, 9.0	H3 (wk), H4, H6, H16, H17	H4, H6	H4 (wk), H6 (wk),H7 (wk) H16, H17
6	45	1.56 (ddq) 9.6, 9.0, 6.0	H3, H5 (wk), H17	H5, H7, H17	H5 (wk), H7, H15, H17
7	42.7	2.08 (ddddd) 9.6, 9.6, 3.0, 3.0, 3.0	H3, H6, H8, H9, H17,	H3, H6, H8, H9, H10	H3, H5 (wk), H6, H8, H17
8	127.9	5.87 (ddd) 9.6, 3.0, 3.0	H6 (wk), H9, H10, ArH	H7, H9, H10	H7, H9, H17
9	129.4	5.74 (ddd) 9.6, 2.4, 2.4	H8, H10	H7, H8, H10	H8, ArH
10	49.4	3.86 (m)	H3, H8, H9, H15, ArH	H7, H8, H9	H3, ArH
11	141.7	-	H9, H10, ArH	-	-
12	129.4	7.07-7.06 (m)	H9, H10, ArH	ArH	H9, H10, H15
13	127.8	7.20-7.17 (m)	H9, H10, ArH	ArH	H9, H10, H15
14	126.7	7.15-7.12 (m)	H9, H10, ArH	ArH	H9, H10, H15
15	13.0	0.92 (s)	H3	-	H4, H6, ArH
16	19.3	0.97 (d) 6.6	H3, H4, H5	H4	H3, H4, H5
17	15.7	1.02 (d) 6.0	H5	H6	H5, H6, H7,H8
18	60.4	3.99 (dq) 10.8, 7.2 and 3.96 (dq) 10.8, 7.2	H19	H19	H19
19	14.2	1.12 (t) 7.2	H18	H18	H18
OH	-	1.62 (br s)	-	-	-

[a] NMR spectrometer (600 MHz, C_6D_6). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to C_6D_6 at 7.16 ppm and to C_6D_6 at 128 ppm

Appendix 14 Table of NMR data for Cycloadduct 275.

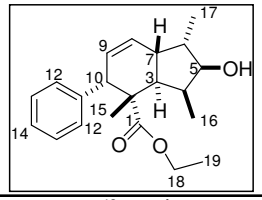


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175.2	-	H3, H15, H18	-	-
2	49	-	H3, H4(w), H9(w), H15	-	-
3	41.1	2.02 (dd) 12.0, 12.0	H4, H15, H16	H4, H7	H5 (wk), H7, H16(v. wk), H17, ArH(12)(wk)
4	45.1	1.57 (ddq) 13.2, 6.6, 6.6	H3, H16	H3, H5, H16	H15, H16
5	89.1	3.35 (dd) 6.6, 1.8	H4, H6, H16, H17	H4	H3 (wk), H6, H16 (wk), H17 (wk)
6	41.2	2.04 (dqd) 7.8, 7,8, 1.8	H3/6, H8, H17	H7, H17	H4 (wk), H5, H15(wk), H17
7	41.3	2.53 (ddddd) 10.8, 7.8, 4.8, 3.0, 1.8	H3/6, H8, H17	H3, H6, H9, H10(w)	H3, H15
8	127.5	5.91 (ddd), 10.2, 1.8, 1.8	H3, H10	H9, H10	H9
9	128.5	5.59 (ddd) 9.6, 4.2, 3.0	H10	H7, H8, H10	H8, H10
10	53.6	3.29 (m)	H3, H8, H9(w), H15, ArH,	H7(wk), H8, H9	H9, H15, ArH(12)
11	141.9	-	-	-	-
12	129.5	7.13-7.11 (m)	H10, ArH	ArH	H3(wk), H10, ArH
13	127.7	7.25-7.22 (m)	ArH	ArH	ArH
14	126.7	7.20-7.18 (m)	ArH	ArH	ArH
15	17.6	1.36 (s)	H3,	-	H4, H7, H6 (wk) H10
16	16.9	0.79 (d) 6.6	H3,	H4	H3 (v. wk), H4, H5
17	16	1.07 (d) 7.8	H4, H5, H6	H6	H3, H5, H6
18	59.7	3.57 (dq) 10.8, 7.2 and 3.23 (dq) 10.8, 7.2	H19	H18, H19	H19
19	13.2	0.69 (t) 7.2	H18	H18	H18
$SiC(\mathbf{CH_3})_3$	25.9	0.89 (s)	$SiC(CH_3)_3$	-	$Si(C\mathbf{H_3})_2$
$Si\mathbf{C}(CH_3)_3$	18	-	$SiC(CH_3)_3$, $Si(CH_3)_2$	-	-
$Si(CH_3)_A$	-4.2	0.07 (s)	$Si(CH_3)_2$	-	$Si(C\mathbf{H_3})_3$
$Si(CH_3)_B$	-4.5	0.05 (s)	$Si(CH_3)_3$	-	$Si(C\mathbf{H_3})_3$

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 15 Table of NMR data for Alcohol 277.

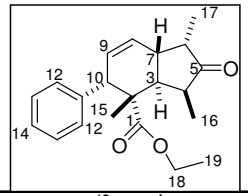


carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{13}C HMBC [a]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	175	-	H3, H15, H18	-	-
2	48.9	-	H3, H4(w), H9, H10(wk), H15	-	-
3	41.7	2.09 (dd) 11.4, 11.4	H4, H15, H16	H4, H7	H4, H5, H7, H16 (wk), H17, ArH
4	44.9	1.55 (ddq) 11.4, 6.6, 6.6	H3, H16	H3, H5, H16	H3/H6, H7, H16
5	88.9	3.41 (dd) 6.6, 1.8	H4, H6, H16, H17	H4, H6(wk)	H3/H6, H16, H17
6	41.2	2.10 (dqd) 7.8, 7,8, 2.4	H5, H6, H17	H5 (wk), H7, H17	H4, H5, H7, H16 (wk), H17, ArH
7	41.1	2.53 (ddddd) 11.4, 7.8, 2.4, 2.4, 2.4	H3, H8, H17	H3, H6, H8, H9, H10(w)	H3/H6, H4, H15
8	127.1	5.92 (ddd), 10.2, 1.8, 1.8	H7, H10, ArH	H7, H9, H10	H9, H17 (wk), ArH(12)
9	128.7	5.61 (ddd) 10.2, 4.2, 3.0	H10, ArH	H7, H8, H10	H8, H10, ArH(12)
10	53.6	3.29 (m)	H3 (wk), H8, H9, H15, ArH,	H7(wk), H8, H9	H9, H15, ArH(12)
11	141.7	-	H10, H15, Ar	-	-
12	129.5	7.12-7.11 (m)	H10, ArH	ArH	H3, H8, H9, H10, ArH
13	127.8	7.25-7.23 (m)	H10, ArH	ArH	ArH
14	126.8	7.21-7.18 (m)	H10, ArH	ArH	ArH
15	17.5	1.37 (s)	H2, H3, H10	-	H7, H10
16	16.9	0.86 (d) 7.2	H3, H4, H5, H15	H4	H3/H6(wk), H4, H5
17	16.2	1.10 (d) 7.2	H5, H6, H7	H6	H3/H6, H5, H8 (wk)
18	59.7	3.58 (dq) 10.8, 7.2 and 3.23 (dq) 11.4, 7.8	H19	H18, H19	H19
19	13.2	0.70 (t) 7.2	H18	H18	H18
OH	-	1.25 (br s)	-	-	-

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HMQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY

[b] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

Appendix 16 Table of NMR data for Ketone 278.



carbon no.	^{13}C δ [a,b]	^{1}H δ(m) J in Hz [a,b]	^{1}H-^{1}H COSY [a]	^{1}H-^{1}H ROESY [a]
1	174.3	-	-	-
2	48.9	-	-	-
3	41.9	2.42 (dd) 12.1, 12.1	H4, H7	H4, H7, H15 (wk), H16 (wk), H17, ArH(12)
4	47.1	2.08 (qdd) 12.1, 6.9, 6.9	H3, H16	H3, H7 (wk), H15, H16
5	220.7	-	-	-
6	43.3	2.65 (qdd) 7.6, 7.6, 0.9	H6, H17	H17
7	39.1	2.58 (ddddd) 12.1, 12.1, 2.6, 2.6, 2.6	H3, H6, H8, H9, H10	H3, H4 (wk), H8, H9, H10, H15
8	125.3	6.04 (ddd) 10.1, 1.8, 1.8	H7, H9, H10	H7, H9, H10, H17
9	129.6	5.74 (ddd) 10.1, 4.2, 2.4	H7, H8, H10	H7, H8, H10, ArH(12)
10	53.2	3.42 (m)	H7, H8, H9	H7, H8, H9, H15, ArH(12)
11	141.0	-	-	-
12	129.4	7.15-7.13 (m)	ArH	H3, H9, H10, H17
13	128	7.30-7.27 (m)	ArH	ArH
14	127.1	7.26-7.23 (m)	ArH	ArH
15	17.3	1.45 (s)	-	H3 (wk), H4, H7, H10, H16 (wk)
16	13.2	0.89 (d) 6.9	H4	H3 (wk), H4, H15 (wk)
17	11.7	1.18 (d) 7.2	H6	H3, H6, H8, ArH(12)
18	60	3.60 (dq) 10.1, 7.2 and 3.25 (dq) 10.1, 7.2	H18, H19	H18, H19
19	13.1	0.69 (t) 7.2	H18	H18

[a] NMR spectrometer (600 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY

[b] NMR spectrometer (75 MHz, $CDCl_3$). Assignments assisted by ^{1}H-^{13}C HMQC

[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm

CHAPTER 8 REFERENCES

1. Jimeno, J. M. *Anti-Cancer Drugs* **2002,** *13(suppl 1)*, S15-S19.
2. Pomponi, S. A. *J. Biotechnol.* **1999,** *70*, 5-13.
3. Weinheimer, A. J.; Spraggins, R. L. *Tetrahedron Lett.* **1969,** *15*, 5185-5188.
4. Blunden, G. *Phytother. Res.* **2001,** *15*, 89-94.
5. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004,** *67*, 1216-1238.
6. Chin, Y.-W.; Balunas, M. J.; Chai, H. B.; Kinghorn, A. D. *AAPS Journal* **2006,** *8*, E239-E253.
7. Mayer, A. M. S.; Gustafson, K. R. *Int. J. Cancer* **2003,** *105*, 291-299.
8. Faulkner, D. J. *Nat. Prod. Rep.* **2000,** *17*, 1-6.
9. Menchaca, R.; Martinez, V.; Rodriguez, A.; Rodriguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem.* **2003,** *68*, 8859-8866.
10. Cuevas, C.; Perez, M.; Martin, M. J.; Chicharro, J. L.; Fernandez-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; Garcia, J.; Polanco, C.; Rodriguez, I.; Manzanares, I. *Org. Lett.* **2000,** *2*, 2545-2548.
11. Manitto, P. *Biosynthesis of Natural Products*; Ellis Horwook Ltd. Publishers: West Sussex, England, 1981.
12. Rohr, J. Bioorganic Chemistry - Deoxysugars, Polyketides and Related Classes: Synthesis Biosynthesis and Enzymes. In *Topics in Current Chemistry;* Meijere, A. d.; Houk, K. N.; Lehn, J.-M.; Ley, S. V.; Thiem, J.; Trost, B. M.; Vogtle, F.; Yamamoto, H. Eds.; Springer: Berlin, Heidelberg, 1997; Vol. 188; pp. 205.
13. Rohr, J. *Angew. Chem. Int. Ed.* **2000,** *39*, 2847-2849.
14. Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, 477-493.
15. McDaniel, R.; Welch, M.; Hutchinson, C. R. *Chem. Rev.* **2005,** *105*, 543-558.
16. Hochlowski, J. E.; Faulkner, D. J. *J. Org. Chem.* **1984,** *49*, 3838-3840.
17. Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986,** *108*, 6680-6682.
18. Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994,** *47*, 2255-2269.
19. Beukes, D. R.; Davies-Coleman, M. T. *Tetrahedron* **1999,** *55*, 4051-4056.
20. Paul, M. C.; Zubia, E.; Ortega, M. J.; Salva, J. *Tetrahedron* **1997,** *53*, 2303-2308.
21. Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984,** *106*, 6748-6750.
22. Manker, D. C.; Faulkner, D. J. *J. Org. Chem.* **1989,** *54*, 5371-5374.
23. Faulkner, D. J. *Nat. Prod. Rep.* **1998**, 113-158.
24. Ziegler, F. E.; Becker, M. R. *J. Org. Chem.* **1990,** *55*, 2800-2805.
25. Paterson, I.; Perkins, M. V. *Tetrahedron* **1996,** *52*, 1811-1834.
26. Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992,** *33*, 801-804.
27. Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002,** *4*, 391-394.
28. Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993,** *115*, 1608-1610.
29. Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994,** *35*, 6929-6932.
30. Manker, D. C.; Faulkner, D. J. *J. Org. Chem.* **1986,** *51*, 814-816.
31. Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004,** *57*, 787-797.
32. Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007,** *46*, 3860-3864.
33. Paterson, I.; Chen, D. Y.-K.; Acena, J. L.; Franklin, A. S. *Org. Lett.* **2000,** *2*, 1513-1516.
34. Lister, T.; Perkins, M. V. *Org. Lett.* **2006,** *8*, 1827-1830.
35. Stocking, E. M.; Williams, R. M. *Angew. Chem. Int. Ed.* **2003,** *42*, 3078-3115.
36. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew.*

Chem. Int. Ed. **2002,** *41*, 1668-1698.
37. Oikawa, H. *Bull. Chem. Soc. Jpn.* **2005,** *78*, 537-554.
38. Huang, X.-H.; van Soest, R.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2004,** *6*, 75-78.
39. Berrue, F.; Thomas, O. P.; Fernandez, R.; Amade, P. *J. Nat. Prod.* **2005,** *68*, 547-549.
40. Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953,** *580*, 44-57.
41. Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954,** *87*, 1318-1330.
42. Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958,** *91*, 61-63.
43. Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959,** *92*, 2499-2505.
44. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961,** *83*, 1733-1738.
45. Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973,** *49*, 4833-4836.
46. Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928,** *160*, 98-122.
47. Shirley, D. A. The Synthesis of Ketones from Acid Halides and Organometallic Compounds of Magnesium, Zinc and Cadmium. In *Organic Reactions;* Adams, R.; Blatt, A. H.; Cope, A. C.; Curtin, D. Y.; McGrew, F. C.; Niemann, C. Eds.; John Wiley and Sons Inc.: New York, 1954; Vol. 8; pp. 28-57.
48. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971,** *44*, 581.
49. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972,** *37*, 2320-2322.
50. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978,** *100*, 3636-3638.
51. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979,** *101*, 4992-4998.
52. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979,** *20*, 3437-3440.
53. Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866-867.
54. Rizzacasa, M.; Perkins, M. V. *Stoichiometric Asymmetric Synthesis*; Sheffield Academic Press: Sheffield, England, 2000.
55. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968,** *18*, 2199-2204.
56. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1976,** *1*, 61-70.
57. Roush, W. R. *J. Org. Chem.* **1991,** *56*, 4151-4157.
58. Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992,** *48*, 4439-4458.
59. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995,** *117*, 6619-6620.
60. Evans, D. A.; Nelson, J. V.; Taber, T. R. Stereoselective Aldol Condensations. In *Topics in Stereochemistry;* Allinger, N. L.; Eliel, E. L.; Wilen, S. H. Eds.; John Wiley and Sons: New York, 1982; Vol. 13; pp. 1-115.
61. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990,** *112*, 8215-8216.
62. Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753-756.
63. Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984,** *40*, 1381-1390.
64. Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353-356.
65. Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992,** *92*, 807-832.
66. Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990,** *112*, 2767-2772.
67. Oppolzer, W. *Pure Appl. Chem.* **1988,** *60*, 39-48.
68. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992,** *114*, 9434-9453.
69. Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981,** *103*, 1566-1568.
70. Evans, D. A. *Aldrichim. Acta* **1982,** *15*, 23-32.

71. Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994,** *35*, 9083-9086.
72. Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992,** *33*, 4233-4236.
73. Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988,** *29*, 585-588.
74. Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989,** *30*, 7121-7124.
75. Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994,** *35*, 9087-9090.
76. Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994,** *35*, 9477-9480.
77. Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **April 1998**, 639-652.
78. Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron: Asymmetry* **1995,** *6*, 2613-2636.
79. Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993,** *49*, 685-696.
80. Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993,** *58*, 4182-4184.
81. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989,** *68*, 77-82.
82. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981,** *103*, 2127-2129.
83. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989,** *68*, 83-89.
84. Evans, D. A.; Ennis, M. D.; Marthre, D. J. *J. Am. Chem. Soc.* **1982,** *104*, 1737-1739.
85. Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997,** *30*, 3-12.
86. Velazquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002,** *6*, 303-340.
87. Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986,** *27*, 4787.
88. Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1992,** *57*, 5173-5177.
89. Reetz, M. T. *Pure Appl. Chem.* **1988,** *60*, 1607-1614.
90. Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986,** *27*, 4721-4724.
91. Reetz, M. T.; Rivadeneira, E.; Niemeyer, C. *Tetrahedron Lett.* **1990,** *31*, 3863-3866.
92. Corey, E. J. *Pure Appl. Chem.* **1990,** *62*, 1209-1216.
93. Corey, E. J.; Lee, D.-H. *Tetrahedron Lett.* **1993,** *34*, 1737-1740.
94. Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981,** *46*, 1296-1309.
95. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995,** *117*, 9073-9074.
96. Schlosser, M. The Stereochemistry of the Wittig Reaction. In *Topics In Stereochemistry;* Eliel, E. L.; Allinger, N. L. Eds.; John Wiley and Sons: United States of America, 1970; Vol. 5; pp. 1-30.
97. Maryanoff, B. A. *Chem. Rev.* **1989,** *89*, 863-927.
98. Reucroft, J.; Sammes, P. G. *Quart. Rev. Chem. Soc.* **1971**, 135-169.
99. Schneider, W. P. *Chem. Commun.* **1969**, 785-786.
100. Vedejs, E.; Peterson, M. J. Stereochemistry and Mechanism in the Wittig Reaction. In *Topics in Stereochemistry;* Eliel, E. L.; Wilen, S. H. Eds.; John Wiley and Sons Inc.: New York, 1994; Vol. 21; pp. 1-157.
101. Schlosser, M.; Christmann, K. F. *Angew. Chem. Int. Ed.* **1966,** *5*, 126.
102. Schlosser, M.; Muller, G.; Christmann, K. F. *Angew. Chem. Int. Ed.* **1966,** *5*, 667-668.
103. Reitz, A. B.; Nortey, S. O.; Jordan, A. D.; Mutter, M. S.; Maryanoff, B. A. *J. Org. Chem.* **1986,** *51*, 3302-3308.
104. Wadsworth, W. S. Chapter 2 Synthetic Applications of Phosphoryl-Stabilized Anions. In *Organic Reactions;* Dauben, W. G.; Baldwin, J. E.; Kende, A. S.; Boswell, G. A.; Marshall, J. A.; Heck, R. F.; Meinwald, J.; Hirschmann, R. F.; Trost, B. M.; Bitman, R.; Weinstein, B. Eds.; John Wiley and Sons, Inc: United States of America, 1977; Vol. 25; pp. 73.

105. Corey, E. J.; Cane, D. E. *J. Am. Chem. Soc.* **1969,** *43*, 3053-3057.
106. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1968,** *90*, 6816-6821.
107. Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc. Perkin Trans 1* **1978**, 834-837.
108. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc. Perkin Trans 1* **1978**, 829-834.
109. Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc. Perkin Trans 1* **1980**, 1045-1050.
110. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc. Perkin Trans 1* **1979**, 1290-1293.
111. Blakemore, P. R. *J. Chem. Soc. Perkin Trans 1* **2002**, 2563-2585.
112. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991,** *32*, 1175-1178.
113. Truce, W. E.; Kreider, E. M.; Brand, W. W. *Organic Reactions*; John Wiley and Sons: New York, 1970; Vol. 18.
114. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993,** *130*, 336-357.
115. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993,** *130*, 856-878.
116. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26-28.
117. Bellingham, R.; Jarowicki, K.; Kocienski, P. J.; Martin, V. *Synthesis* **1996**, 285-296.
118. Prilezhaeva, E. N. *Russ. Chem. Rev.* **2000,** *69*, 367-408.
119. Alder, K.; Stein, G. *Angew. Chem.* **1937,** *50*, 510-519.
120. Martin, J. G.; Hill, R. K. Stereochemistry of the Diels-Alder Reaction, 1961; pp. 537-562.
121. Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984,** *106*, 203-208.
122. Sauer, J. *Angew. Chem. Int. Ed.* **1967,** *6*, 16-33.
123. Montgomery, L. K.; Schueller, K.; Bartlett, P. D. *J. Am. Chem. Soc.* **1964,** *86*, 622-628.
124. Bartlett, P. D.; Montgomery, L. K. *J. Am. Chem. Soc.* **1964,** *86*, 628-631.
125. Woodward, R. B.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **1969,** *8*, 781-853.
126. Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001,** *66*, 5192-5200.
127. Corey, E. J. *Angew. Chem. Int. Ed.* **2002,** *41*, 1650-1667.
128. Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001,** *12*, 597-622.
129. Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1951,** *73*, 4501.
130. Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1953,** *75*, 384-392.
131. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1950,** *72*, 4839-4840.
132. Takao, K.-I.; Munakata, R.; Tadano, K.-I. *Chem. Rev.* **2005,** *105*, 4779-4807.
133. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982,** *104*, 5555-5557.
134. Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982,** *104*.
135. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982,** *104*, 5560-5562.
136. Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982,** *104*, 5558-5560.
137. Abe, N.; Sugimoto, O.; Tanji, K.-I.; Hirota, A. *J. Am. Chem. Soc.* **2000,** *122*,

12606-12607.
138. Abe, N.; Murata, T.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1998,** *62*, 661-666.
139. Hilvert, D.; Hill, K. W.; Nared, K. D.; Auditor, M.-T. M. *J. Am. Chem. Soc.* **1989,** *111*, 9261-9262.
140. Braisted, A. C.; Schultz, P. G. *J. Am. Chem. Soc.* **1990,** *112*, 7430-7431.
141. Oikawa, H.; Katayama, K.; Suzuki, V.; Ichihara, A. *J. Chem. Soc. Chem. Commun.* **1995**, 1321-1322.
142. Katayama, K.; Kobayashi, K.; Oikawa, H.; Honma, M.; Ichihara, A. *Biochim. Biophys. Acta* **1998,** *1384*, 387-395.
143. Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van den Heever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000,** *122*, 11519-11520.
144. Watanabe, K.; Mie, T.; Ichihara, A.; Oikawa, H.; Honma, M. *J. Biol. Chem.* **2000,** *275*, 38393-38401.
145. Oikawa, H.; Watanabe, K.; Yagi, K.; Ohashi, S.; Mie, T.; Ichihara, A.; Honma, M. *Tetrahedron Lett.* **1999,** *40*, 6983-6986.
146. Watanabe, K.; Oikawa, H.; Yagi, K.; Ohashi, S.; Mie, T.; Ichihara, A.; Honma, M. *J. Biochem.* **2000,** *127*, 467-473.
147. Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004,** *21*, 321-352.
148. Negishi, E.-I.; Liu, F. 1. Palladium- or Nickel-catalysed Cross-coupling with Organometals Containing Zinc, Magnesium, Aluminium and Zirconium. In *Metal Catalysed Cross-coupling Reactions;* Diederich, F.; Stang, P. J. Eds.; Wiley-VHC: Weinheim, Federal Republic of Germany, 1998; pp. 1-47.
149. Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982,** *104*, 180-186.
150. Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984,** *106*, 158-163.
151. Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972,** *94*, 9268-9269.
152. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972,** *94*, 4374-4376.
153. Tamao, K.; Zembayashi, M.; Kiso, Y.; Kumada, M. *J. Organomet. Chem.* **1973,** *55*, C91-C94.
154. Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun.* **1972**, 144.
155. Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-I.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979,** *44*, 2408-2417.
156. Baba, S.; Negishi, E.-I. *J. Am. Chem. Soc.* **1976,** *98*, 6729-6731.
157. Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975,** *93*, 259-263.
158. Cassar, L. *J. Organomet. Chem.* **1975,** *93*, 253-257.
159. Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1976,** *118*, 349-354.
160. Yamamura, M.; Moritani, I.; Murahashi, S.-I. *J. Organomet. Chem.* **1975,** *91*, C39-C42.
161. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975,** *16*, 4467-4470.
162. Negishi, E.-I.; Baba, S. *J. Chem. Soc. Chem. Commun.* **1976**, 596-597.
163. Fauvarque, J.-F.; Jutand, A. *Bull. Soc. Chim. Fr.* **1976,** *5-6*, 765-770.
164. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005,** *44*, 4442-4489.
165. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001,** *40*, 4544-4568.
166. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95*, 2457-2483.
167. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002,** *58*, 9633-9695.

168. Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005,** *38*, 71-88.
169. Stille, J. K. *Angew. Chem. Int. Ed.* **1986,** *25*, 508-524.
170. Sonogashira, K. *J. Organomet. Chem.* **2002,** *653*, 46-49.
171. Tsuji, J. *Tetrahedron* **1986,** *42*, 4361-4401.
172. Trost, B. M. *Accounts Chem. Res.* **1980,** *13*, 385-393.
173. Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977,** *42*, 1821-1823.
174. Negishi, E.-I. *Accounts Chem. Res.* **1982,** *15*, 340-348.
175. Link, J. T.; Overman, L. E. 6. Intramolecular Heck Reactions in Natural Products Chemistry. In *Metal Catalysed Cross-Coupling Reactions;* Diederich, F.; Stang, P. J. Eds.; Wiley-VHC: Weinheim, Federal Republic of Germany, 1998; pp. 231-269.
176. Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989,** *54*, 4738-4739.
177. Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991,** *56*, 4093-4094.
178. Kagechika, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **1993,** *49*, 1773-1782.
179. Mitchell, T. N. 4. Organotin Reagents in Cross-Coupling. In *Metal Catalysed Cross-Coupling Reactions;* Diederich, F.; Stang, P. J. Eds.; Wiley-VHC: Weinheim, Federal Republic of Germany, 1998; pp. 167-202.
180. Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993,** *115*, 4419-4420.
181. Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Euro. J. Org. Chem.* **1995,** *1*, 318-333.
182. Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994,** *59*, 3755-3757.
183. Shair, M. D.; Yoon, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1995,** *34*, 1721-1723.
184. Shair, M. D.; Yoon, T.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996,** *118*, 9509-9525.
185. Suzuki, A. 2. Cross-coupling Reactions of Organoboron Compounds with Organic Halides. In *Metal Catalysed Cross-Coupling Reactions;* Diederich, F.; Stang, P. J. Eds.; Wiley-VHC: Weinheim, Federal Republic of Germany, 1998; pp. 49-97.
186. Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994,** *116*, 11205-11206.
187. Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989,** *111*, 7530-7533.
188. Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989,** *111*, 7525-7530.
189. Nakamura, M.; Mori, Y.; Okuyama, K.; Tanikawa, K.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Org., Biomolec. Chem.* **2003,** *1*, 3362-3376.
190. Nicolaou, K. C.; Webber, S. E. *J. Am. Chem. Soc.* **1984,** *106*, 5734-5736.
191. Furstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998,** *120*, 2817-2825.
192. Furstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999,** *64*, 2361-2366.
193. Hu, T.; Panek, J. S. *J. Org. Chem.* **1999,** *64*, 3000-3001.
194. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons Inc.: New York, 1999.

195. Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031-1069.
196. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972,** *94*, 6190-6191.
197. Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993,** *115*, 11446-11459.
198. Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990,** *55*, 410-412.
199. Widmer, U. *Synthesis* **1987**, 568-570.
200. Nalajima, N.; Abe, R.; Yonemitsu, O. *Chem. Pharm. Bull.* **1988,** *36*, 4244.
201. Hodgson, A. N. The Biology of Siphonariid Limpets (Gastropoda:Pulmonata). In *Oceanography and Marine Biology: An Annual Review;* Ansell, A. D.; Gibson, R. N.; Barnes, M. B. Eds.; Taylor and Francis: London, 1999; Vol. 37; pp. 245-314.
202. Sampson, R. A.; Perkins, M. V. *Org. Lett.* **2002,** *4*, 1655-1658.
203. Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem. Int. Ed.* **1997,** *36*, 2738-2747.
204. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981,** *22*, 3815-3818.
205. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978,** *43*, 2480-2482.
206. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985,** *50*, 2095-2105.
207. Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002,** *67*, 4275-4283.
208. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981,** *22*, 3455-3458.
209. Chuck, J.-A.; McPherson, M.; Huang, H.; Jacobsen, J. R.; Khosla, C.; Cane, D. E. *Chem. Biol.* **1997,** *4*, 757-766.
210. Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991,** *47*, 3471.
211. Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998,** *63*, 7811-7819.
212. Cane, D. E.; Tan, W.; Ott, W. R. *J. Am. Chem. Soc.* **1993,** *115*, 527-535.
213. DiBattista, J. P.; Webster, F. X. *Bioorg. Med. Chem.* **1996,** *4*, 423-428.
214. Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001,** *3*, 123-126.
215. Perkins, M. V.; Sampson, R. A. *Tetrahedron Lett.* **1998,** *39*, 8367-8370.
216. Arimoto, H.; Yokoyama, R.; Okumura, Y. *Tetrahedron Lett.* **1996,** *37*, 4749-4750.
217. Arimoto, H.; Yokoyama, R.; Nakamura, J.; Okumura, Y.; Uemura, D. *Tetrahedron* **1996,** *52*, 13901-13908.
218. Pawlik, J. R.; Chanas, B. C.; Toonen, R. J.; Fenical, W. *Mar. Ecol-Prog. Ser.* **1995,** *127*, 183-194.
219. Sipkema, D.; Franssen, M. C. R.; Osinga, R.; Tramper, J. *Mar. Biotechnol.* **2005,** *7*, 142-162.
220. Braekman, J.-C.; Daloze, D. *Phytother. Res.* **2004,** *3*, 275-283.
221. Burns, E.; Ifrach, I.; Carmeli, S.; Pawlik, J. R.; Ilan, M. *Mar. Ecol-Prog. Ser.* **2003,** *253*, 105-115.
222. Faulkner, D. J. *Nat. Prod. Rep.* **2002,** *19*, 1-48.
223. del Sol Jimenez, M.; Garzon, S. P.; Rodriguez, A. D. *J. Nat. Prod.* **2003,** *66*, 655-661.
224. Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980,** *45*, 3396-3401.
225. Ravi, B. N.; Armstrong, R. W.; Faulkner, D. J. *J. Org. Chem.* **1979,** *44*, 3109-3113.
226. Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978,** *43*, 3454.
227. Fattorusso, E.; Taglialatela-Scafati, O.; Di Rossa, M.; Ianaro, A. *Tetrahedron* **2000,** *56*, 7959-7967.

228. Qureshi, A.; Stevenson, C. S.; Albert, C. L.; Jacobs, R. S.; Faulkner, D. J. *J. Nat. Prod.* **1999,** *62*, 1205-1207.
229. Kobayashi, J.; Takeuchi, S.; Ishibashi, M.; Shigemori, H.; Sasaki, T. *Tetrahedron Lett.* **1992,** *33*, 2579-2580.
230. Hofheinz, W.; Schonholzer, P. *Helv. Chim. Acta* **1977,** *60*, 1367-1370.
231. Ishizaki, M.; Hara, Y.; Kojima, S.; Hoshino, O. *Heterocycles* **1999,** *50*, 779-790.
232. Mehta, G.; Kunda, U. K. *Org. Lett.* **2005,** *7*, 5569-5572.
233. Kirkham, J. E.; Lee, V.; Baldwin, J. E. *Org. Lett.* **2006,** *8*, 5537-5540.
234. Kirkham, J. E.; Lee, V.; Baldwin, J. E. *Chem. Commun.* **2006**, 2863-2865.
235. Diederich, F.; Stang, P. J. Metal Catalysed Cross-coupling Reactions; Wiley-VHC: Weinheim, Federal Republic of Germany, 1998.
236. McDonald, R. N.; Campbell, T. W. *J. Org. Chem.* **1959,** *24*, 1969-1975.
237. Desert, S.; Metzner, P. *Tetrahedron* **1992,** *48*, 10327-10338.
238. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982,** *104*, 5555-5557.
239. Smith III, A. B.; Beaucham, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000,** *122*, 8654-8664.
240. Onaran, M. B.; Seto, C. T. *J. Org. Chem.* **2003,** *68*, 8136-8141.
241. Yadav, V. K.; Babu, K. G. *Tetrahedron* **2003,** *59*, 9111-9116.
242. Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. *J. Org. Chem.* **2001,** *66*, 8135-8138.
243. Benson, S. W.; Egger, K. W.; Golden, D. M. *J. Am. Chem. Soc.* **1965,** *87*, 468-476.
244. Dickinson, R. G.; Lotzkar, H. *J. Am. Chem. Soc.* **1937,** *59*, 472-476.
245. Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 5 ed.; Tata McGraw Hill: New Delhi, 2004.
246. Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc. Chem. Commun.* **1992**, 979-980.
247. Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992,** *57*, 468-481.
248. Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1997,** *38*, 1443-1446.
249. Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979,** *41*, 3981-3982.
250. Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990,** *55*, 6260-6268.
251. Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002,** *124*, 11368-11378.
252. Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979,** *44*, 1247.
253. Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977,** *42*, 918-920.
254. McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993,** *58*, 3568-3571.
255. Jeffery, D. W.; Perkins, M. V. *Tetrahedron Lett.* **2004,** *45*, 8667-8671.
256. Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995,** *60*, 6604-6607.
257. Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chadhary, K. *J. Org. Chem.* **2001,** *66*, 894-902.
258. Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc. Perkin Trans 1* **1980**, 2470-2473.
259. Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000,** *2*, 775-777.
260. Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998,** *120*, 9084-9085.
261. Hughes, D. L. The Mitsunobu Reaction. In *Organic Reactions;* Paquette, L. A. Ed.; John Wiley and Sons Inc.: New York, 1992; Vol. 42; pp. 335.
262. Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963,** *28*, 1140-

1142.
263. Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996**, 652-666.
264. Freidrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989,** *54*, 751-756.
265. Aboujaoude, E. E.; Collignon, N. *Synthesis* **1983**, 634-636.
266. Sellanes, D.; Manta, E.; Serra, G. Q. *Tetrahedron Lett.* **2007,** *48*, 1827-1830.
267. Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986,** *51*, 5032-5036.
268. Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999,** *1*, 1823-1826.
269. Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987,** *52*, 4047-4052.
270. Cohen, R. J.; Fox, D. L.; Eubank, J. F.; Salvatore, R. N. *Tetrahedron Lett.* **2003,** *44*, 8617-8621.
271. Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002,** *124*, 2263-2266.
272. Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005,** *127*, 11505-11515.
273. Yadav, V. K.; Rajaiah, G. *Synlett* **2004**, 1743-1746.
274. Ward, R. S.; Roberts, D. W.; Diaper, R. L. *Sulfur Lett.* **2000,** *23*, 139-144.
275. Llauger, L.; He, H.; Chiosis, G. *Tetrahedron Lett.* **2004,** *45*, 9549-9552.
276. Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000,** *122*, 4280-4285.
277. Yadav, V. K.; Reddy, P. V.; Chandraiah, L. *Tetrahedron Lett.* **2007,** *48*, 145-148.
278. Baudin, J. B.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993,** *130*, 856-878.
279. Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962,** *27*, 282-284.
280. McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987,** *43*, 1753-1758.
281. Guertin, K. R.; Kende, A. S. *Tetrahedron* **1993,** *34*, 5369-5372.
282. Alonso, D. A.; Fuensanta, M.; Najera, C. *Euro. J. Org. Chem.* **2006**, 4747-4754.
283. Alonso, D. A.; Fuensanta, M.; Najera, C.; Varea, M. *J. Org. Chem.* **2005,** *70*, 6404-6416.
284. Marko, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001,** *57*, 2609-2619.
285. Marko, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996,** *37*, 2089-2092.
286. Pospisil, J.; Pospisil, T.; Marko, I. E. *Org. Lett.* **2005,** *7*, 2373-2376.
287. Speed, T. J.; McIntyre, J. P.; Thamattoor, D. M. *J. Chem. Ed.* **2004,** *81*, 1355-1356.
288. Naskar, D.; Roy, S. *Tetrahedron* **2000,** *56*, 1369-1377.
289. Negishi, E.-I.; King, A. O.; Tour, J. M. *Org. Synth.* **1985,** *64*, 44-49.
290. Negishi, E.-I.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980,** *102*, 3298-3299.
291. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986,** *108*, 7408-7410.
292. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993,** *115*, 4497-4513.
293. Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005,** *70*, 2225-2234.
294. Smith, B. B.; Hill, D. E.; Cropp, A.; Walsh, R. D.; Cartrette, D.; Hipps, S.; Shachter, A. M.; Pennington, W. T.; Kwochka, W. R. *J. Org. Chem.* **2002,** *67*, 5333-5337.
295. Kaffy, J.; Pontikis, R.; Florent, J.-C.; Monneret, C. *Org., Biomolec. Chem.* **2005,** *3*, 2657-2660.
296. Organ, M. G.; Wang, J. *J. Org. Chem.* **2003,** *68*, 5568-5574.

297. Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, 1745-1747.
298. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *36*, 3767-3772.
299. Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001,** *3*, 707-710.
300. Humphrey, J. M.; Aggen, J. B.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1996,** *118*, 11759-11770.
301. Brown, H. C.; Cole, T. E. *Organometallics* **1983,** *2*, 1316-1319.
302. Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974,** *73*, 1-15.
303. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994,** *116*, 11287-11314.
304. White, J. D.; Bolton, G. L.; Dantanarayana, A. P.; Fox, C. M. J.; Hiner, R. N.; Jackson, R. W.; Sakuma, K.; Warrier, U. S. *J. Am. Chem. Soc.* **1995,** *117*, 1908-1939.
305. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988,** *29*, 4139-4142.
306. Walkup, R. D.; Kahl, J. D.; Kane, R. R. *J. Org. Chem.* **1998,** *63*, 9113-9116.
307. Takeda, K.; Tsuboyama, K.; Torii, K.; Marata, M.; OGura, H. *Tetrahedron Lett.* **1988,** *29*, 4105-4108.
308. Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000,** *65*, 295-296.
309. Chou, S.-S., P.; KuoH.-L.; Wang, C.-J.; Tsai, C.-Y.; Sun, C.-M. *J. Org. Chem.* **1989,** *54*, 868-872.