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Chiral auxiliaries and substrate directable reactions to access highly functionalised chiral lactones

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Chiral auxiliaries and substrate directable reactions to access highly functionalised chiral lactones

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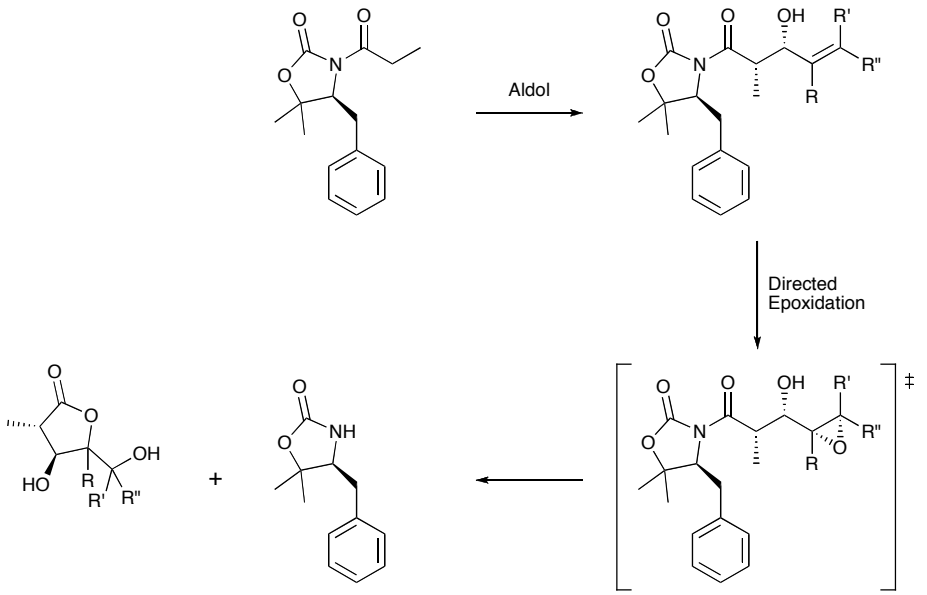
For my mum and dad

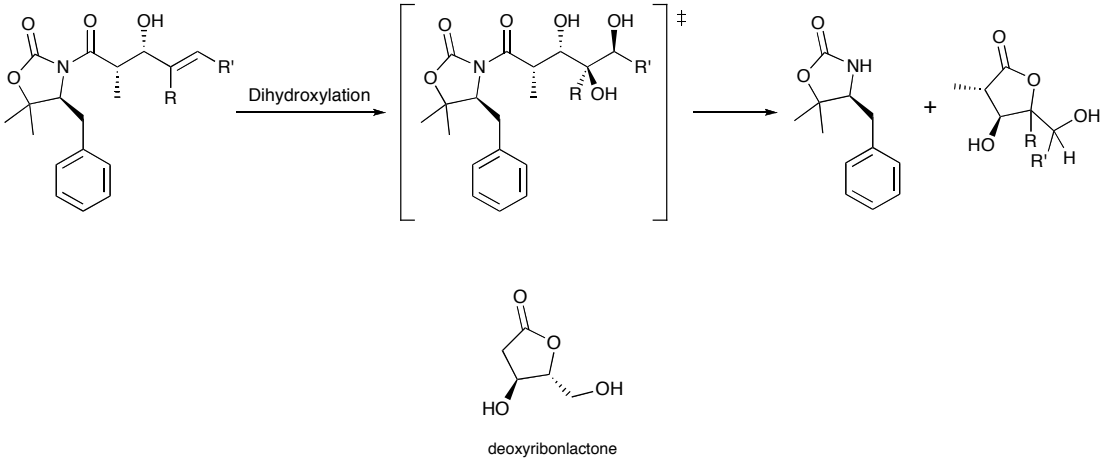
Abstract

This thesis describes the development of chiral auxiliary based methodologies for the asymmetric synthesis of hydroxylated γ-lactones and δ-lactones containing multiple contiguous stereocentres. The first chapter introduces the concept of chirality and provides a general overview of the range of strategies available for the preparation of chiral molecules in enantiomerically pure forms. The second chapter critically reviews the range of synthetic methodology that is currently available for the asymmetric synthesis of chiral α-lactones that are either natural products or useful chiral building blocks for synthesis. The third chapter describes the development of novel methodology for the epoxidation/lactonisation of a range of β-vinyl-*syn*-aldols to directly afford γ-lactones containing up to four contiguous stereocentres in high de. These reactions were shown to proceed *via* a mechanism whereby hydroxyl-directed diastereoselective epoxidation is followed by intramolecular attack of their *N*-acyl-oxazolidin-2-one fragment, to directly afford the desired chiral γ-lactone. The 'self-cleavage' aspect of these reactions was exploited to enable this methodology to be transferred to polymer-support using an immobilised Evans'-oxazolidin-2-one for asymmetric synthesis.

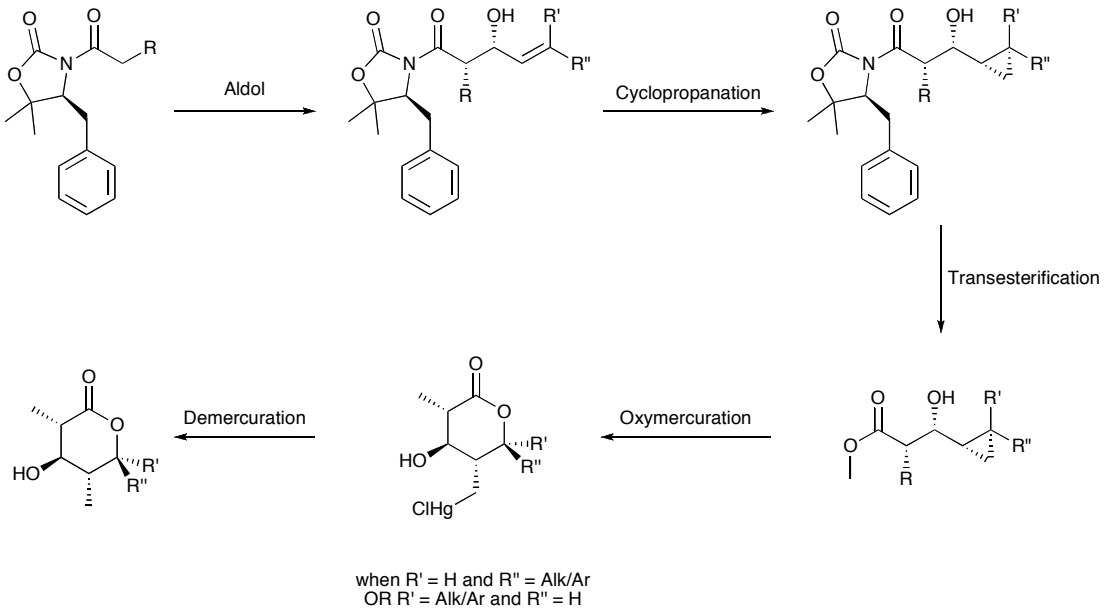


Chapter 4 describes the development of a complementary methodology for the asymmetric synthesis of this type of hydroxylated γ-lactone based on a strategy involving dihydroxylation of *N*-acyl-oxazolidin-2-one-β-vinyl-*syn*-aldols using catalytic amounts of osmium tetroxide. This methodology was developed as part of a reinvestigation of previously reported dihydroxylation reactions by Dias and coworkers, where we have clearly shown that the stereochemistry of the

lactones reported in their paper have been incorrectly assigned. This diastereoselective dihydroxylation methodology has been successfully applied to the asymmetric synthesis of the natural product deoxyribonolactone.



Finally, Chapter 5 describes the development of methodology for the asymmetric synthesis of chiral δ-lactones containing four contiguous stereocentres of use as potential chiral building blocks for the synthesis of polyketide natural products. In this approach, cyclopropanation of *N*-acyl-oxazolidin-2-one-β-vinyl-*syn*-aldols occurs under the sterodirecting effect of the β-hydroxyl group to afford cyclopropyl-aldols in very high de. These cyclopropyl-aldols are then ring opened in the presence of mercuric ions, with their *N*-acyl-oxazolidin-2-one fragment acting as an internal nucleophile, to afford highly functionalised alkyl-mercury species that may be subsequently reduced to afford their corresponding δ-lactones in high de.



Contents

Acknowledgements

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I would also like to thank my family (Dad, Rhiannon and Tim) without your love and support I would not be where I am today. A special thanks to my Dad, you have been my rock and my biggest supporter… I cannot put my gratitude into words but I dedicate this thesis to both you and Mum… I wish she could have seen this.

Abbreviations

$A^{1,2}$	1,2-Allylic Strain
$A^{1,3}$	1,3-Allylic Strain
Ac	Acetyl
acac	Acetylacetonate
app.	Apparent
9-BBN	9-Borabicyclo[3.31]nonane
BINAP	2,2'-Bis(diphenylphosphino-1,1'-binaphthyl
Bn	Benzyl
Boc/BOC	*tert*-Butyloxycarbonyl
br.	Broad
Bu	Butyl
^{n}Bu	*normal*-Butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-butyl
BVMO	Baeyer Villiger Mono Oxygenase
CAN	Ceric ammonium nitrate
Cp.	Pentamethylcyclopentadienyl
δ	Chemical Shift
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
de	diastereomeric excess
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMD	Dimethyl dioxirane
DME	1,2-Dimethoxy-ethane
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethylsulfoxide
ds	Diastereoselectivity
ee	enantiomeric excess
E	Entegen (opposite, trans)
EI	Electron Impact
Et	Ethyl
ether	Diethyl ether
g	Grams
h	Heptet
Hz	Hertz
IR	Infra red
J	Coupling Constant
L	Ligand
Lindlar's	Pd on $CaCO_3$/PbO
M	Molar
m	Multiplet
M+	Molecular Ion
Me	Methyl
Mg	Milligrams
MOM	Methoxymethyl
MTO	Metyltrioxo rhenium ($MeReO_3$)
MPEG550	Polyethylene-Methoxy-glycol

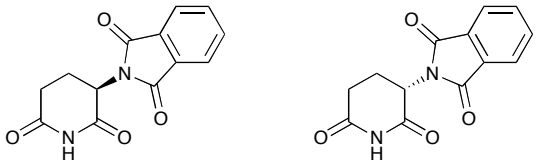
NMO	*N*-methylmorpholine-*N*-*oxide*
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
OTf	Trifluromethanesulfonyl / Triflate
p	Pentet
Petrol	Petroleum Ether (fraction at 40-60 °C)
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
PMHS	Polymethylhydrogensiloxane
PPL	Lipase
ppm	parts per million
^{i}Pr	*iso*-Propyl
psi	Pounds per square inch
q	Quartet
RAMP	*R*-1-amino-2-(methoxymethyl) pyrrolidine
RCM	Ring closing metathesis
Rf	Retention factor
RT	Room temperature
s	Singlet
SAMP	*S*-1-amino-2-(methoxymethyl) pyrrolidine
sept.	Septet
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethyl silyl
TPAP	Tetra-*N*-propylammonium perruthenate
Ts	p-Toluenesulfonyl / Tosyl
UHP	Urea hydrogen peroxide
WSC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
χ	Chiral Auxiliary
χ_p	(*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one
Z	Zusammen (together, *cis*)

Chapter 1: Introduction

This thesis deals with the development of methodology for the asymmetric synthesis of chiral lactones that contain multiple stereocentres as potentially useful chiral building blocks for natural product synthesis. Consequently, this introduction serves to introduce some of the fundamental concepts associated with the synthesis of chiral molecules as well as describing the different types of strategy that can be employed for their synthesis.

1.1 Chirality

Chirality is an inherent property of a molecule that has no plane of symmetry, i.e. it is non-superimposable upon its mirror image. These mirror images are known as enantiomers, and in the absence of a chiral environment, they display the same physical and chemical properties, only differing in the fact that they rotate the plane of polarised light in opposite directions. However, in a chiral environment, such as a biological receptor, or the active site of an enzyme, their 'handedness' becomes significant because of the potential to afford diastereoisomeric transition states (or complexes). Therefore, whilst there are examples of enantiomers or diastereoisomers of chiral molecules having the same biological activity, there are many other examples where they differ significantly in their mode of action.[1]



(*R*)-**1** (*S*)-**1**

Figure 1.1: Enantiomers of Thalidomide

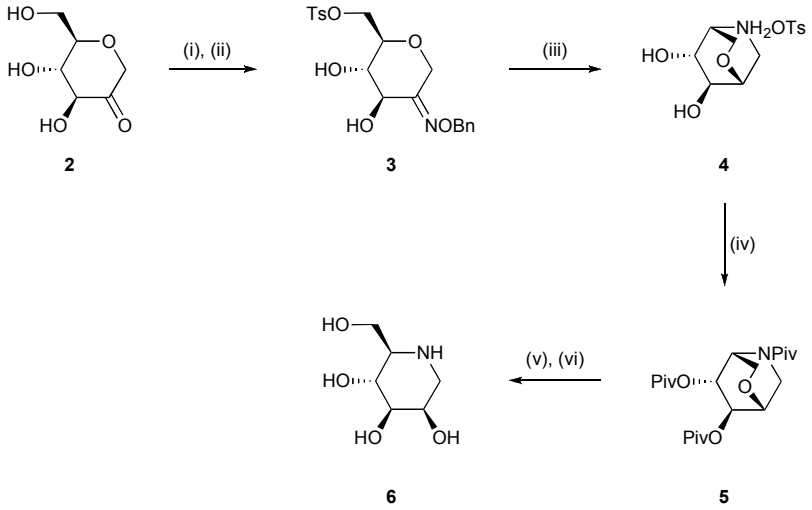
One famous example from the pharmaceutical industry is the drug Thalidomide **1**, which was sold during the 1960s as a racemate and marketed as an effective treatment for morning sickness. Tragically, it was later determined that its enantiomers displayed very different biological activity. Whilst (*R*)-Thalidomide was shown to be a potent anti-emetic and analgesic, (*S*)-Thalidomide displayed teratogenic properties. Consequently, prescription of this racemate to pregnant women led to the birth of many malformed children, clearly illustrating how important the use of single enantiomer drugs can be in the treatment of disease.

In recent years the development of enantioselective methodologies for the asymmetric synthesis of chiral molecules has been one of the main goals of organic chemistry, particularly in developing protocols that enable the rapid synthesis of molecules containing multiple stereocentres. There are many methods available within the organic chemistry arsenal for this purpose and I will now briefly describe the range of strategies that are available to synthetic chemists for the preparation of enantiopure compounds.

1.2 Chiral pool

At the molecular level many of the compounds that Nature produces in large quantities are chiral and for many years the synthesis of enantiopure compounds on a large scale relied on access to this chiral pool.[2] Indeed, Nature's production of a wide range of amino acids, sugars and other natural products has enabled these chiral molecules to be used as useful chiral building blocks for asymmetric synthesis.

For example, Lundt *et al* have recently demonstrated that 1,5-anhydro-D-fructose can be used as an effective chiral synthon for the synthesis of the glucosidase inhibitor 1-deoxymannojirimycin **6** (See Scheme 1.1).[3] Initially, lactone **2** was treated with *O*-benzylhydroxylamine to generate an oxime, which was selectively mono-tosylated to yield 6-*O*-tosylated-oxime **3**. Subsequent hydrogenation of **3** with H_2 over Pd/C resulted in direct formation of the bicyclic imino-sugar **4**. The final steps required cleavage of the ether bond, which was carried out by removal of the *O*-tosyl-protecting group, subsequent pivaloylation of the free alcohol and amino functionality to yield **5**, followed by treatment with BBr_3, and addition of NaOMe in methanol to yield the desired 1-deoxymannojirimycin **6** in an overall 35% yield.



Reagents and conditions: (i) NH_2.OBn·HCl, KOH, RT, EtOH, 91 %; (ii) TsCl (1.2 equiv), pyridine, -20 ^{o}C, 77 %; (iii) H_2, Pd/C, MeOH/HCl. 30 bar, RT, then pyridine, RT, 62 %; (iv) PivCl, DMAP, pyridine, RT, 93 %; (v) BBr_3 (1.5 equiv), $CHCl_3$, then MeOH, RT (vi) NaOMe, MeOH, RT, 67 % (2 steps)

Scheme 1.1: Synthesis of glucosidase inhibitor 1-deoxymannojirimycin (**6**).

Although these types of chiral pool strategies have been shown to be highly effective at accessing specific enantiopure materials, the chiral pool approach is often limited in its scope. This is due to its dependence on the availability of enantiopure starting materials in large amounts, the fact that compounds are often limited to a single enantiomeric series, and the large number of synthetic steps that are often required to remove redundant functionality.

1.3 Asymmetric catalysis

A catalyst is a substance that increases the rate of a reaction, which occurs *via* incorporation of the catalyst into the reaction transition state, but remains unchanged by the process. Introduction of chirality into the catalyst (present as a single enantiomer) allows for the potential formation of transient diastereomeric transition states (cat***-s**, Figure 1.2), of different energies; thus favouring the formation of one enantiomer of a product over its antipode. There are three main strategies employed for asymmetric catalysis; transition metal catalysis, organocatalysis and biocatalysis.

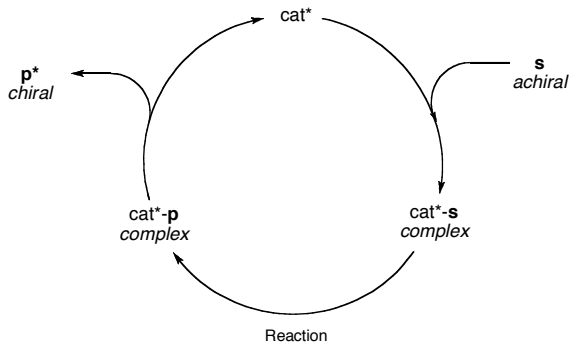
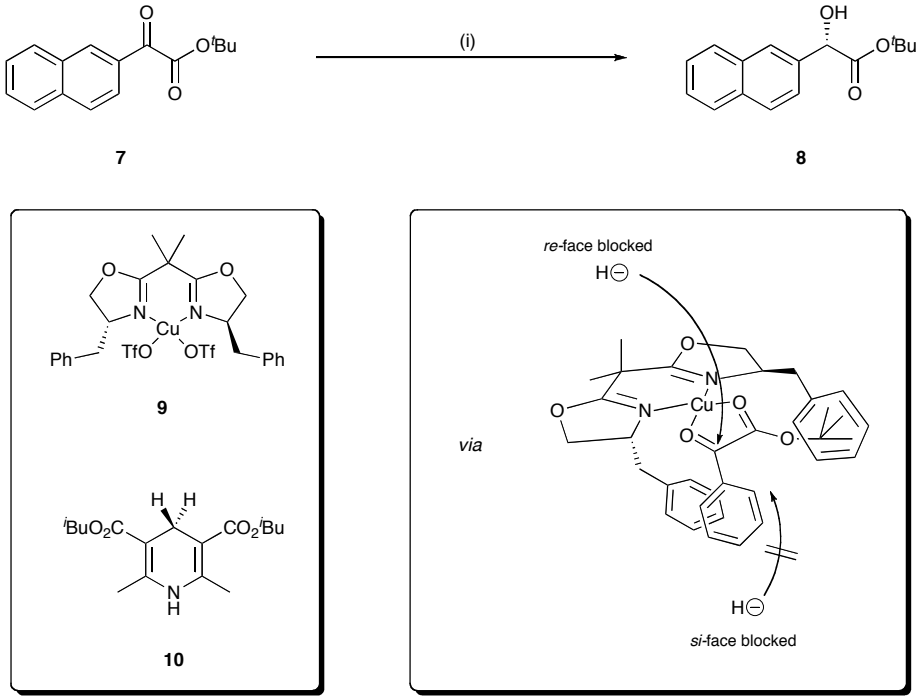


Figure 1.2: Generic mechanism of chiral catalysis starting from an achiral substrate **s** leading to a chiral product **p***.

1.3.1 Transition metal mediated catalysis

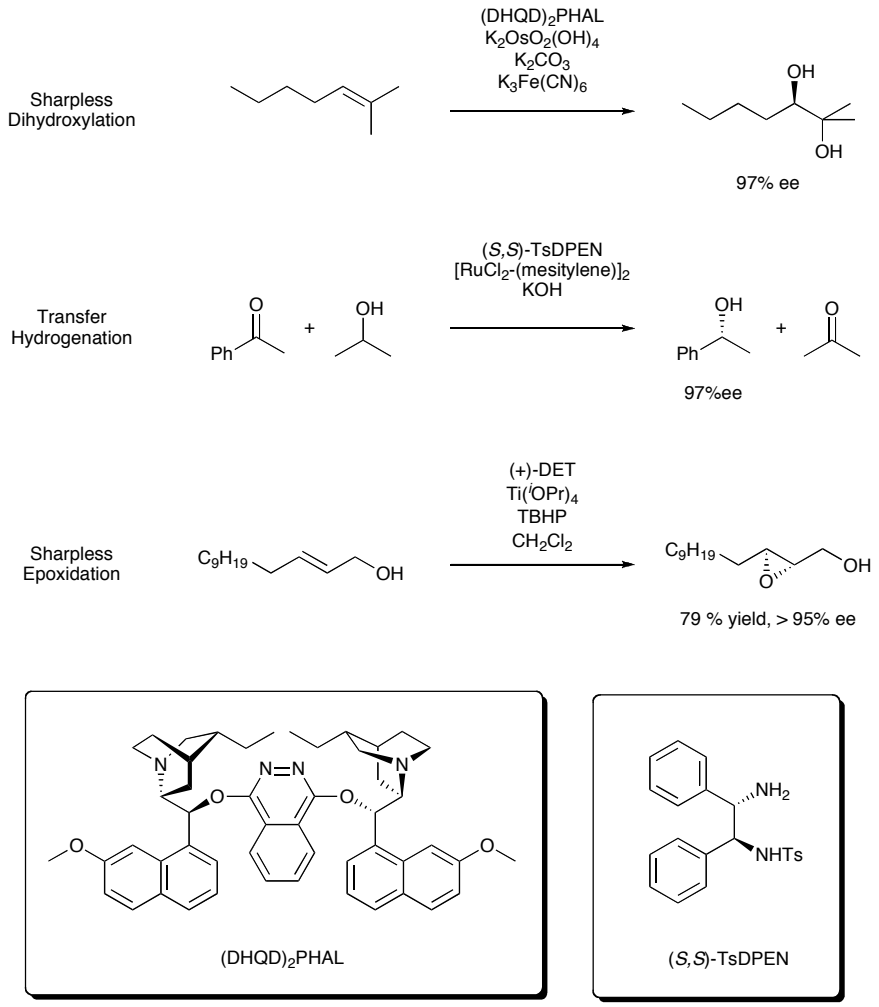
Chiral transition metal complexes have often been employed as asymmetric catalysts in organic transformations where efficient transfer of chirality from the catalyst results in the formation of chiral products in high ee. Many of the transition metal complexes that have been developed show very high activity. However, a number of chiral catalysts are often derived from expensive/toxic metals such as palladium or rhodium, although catalysts derived from more environmentally benign metals such as iron, zinc and copper have also been developed.[4] For example, List has demonstrated the use of copper catalysts in the catalytic asymmetric transfer hydrogenation of α-keto-esters using Hantzsch esters as hydride donors (Scheme 1.2).[5] Treatment of ketone **7** under optimised reaction conditions of copper(II) triflate, bisoxazoline ligand **9** and Hantzsch ester **10** (which is the hydrogen source) resulted in an almost clean conversion to the alcohol **8** in 82% isolated yield and 94% de. The stereochemical outcome of this reaction is dictated by coordination of the chiral catalyst to the carbonyl of the prochiral ketone functionality, which results in formation of diastereotopic transition states that are different in energy, which results in a hydride equivalent being selectively delivered to one face of the carbonyl group to afford an (*S*)-configured alcohol.



Reagents and conditions: (i) **9** (10 mol%), **10** (1.4 equiv), $CHCl_3$, 82 %, 97:3 er

Scheme 1.2: Selective reduction of β-keto-ester **7**.

The wide-ranging effect that asymmetric catalysis has had in supplying new types of chiral building blocks for organic synthesis has been recognised by the joint award of the Nobel Prize to Noyori, Knowles and Sharpless in 2001. A representative series of popular catalytic transformations that are now widely used in organic synthesis are described in Scheme 1.3, with well over 1000 applications of these methodologies having been reported to date.[6-8]



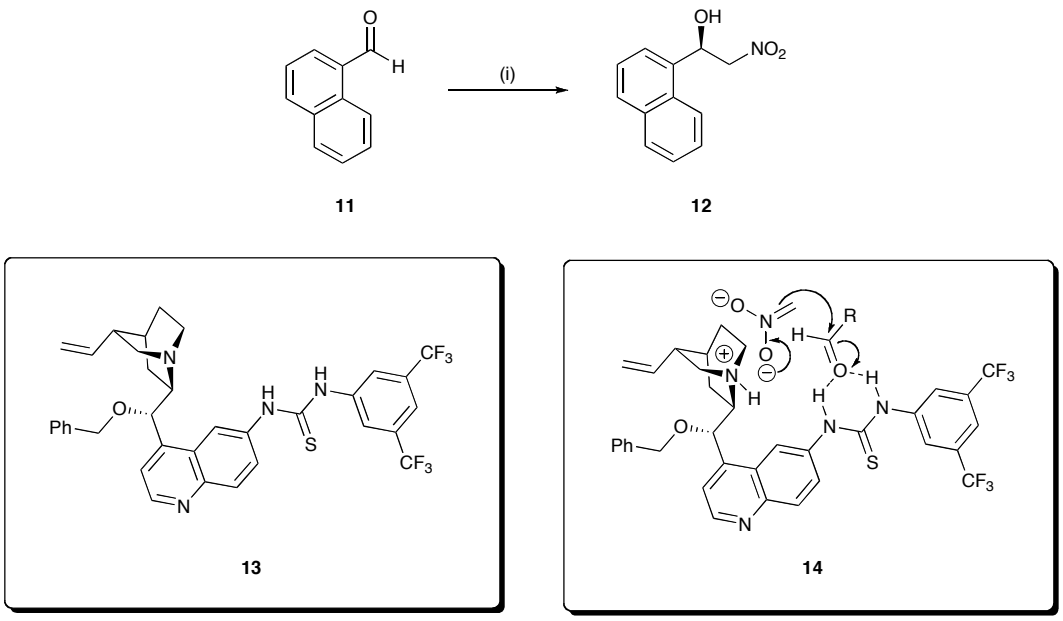
Scheme 1.3: Representative selection of asymmetric catalytic strategies.

1.3.2 Organocatalysis

Organocatalysis utilises the chirality of small organic molecules that can catalyse reactions to relay stereocontrol for the formation of chiral products. In recent years, the field of organocatalysis has developed rapidly and a number of these catalysts can now compete with the more established fields of metal mediated and biocatalysis in terms of stereocontrol.[9-11] However, reaction times of >24 hrs using catalyst loadings of 20 mol% are often required for their reactions to proceed and as a consequence significant improvements in their catalytic activity, particularly reductions in catalyst loading, are still required in many cases.

For example, Hiemstra and co-workers have demonstrated the application of a bifunctional thiourea catalyst in the asymmetric Henry reaction (Scheme 1.4).[12] Treatment of 1-naphthaldehyde with 10 mol% of chiral thiourea catalyst **13** and nitromethane resulted in

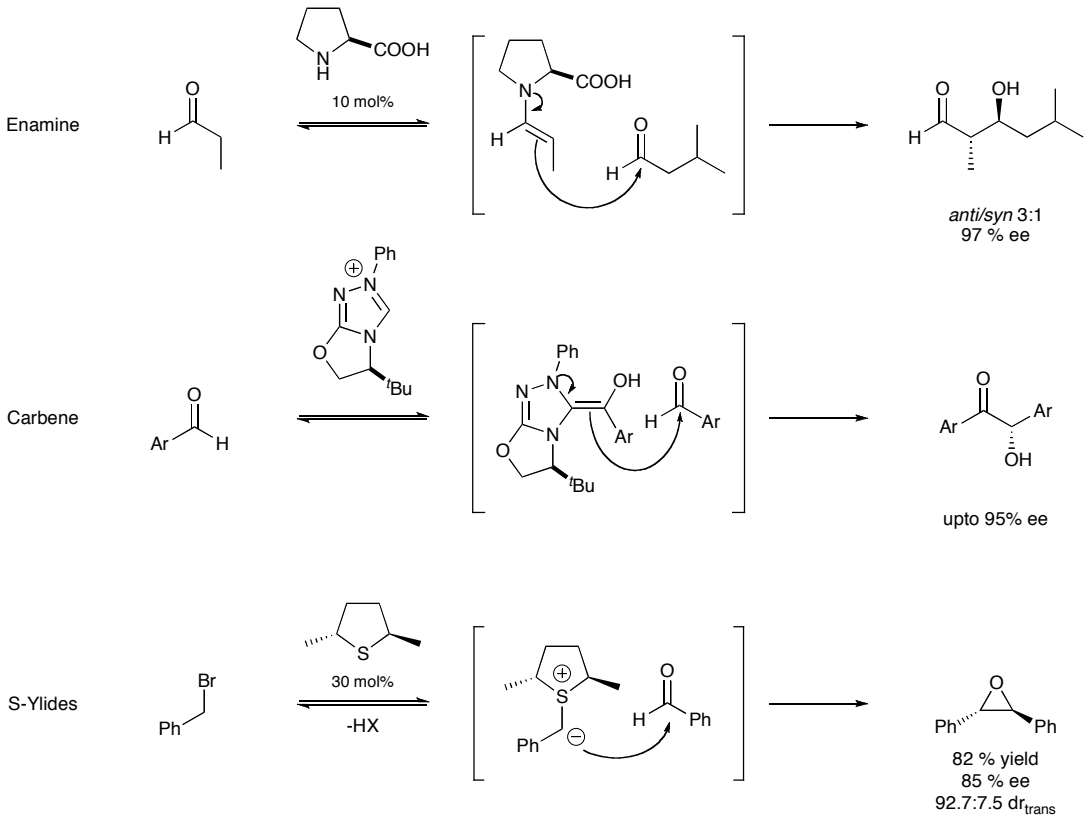
formation of the aldol product **12** in 99% yield and 92% ee. It was postulated that asymmetric induction occurs *via* hydrogen bonding of the thiourea moiety to the aldehyde functionality, with the basic quinuclidine fragment catalysing formation of the nitromethane enolate that then undergoes nucleophilic attack *via* the postulated transition state **14**.[12] Despite the observed selectivity and excellent yields obtained for aromatic aldehydes, the scope of this reaction was limited when it came to aliphatic aldehydes both in terms of reduced rates and enantioselectivity.



Reagents and conditions: (i) **13** (10 mol%), $MeNO_2$ (10 equiv), THF, -20 °C, 48 h, 99%, 92% ee

Scheme 1.4: Thiourea catalysed Henry reaction.

The origins of organocatalysis lie in the pioneering work of Hajos-Parrish in the 1970's who first reported the development of intramolecular organocatalytic aldol chemistry for Robinson annulation reactions. However, the use of organocatalysis as a strategy for asymmetric synthesis remained relatively dormant until the recent explosion in activity in the late 1990's that was triggered by the discovery that organocatalysts could be used to catalyse intermolecular reactions in high ee. Indeed, the rapid evolution of organocatalysis in recent times as a strategy for asymmetric synthesis has provided organic chemists with completely new types of chiral building blocks for natural product synthesis and drug-discovery applications. A representative range of popular organocatalytic transformations that are now widely employed in organic synthesis are described in Scheme 1.5,[9] with well over 1000 reports of these methodologies having been reported to date.



Scheme 1.5: Representative organocatalytic reactions.

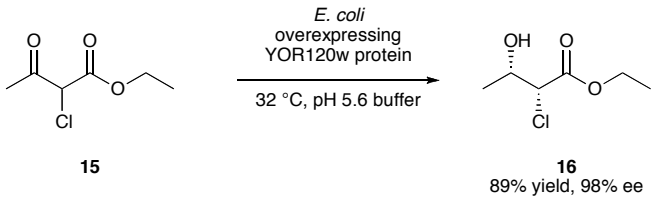
1.3.3 Biocatalysis

Enzymes are Nature's catalysts which can often catalyse highly stereoselective reactions, with the application of both whole cells and enzymes for organic synthesis continuing to increase.[13] This is because the use of biocatalysts provide an often clean and environmentally friendly methodology for transforming natural and non-natural substrates with high levels of stereocontrol.[14]

Enzymes are polypeptides that adopt rigid three-dimensional structures with specific chiral environments/active sites where stereoselective reactions occur that allows for the reliable and dependable preparation of enantiopure materials. They offer an efficient strategy to resolve or produce products containing one or more chiral centres, under mild reaction conditions using protocols that often do not require the use of protection/deprotection strategies. On the other hand, they are often limited to specific compound types, can have poor substrate specificity profiles and suffer from the limited solubility of many organic compounds in water.[14] However, in recent years there has been much interest in addressing these problems using molecular

biological techniques to modify the structures of enzymes to improve their specificity, stability and catalytic profile.[15-17]

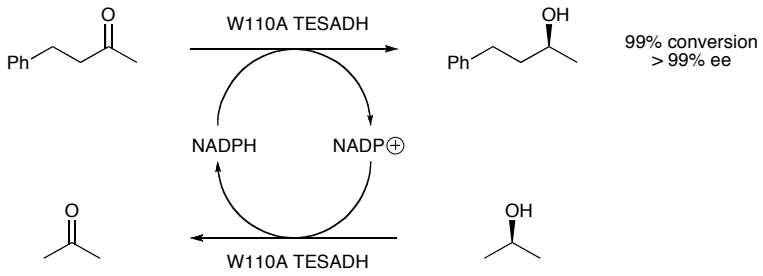
For example, Stewart and co-workers have demonstrated the power of whole cell strategies for the directed reduction of α-chloro-β-keto-ethyl ester **15**.[18] Treatment with engineered *Escherichia coli* (Over expressing YOR120w) under acidic conditions furnished the α-chloro-β-hydroxy-ethyl ester **16** in excellent yield and 98% ee.



15 **16**
89% yield, 98% ee

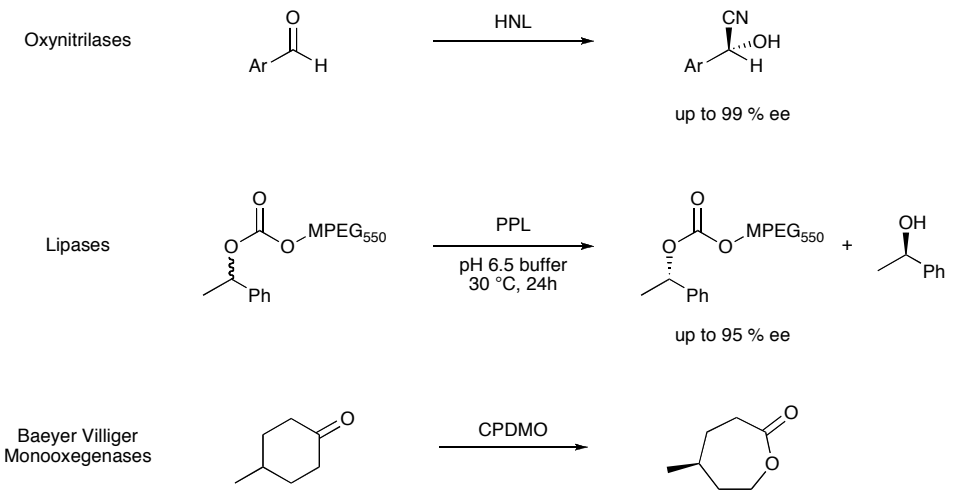
Scheme 1.6: Whole cell reduction of α-chloro-β-ketoethyl ester **15**.

Philips has also described an enantioselective asymmetric reduction of prochiral ketones using W110A secondary alcohol dehydrogenase from *Thermoanaerobacter ethanolicus* in Tris buffer using propan-2-ol as co-solvent and a hydrogen source for cofactor regeneration (Scheme 1.7). The resulting secondary alcohol was obtained in 99% conversion and in >99% ee.[19] These high levels of enantiocontrol under mild reaction conditions clearly show the potential for biocatalysis to compete with organocatalysis and transition metal mediated catalysis in asymmetric synthesis.



Scheme 1.7: Asymmetric reduction of 4-phenylbutan-2-one using secondary alcohol dehydrogenase.

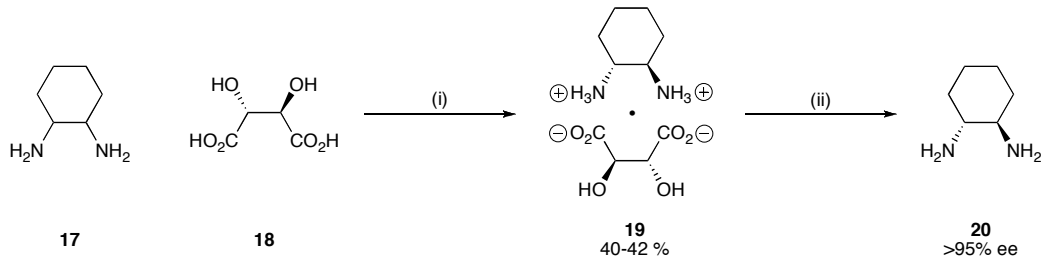
Biotransformations are becoming increasingly important in the pharmaceutical industry, a representative series of popular enzymatic transformations that are now widely used 'on-scale' being described in Scheme 1.8.[20-22]



Scheme 1.8: Representative selection of enzyme catalysed reactions.

1.4 Kinetic resolution

An alternative strategy for accessing enantiomerically pure material is to carry out resolution of a racemic mixture. Chiral resolution is the separation of enantiomers by physical (chromatography or crystallisation) or chemical (reaction with a chiral catalyst) means.[23] A simple example of a physical resolution has been demonstrated by Jacobsen (Scheme 1.9); whereby treatment of diamine **17** with a stoichiometric amount of (2*R*,3*R*)-2,3-dihydroxysuccinic acid **18** under acidic conditions generates the salt **19** which is readily recrystallised to afford a single diastereomer in approximately 42% yield. Subsequent treatment of the salt **19** under basic conditions releases the resolving agent thus allowing access to the enantiopure diamine **20** in >95% ee.[24]



Reagents and conditions: (i) H_2O/HOAc, 90 °C to 5 °C; (ii) K_2CO_3 (2 equiv), H_2O/EtOH

Scheme 1.9: Physical resolution of racemic diamine **17**.

Classical kinetic resolution involves reaction of a racemate with a chiral reagent or catalyst under conditions whereby one enantiomer reacts faster than its corresponding antipode to

ideally generate a single enantiomer of a chiral product and an enantioenriched starting material (Figure 1.3).[25,26]

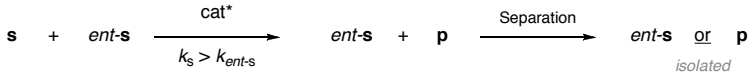
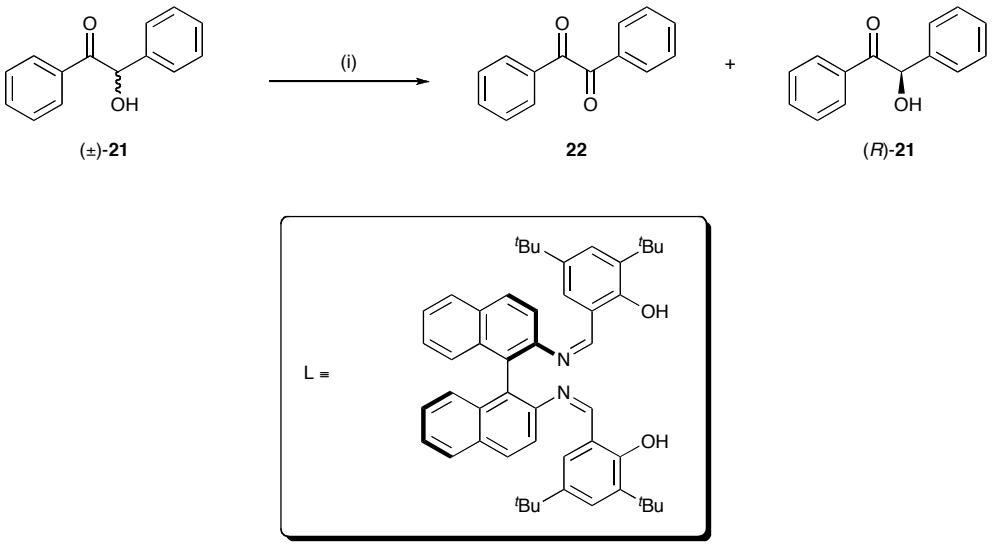


Figure 1.3: Generic representation of catalytic kinetic resolution

For example, Sekar has demonstrated the use of oxidative kinetic resolution for the resolution of racemic secondary alcohols (See Scheme 1.11).[27] Racemic benzoin **21** is treated with a chiral binaphthyl-Fe(OAc)$_2$ complex (10 mol%), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (5 mol%) in the presence of molecular oxygen, which oxidised 76% of the starting material to its corresponding achiral dione **22**. This enabled separation by chromatography to allow access to recovered enantiomerically enriched (*R*)-benzoin in an isolated 21 % yield and an excellent 98% *ee*.

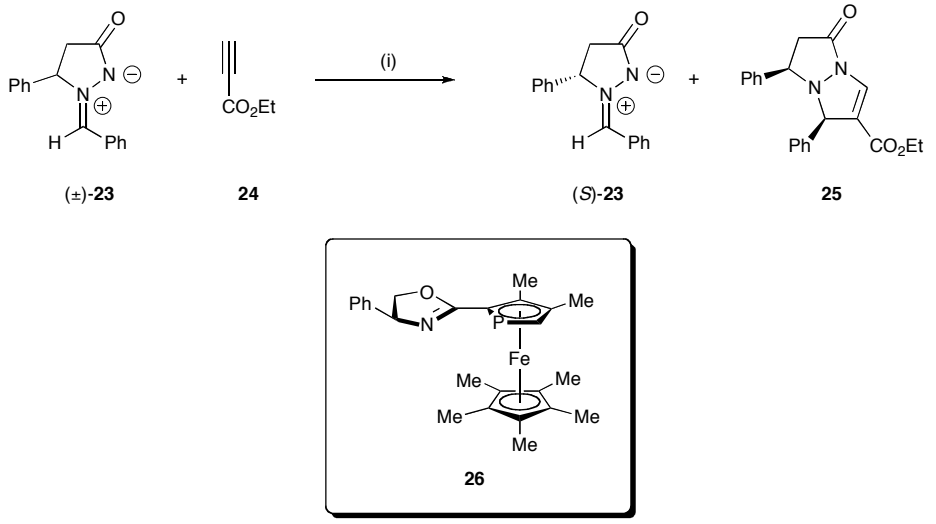


Reagents and conditions: (i) L-Fe(OAc)$_2$ (10 mol%), TEMPO (5 mol%), Hexanes, O_2, 60 °C.

Scheme 1.10: Oxidative kinetic resolution of (±)-benzoin catalysed by chiral iron complexes

Another example is the copper catalysed resolution of azomethine imines described by Fu and co-workers.[28] The racemate is resolved *via* a catalytic asymmetric [3+2] cycloaddition of azomethine imine **23** with terminal alkyne **24** using a chiral copper catalyst. Azomethine imine **23** was treated with copper(I) iodide, chiral phosphaferrocene-oxazoline derivative **26** and a base at ambient temperature, with the bicyclic pyrazolidinone derivative **25** and

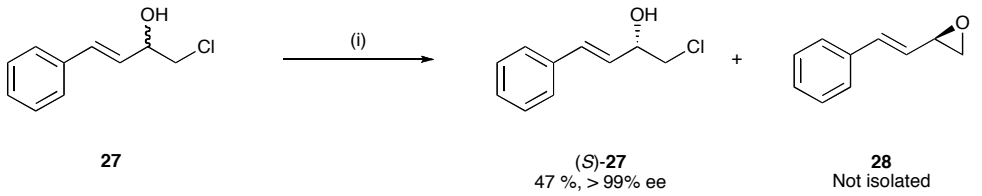
enantioenriched dipole (*S*)-**23** (42 % yield, 99 % ee) being separated *via* column chromatography.



Reagents and conditions: (i) **26** (1.1 mol%), CuI (1 mol%), **24** (0.5 equiv), Cy_2NMe (0.5 equiv) CH_2Cl_2, RT

Scheme 1.11: Kinetic resolution of azomethine imine **23**.

Enzymatic kinetic resolution can utilise the specific chiral environment of the chiral pocket of an enzyme active site to dynamically resolve a racemic substrate. For example, Feringa and co-workers have demonstrated the use of haloalcohol dehalogenase HheC as an efficient biocatalyst for accessing enantiomerically enriched vicinal chloroalcohols by selectively converting its (*R*)-enantiomer into its corresponding epoxide **28**.[29]



Reagents and conditions: (i) HheC, Tris-sulphate pH 8.1 buffer solutions.

Scheme 1.12: HheC-catalysed kinetic resolution of vicinal chloro alcohol **27**

Despite being a practical method for the isolation of enantiopure materials, classical kinetic resolution strategies are limited, since the maximum theoretical yield from any racemate is 50 % and as such is inherently inefficient. Dynamic kinetic resolution protocols can address this problem, because resolution occurs under conditions where the starting material is being

continually racemised *in situ,* such that >50 % yields of chiral products can be achieved (Figure 1.4).[30,31]

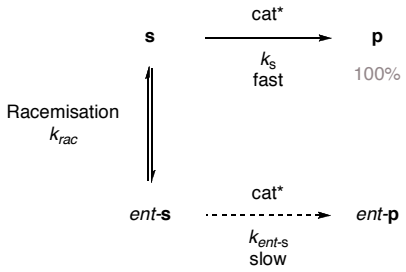
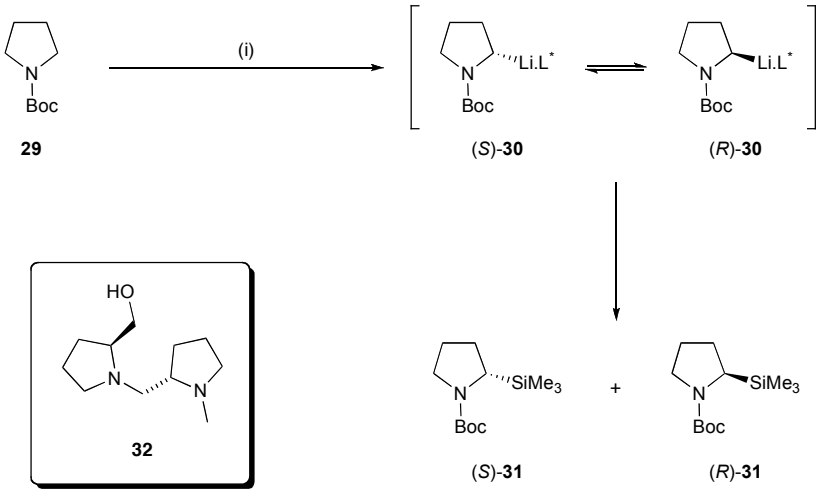


Figure 1.4: Principal of dynamic kinetic resolution of a racemic substrate (**s** and *ent*-**s**) affording 100% of the enantiomerically pure product (**p**).

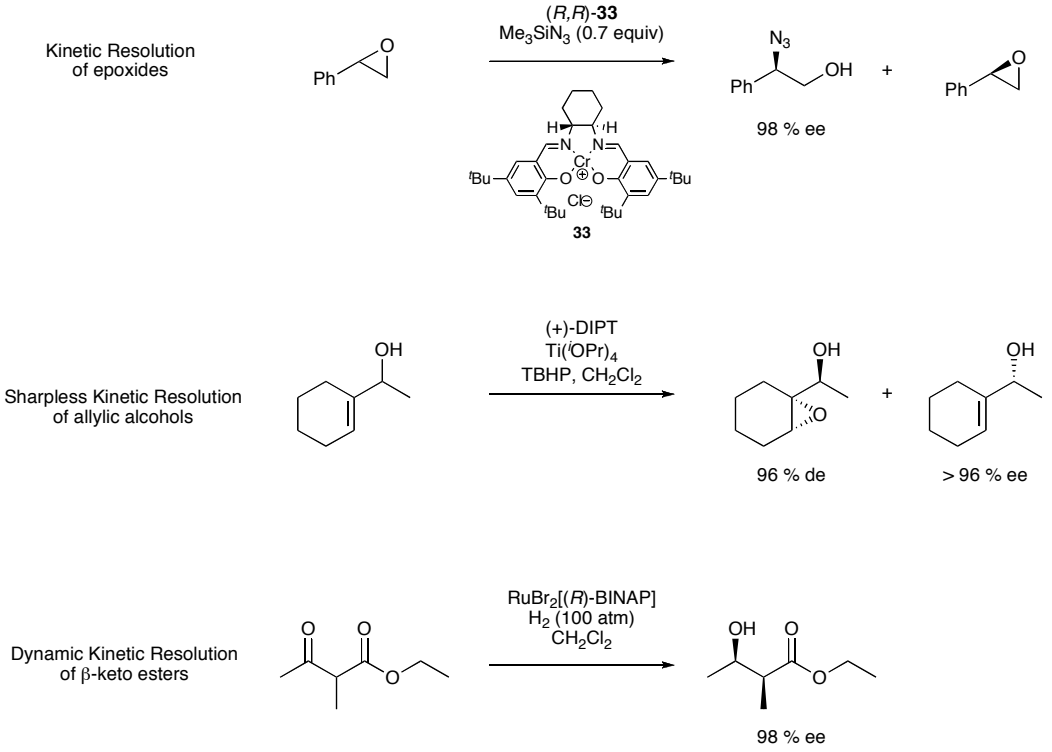
There are also many methods reported in the literature of non-enzymatic dynamic kinetic resolutions of racemates. For example, Coldham and co-workers have demonstrated the resolution of 2-lithiopyrrolidine **30** (See Scheme 1.14).[32] Initially pyrrolidine **29** is lithiated in the presence of a chiral bis-pyrrolidine-ligand, with the resultant diastereoisomeric intermediates (*S*)-**30** and (*R*)-**30** being rapidly racemised *in situ*. Treatment of this intermediate with excess *n*-butyllithium results in the (*S*)-2-lithiopyrrolidine enantiomer reacting faster with the electrophile TMSCl than its corresponding (*R*)-enantiomer, yielding (*S*)-silylated pyrrolidine **31** in 57% yield and 90% ee.



Reagents and conditions: (i) ^{s}BuLi (2.6 equiv), **32** (1.5 equiv), Et_2O, -78 °C; (ii) ^{n}BuLi (10 equiv) then -20 °C, Me_3SiCl (1.0equiv), 57% yield, 90% ee (*S:R*).

Scheme 1.13: Resolution of 2-lithium pyrrolidine.

Both classical and dynamic kinetic resolutions are becoming increasingly popular and a representative series of popular resolutions that are now widely used in organic synthesis are described in Scheme 1.15.[33-35]



Scheme 1.14: Representative selection of widely used kinetic resolution strategies

1.5 Chiral Auxiliaries

A chiral auxiliary is an enantiopure compound that can be used to direct an organic reaction using a chiral controlling group to control the outcome of the reaction, which is achieved through the reversible attachment of the chiral auxiliary to a prochiral starting material. A general chiral auxiliary strategy is described in Figure 1.5; initially the chiral auxiliary (CA) is coupled to the starting material (**s**) to generate an intermediate (CA-**s**) that now contains a transformable functional group that has diastereotopic faces. Subsequent reaction of CA-**s** occurs under the control of the stereodirecting effect of the chiral auxiliary fragment to ideally afford CA-**p** with a new stereocentre in very high de. Purification of the major diastereomer to homogeneity *via* chromatography/recrystallisation is then followed by cleavage of **p** in very high ee.

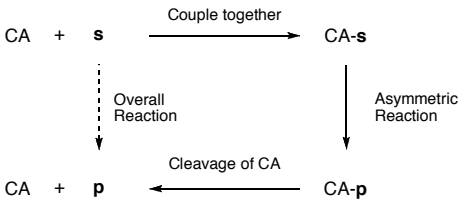
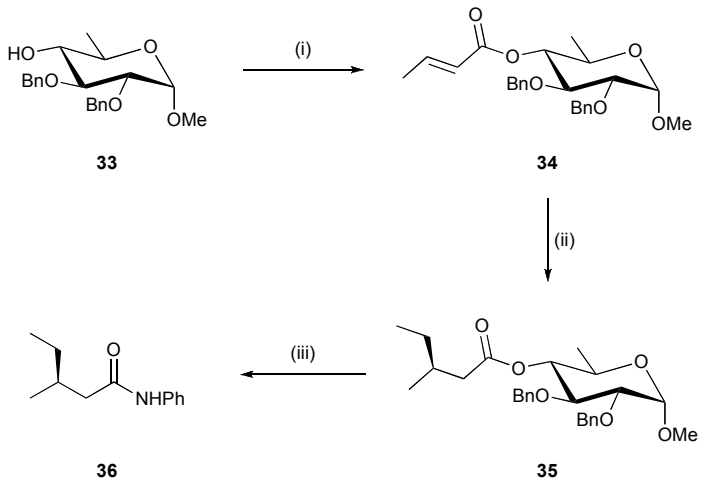


Figure 1.5: General chiral auxiliary strategy for the transformation of an achiral substrate (**s**) into a chiral product (**p**) *via* a diastereotopic intermediate (CA-**p**)

The key requirements for a chiral auxiliary are that it can be easily attached to a prochiral substrate in quantitative yield, that it can direct reactions with high stereoselectivity and that it can be quantitatively removed and recycled without racemisation of the newly formed chiral centre.

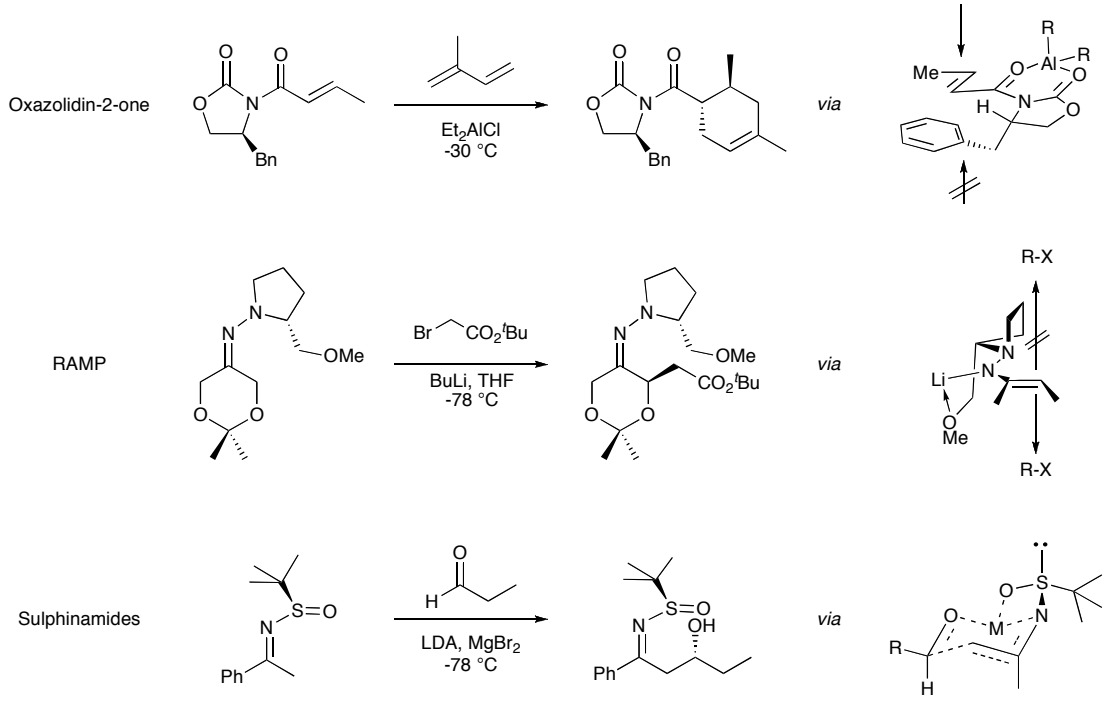
For example, Tadano has demonstrated the use of sugar derivatives as effective chiral auxiliaries for the enantioselective 1,4-addition of magnesium divinylcuprates to Michael acceptors (See Scheme 1.16).[36] Initially, a crotonyl acceptor is added to the chiral auxiliary **33** to yield *O*-crotonyl-**34**, which is followed by conjugate addition of magnesium divinylcuprate to yield the alkylated product **35** containing a new β-stereocentre in >95% de. The auxiliary fragment of **35** is then cleaved to yield the desired enantiopure chiral amide **36** in an overall 71% yield and >95% ee.



Reagents and Conditions: (i) $(CH_3CH{=}CHCO)_2O$; (ii) EtMgBr (10.0 equiv), CuBr.Me_2S (5.0 equiv), THF-Me_2S (2:1); (iii) (a) 4M KOH-MeOH (1:1), reflux; (b) WSC, aniline, DMAP, DCM (overall yield 71%, 96% de)

Scheme 1.15: The use of sugars as chiral auxiliaries.

There are many types of chiral auxiliary that have been developed that enable the stereoselectivity of a wide range of transformations to be controlled. Popular examples include the use of chiral oxazolidin-2-ones, RAMP/SAMP-auxiliaries and sulphinamides that have been applied for stereocontrol in a wide range of reaction scenarios (Scheme 1.17).[37-39]



Scheme 1.16: Representative reactions utilising chiral auxiliary strategies

1.6 Conclusions

As we have seen, there are numerous strategies available for the synthesis of enantiomerically pure compounds; ranging from the chiral pool approach, through resolution to chiral catalysis and the use of chiral auxiliaries. However, it is worthy to note that there is generally no single approach that can be applied to obtain every class of chiral product currently required by academia and industry, with many of the developed methods often being applicable to defined classes of substrate. Therefore, whilst many chiral auxiliary approaches can often appear at first sight to be inferior to asymmetric catalyst approaches, their ability to reliably produce defined classes of enantiopure products in a predictable manner often means that they are employed as frontline 'state of the art' technology for asymmetric synthesis.

Chapter 2: The synthesis of γ-lactones

The majority of research described in this thesis deals with the development of novel chiral auxiliary methodology for the asymmetric synthesis of chiral γ- lactones and as a consequence a brief review of existing methodology for their preparation in enantiopure form is now described.

2.1 Lactones

Lactones are cyclic esters, where the ester bond is incorporated into the ring system. Under IUPAC convention, lactones are named as oxacycloalkanones. However, their names are more commonly derived from the acid that contains the same number of carbon atoms, e.g. butyrolactones contain four carbon atoms and propiolactones contain three carbon atoms. The size of the ring is designated by a Greek letter and refers to the number of carbon atoms between the carbonyl and the oxygen atom that makes up the lactone ring (See Figure 2-1).

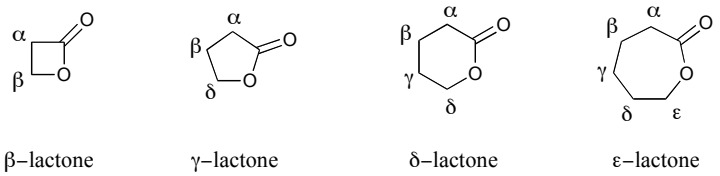


Figure 2.1: Lactone nomenclature

2.2 Applications of γ-lactones

The γ-lactone motif is ubiquitous in Nature and can be considered to be a privileged fragment that occurs in the structures of a wide range of natural product motifs (See Figure 2-2). These products display a wide range of biological activity, displaying antimicrobial, antitumour and cytoxic activity as well as being of great use in the perfume and flavouring industries.

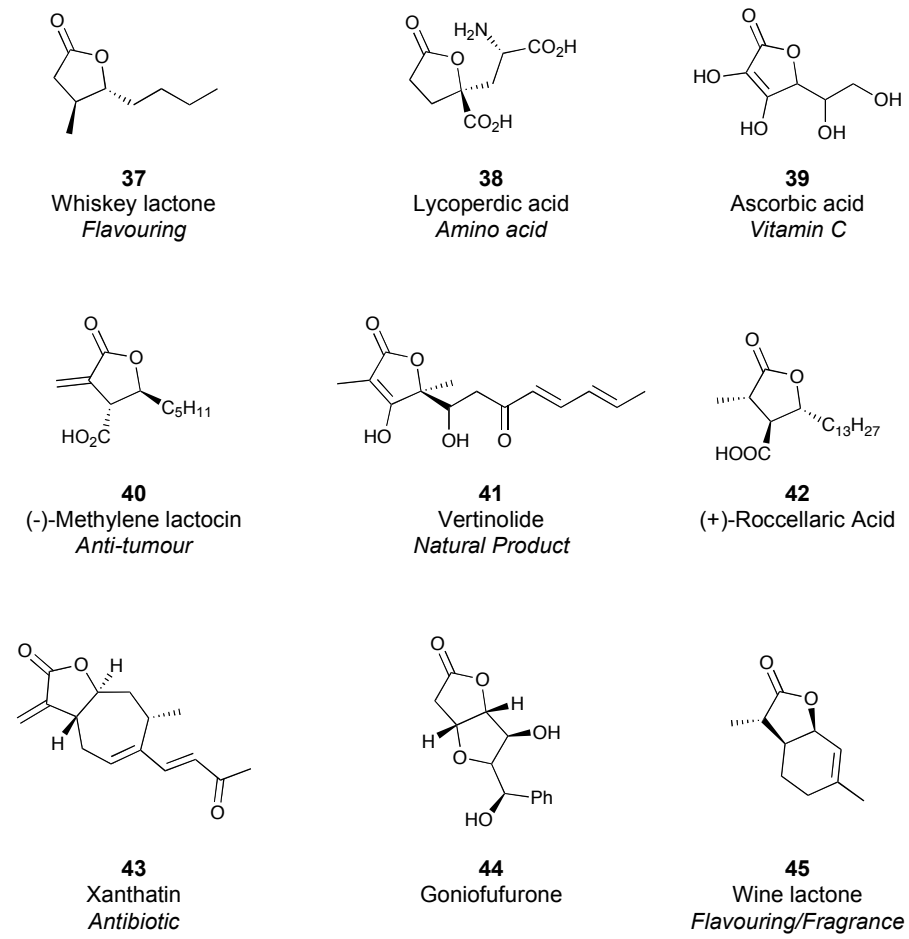
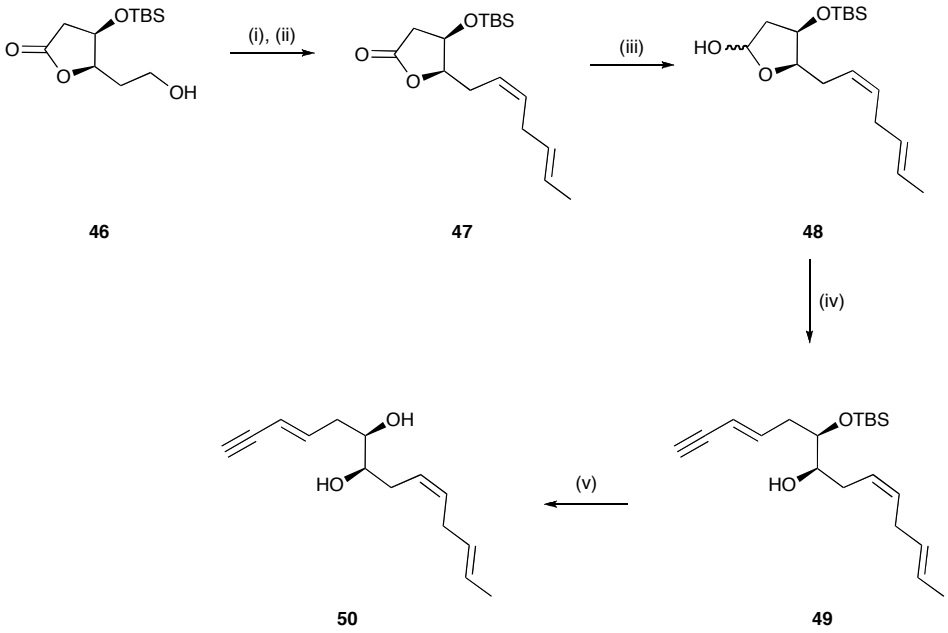


Figure 2.2: Examples of biologically active γ-lactones.

γ-Butyrolactones have also been shown to be valuable synthetic precursors for the synthesis of a wide number of natural products.[40,41] For example, *trans*-(+)-laurediol **50**, was prepared from chiral β,γ-disubstituted-γ-butyrolactone **46**, *via* oxidation with pyridinium chlorochromate to give its corresponding aldehyde, followed by subsequent stereoselective Wittig reaction to afford *Z*-alkene **47**. The lactone functionality of **47** was next reduced to its corresponding lactol **48** using DIBAL-H, which was subjected to a second Wittig olefination to afford *trans*-enyne **49**. Finally, removal of the silyl protecting group using *tetra*-butylamine fluoride gave the natural product *trans*-(+)-laurediol **50**.[41]



Reagents and conditions: (i) PCC, NaOAc, CH_2Cl_2, 4 Å MS; (ii) (*E*)-EtCH=CHCH$_2$CH$_2$PPh$_3^+$I$^-$, KN(TMS)$_2$, THF, -78 °C, 4 Å MS, 36 % over two steps; (iii) DIBAL-H (1.0 equiv), Et_2O, -78 °C; (iv) TMSC≡CCH$_2$PPh$_3^+$Br$^-$, ^{t}BuOK, Et_2O, 0 °C to RT; (v) nBu$_4$NF, THF, RT, 78 % over two steps.

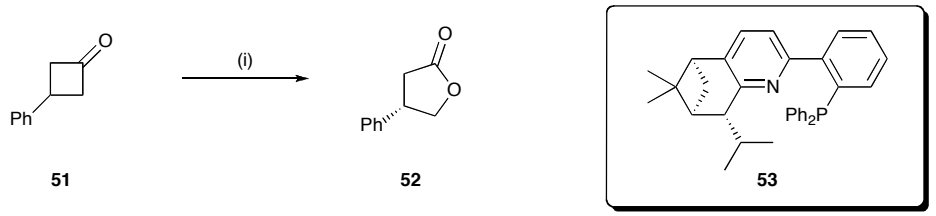
Scheme 2.1: Synthesis of *trans*-(+)-laurediol **50**.

The diverse range of biological activity and synthetic versatility observed for γ-butyrolactones has resulted in much attention being directed towards the synthesis of these interesting frameworks.[42-44] However, there are few general strategies available to access all of the different types of naturally occurring chiral γ-butyrolactone, with most strategies being directed towards the synthesis of a specific class of γ-butyrolactone natural product.[42] Consequently, I shall now briefly describe some of the more popular and powerful methodologies that are currently available for the synthesis of chiral γ-butyrolactone frameworks in enantiopure form.

2.3 Oxidative and Reductive Strategies

One of the simplest strategies for accessing γ-butyrolactones is *via* an oxidative ring expansion reaction. The conversion of ketones to esters *via* the Baeyer-Villiger reaction is well established in the literature, with the application of this oxidation reaction to the conversion of functionalised cyclobutanones to their corresponding chiral γ-lactones having been widely investigated.[45-48] For example, Malkov and co-workers have reported the palladium catalysed Baeyer-Villiger oxidative desymmeterisation of prochiral cyclobutanone **51** in the presence of a

chiral phosphine ligand **53**, using urea-H_2O_2 complex as a stoichiometric oxidant,[49] which gave (*S*)-4-phenyldihydrofuran-2(3*H*)-one **52** in high ee.

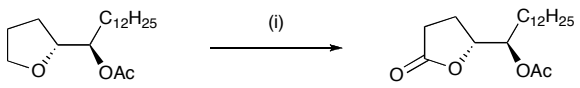


51 **52** **53**

Reagents and conditions: (i) $(NH_2)_2CO$-H_2O_2 (1.3 equiv), $(PhCN)_2PdCl_2$ (5 mol%), **53** (5.5 mol%), $AgSbF_6$ (10 mol%), THF, -40 °C, 97 % yield, 81 % ee (*S*).

Scheme 2.2: Baeyer-Villiger oxidation of cyclobutanone **51**.

Another simple strategy to access γ-lactones is *via* regioselective oxidation of chiral tetrahydrofurans.[50,51] Using modified Sharpless conditions, Nagaoka and co-workers showed that treatment of functionalised cyclic ether **54** with ruthenium tetroxide yielded γ-butyrolactone **55** in 66% yield *via* regioselective oxidation of its CH_2-O methylene unit to its corresponding lactone moiety (Scheme 2.3).[51]

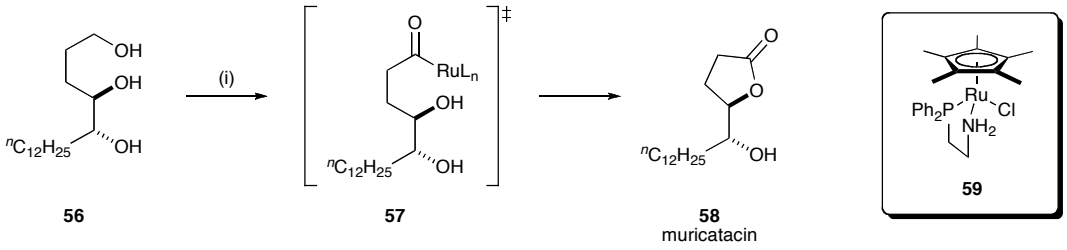


54 **55**

Reagents and conditions: (i) $RuCl_3{\cdot}nH_2O$, $NaHCO_3$, $NaIO_4$, CCl_4, MeCN, H_2O, RT, 66%

Scheme 2.3: Synthesis of γ-butyrolactone **55.**

Another widely employed strategy to access γ-butyrolactones, is to form the lactone ring *via* cyclisation of a chiral γ-hydroxy-acid substrate that can be generated using either oxidative or reductive protocols.[52-54] For example, Ikariya have demonstrated that the primary alcohol of triol **56** could be regioselectively oxidised to afford an unstable chiral γ-hydroxy-acid intermediate that cyclised *in-situ* to afford its corresponding hydroxyl-lactone, (-)-muricatacin **58** (Scheme 2.4).[55] Therefore, treatment of 1,4,5-triol **56** with a Cp*Ru(II) catalyst **59** and potassium-*tert*-butoxide in acetone at 30 °C resulted in clean oxidative cyclisation to afford muricatacin **58** in >99 % yield. [55]

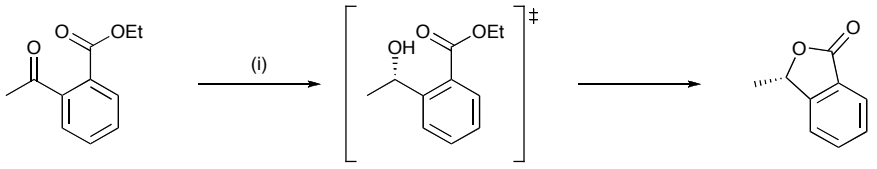


56 **57** **58** muricatacin

Reagents and conditions: (i) **59** (1 mol%), ^{t}BuOK (1 mol%), acetone, 30 °C, 1-2 hours, >99 % yield

Scheme 2.4: Oxidative lactonisation strategy for the asymmetric synthesis of (-)-muricatacin **58**.

Complementary to this approach, are strategies that rely on the stereoselective reduction of a substrate containing a γ-ketone functionality to afford a chiral γ-alcohol functionality that subsequently cyclises onto its ester functionality to afford its lactone ring.[56-61] For example, Noyori and co-workers have reported that reduction of ethyl-*o*-acetyl-benzoate **60** with (*S*)-BINAP (0.4 mol%) in ethanol under 100 atmospheres of hydrogen at 35 °C for 165 hrs, resulted in formation of (*S*)-phthalide **61** in 97 % ee and 97 % yield.[62]



60 **61**

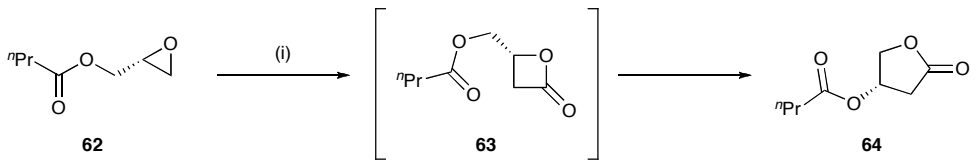
Reagents and conditions: (i) (*S*)-BINAP (0.4 mol%), H_2 (100 atm), ethanol, 35 °C, 165 h.

Scheme 2.5: Synthesis of chiral γ-butyrolactone **61**.

2.4 From epoxides

As we will discuss later, chiral epoxides are powerful reaction precursors that can be readily ring-opened by nucleophiles in an intramolecular fashion to afford chiral. In this respect, Coates and co-workers have developed an efficient epoxidation carbonylation catalyst $[(OEP)Cr(THF)_2][Co(CO)_4]$ that can ring open chiral epoxides with concomitant C1-homologation to afford β-lactones which in the presence of an appropriate internal ester nucleophile can undergo further ring expansion to yield chiral γ-butyrolactone skeletons **62**.[63] Mechanistic studies revealed that the Lewis acid catalysed ring expansion of β-lactone **63** was occurring, whereby coordination of $[(OEP)Cr(THF)_2]^{+}$ to the carbonyl of β-lactone (*R*)-**63** resulted in intramolecular nucleophilic attack of its ester group at its β-position to afford a

dioxycarbenium ion intermediate **66**, that then undergoes a further ring opening reaction at its γ-position to give the stable γ-lactone (*S*)-**64**.



Reagents and conditions: (i) [(OEP)Cr(THF)$_2$][Co(CO)$_4$] (5 mol%), CO (900 psi), 60 °C

Scheme 2.6: Carbonylation/Lewis acid mediated ring expansion reaction of terminal epoxide **62**.

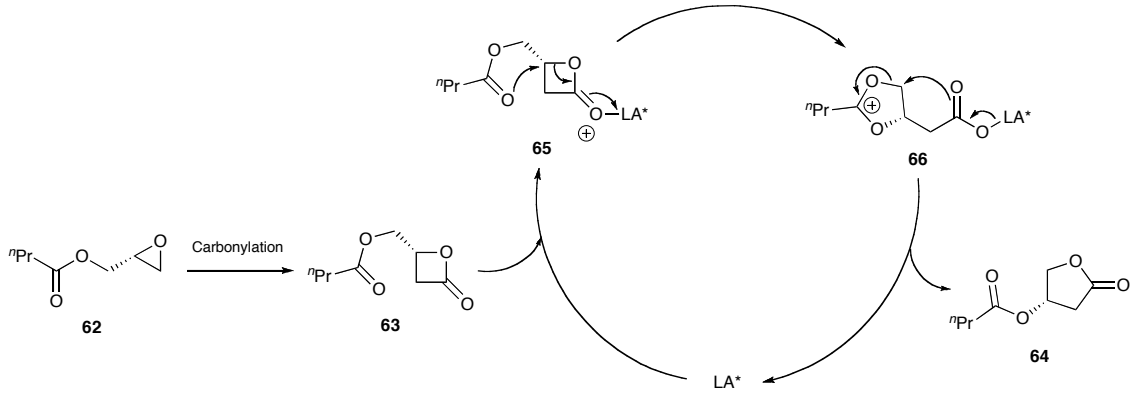
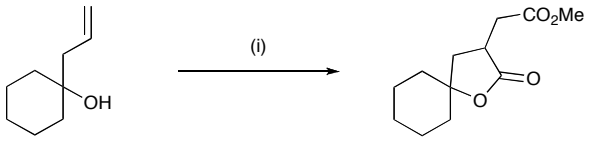


Figure 2.3: Proposed mechanism of carbonylation of epoxide **62** and ring expansion to access γ-lactone **64**.

This type of carbonylation reaction is not simply limited to ring expansion strategies, since it can also be employed as a key reaction to catalytically introduce the carbonyl group of a lactone ring.[64] For example, Tamaru have reported an elegant palladium(II)-catalysed bis carbonylation of 3-butenol **67**, which upon treatment with palladium(II) chloride in methanol and dichloromethane under 1 atmosphere of carbon monoxide generates the spiro-γ-lactone **68** in good yield (Scheme 2.7).[65]

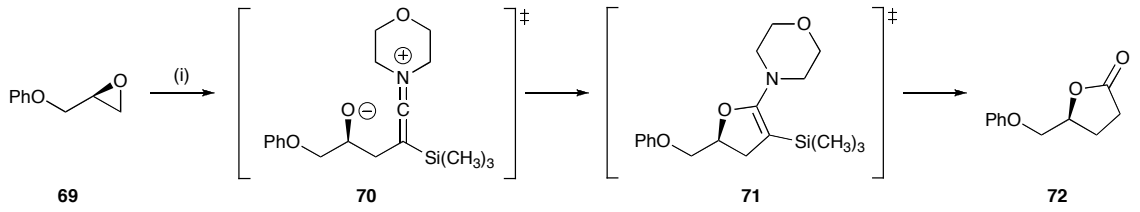


67 68

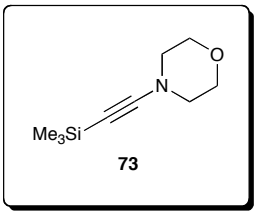
Reagents and conditions: (i) CO (1 atm), $PdCl_2$ (0.1 equiv), Propylene oxide (5 equiv), $MeC(OEt)_3$ (0.4 equiv), $MeOH/CH_2Cl_2$, 84%

Scheme 2.7: Biscarbonylation/lactonisation of 3-butenol **67**.

Chiral epoxides can also be used as substrates in 'formal' carbonylation reactions to directly afford chiral γ-butyrolactones.[66,67] Therefore, Jacobsen and co-workers have shown that treatment of terminal epoxide (*S*)-2-(phenoxymethyl)oxirane **69** with a Lewis acid and ynamine **73** results in clean conversion to γ-butyrolactone **72** with complete retention of configuration.[67] Initially, epoxide **69** is ring opened *via* Lewis acid mediated nucleophilic attack of C_1 of ynamine **73** at its methylene centre to generate an unstable intermediate **70** whose hydroxyl group cyclises back onto its imminium group to generate cyclic keteneaminal **71**. Subsequent hydrolysis and protodesilylation of **71** furnishes the γ-butyrolactone **72** in 92% yield with complete retention of stereochemistry.



69 70 71 72



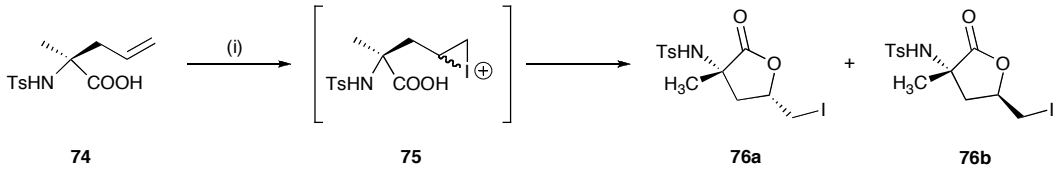
73

Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, **73**, 0 °C, CH_2Cl_2, 30 mins then KHF_2, H_2O, CH_3CN, 30 mins, 92%, >99% ee

Scheme 2.8: Conversion of terminal epoxide **69** to γ-butyrolactone **72**.

2.5 Ring Opening Reactions

Electrophilic cyclisation reactions that employ carboxylic acid equivalents as intramolecular nucleophiles to cyclise onto appended alkene functionalities represent a particularly useful method for constructing γ-butyrolactone ring systems.[68-70] These reactions proceed similarly to the Lewis acid mediated ring opening of epoxide systems discussed previously as demonstrated for the stereoselective iodocyclisation reactions of (*S*)-allyalanine derivatives shown in Scheme 2.9.[71] Initially, *N*-Iodo-Succinimide acts as a source of I^+ which adds across the alkene double bond to reversibly generate diastereoisomeric cyclic iodonium intermediates (**75**), that are intercepted by intramolecular nucleophilic attack of its carboxylic acid functionality at the γ-position, to afford iodo-γ-butyrolactone **76a** as the major product in 60 % de.[72-74]

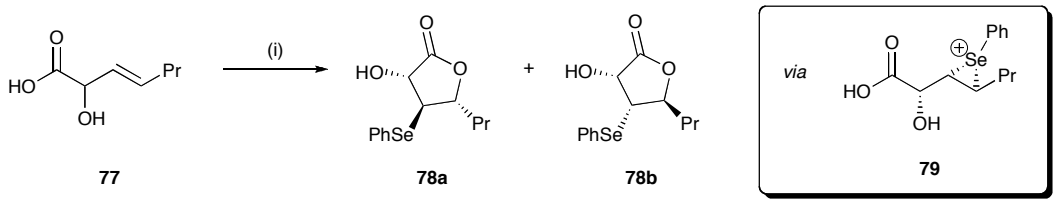


74 **75** **76a** **76b**

Reagents and conditions: (i) NIS (1.2 equiv), Ti(^{i}OPr)$_4$, CH_2Cl_2, RT, 0.5 h, 98%, 80:20 (**76a**:**76b**).

Scheme 2.9: Stereoselective iodolactonisation.

It has been observed that treatment of unsaturated α-hydroxy-β-vinyl-carboxylic acid **77** with phenyl selenyl bromide selectively generates a seliniranium ion intermediate **79**, which is ring-opened by attack by its remote carboxylic acid in a 5-*endo* cyclisation ring opening reaction to yield selenyl-γ-lactone **78a** as the major diastereomer in a 9:1 ratio (See Scheme 2.10). The high levels of diastereoselectivity observed for formation of **79** occurs because of selective coordination of the phenyl selenyl bromide to the α-hydroxyl functionality, which results in selenium being selectively delivered to the *syn*-face of its alkene bond.

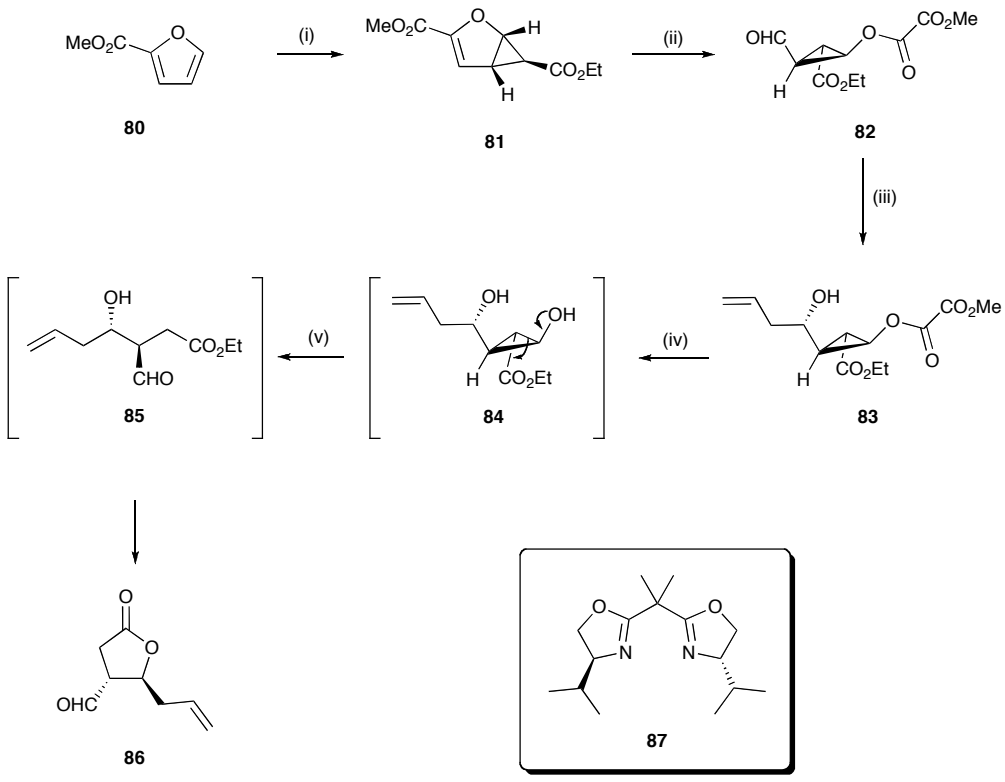


77 **78a** **78b** **79**

Reagents and conditions: (i) PhSeBr, K_2CO_3, CH_2Cl_2, - 78 °C, 33% yield, 9:1 (**78a**:**78b**)

Scheme 2.10: Selenolactonisation reaction α-hydroxy-β,γ-unsaturated carboxylic acid **77**.

Further to this, Reiser has utilised cyclopropanes for the synthesis of β,γ-disubstituted-γ-butyrolactones (Scheme 2.11).[42,75,76] Copper(I) catalysed cyclopropanation of furan **80** with diazoester **88** was shown to proceed in 81% ee using bisoxazoline **87** as a chiral ligand to induce stereocontrol, with recrystallisation of the crude reaction mixture allowing for access to cyclopropane furan **81** in 35% yield and >99% ee. Ozonolysis of cyclopropyl-furan **81** readily furnishes the cyclopropane carboxaldehyde **82**, with subsequent Lewis acid catalysed addition of allyltrimethylsilane yielding allylalcohol **83** in >95% de and was carried forward without the need for further purification. Treatment of **83** with barium hydroxide resulted in ester hydrolysis to afford an alkoxide (**84**) that underwent a clean *retro*-aldol reaction that resulted in cleavage of the strained cyclopropane ring to afford an unstable open chain derivative (**85**) that cyclised to afford γ-lactone **86** in 64% yield and >95% de.[76]

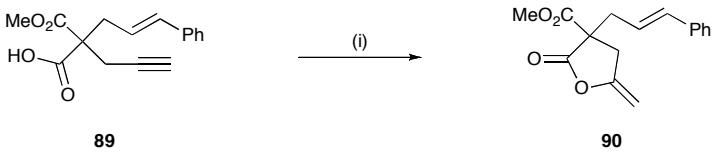


Regents and conditions: (i) $Cu(OTf)_2$ (2.0 mol%), **87** (2.5 mol%), diazoacetate **88** (1.0 equiv); (ii) O_3, CH_2Cl_2, -78 °C then Me_2S, Na_2CO_3 (sat. aq.); (iii) $BF_3{\cdot}OEt_2$ (1.0 equiv), allyltrimethylsilane (1.5 equiv), CH_2Cl_2, -78 °C; (iv) $Ba(OH)_2{\cdot}8H_2O$ (0.5 equiv), MeOH

Scheme 2.11: Enantioselective synthesis of β,γ-disubstituted γ-butyrolactone **86**.

A number of protocols for the synthesis of γ-lactones have been developed which rely on the intramolecular addition of a carboxylic acid nucleophile onto an activated alkyne functionality.[77-80] This type of cyclisation reaction is normally carried out using gold catalysis,[81,82,83-85] with Genêt having shown that treatment of acetylenic acid **89** with gold(I)

chloride results in a clean cycloisomerisation to afford its corresponding the γ-butyrolactone **90** in good yield.[86]



89 **90**

Reagents and conditions: (i) AuCl (5 mol%), CH_3CN, RT, 2 hours, 90 %.

Scheme 2.12: Cycloisomerisation of acetylenic acid **89**.

Gold has a particularly high affinity for the *pi*-systems of alkynes and initially it is postulated that gold(I) coordinates to the alkynyl functionality of alkyne **89** to generate the activated intermediate **90**. Subsequent nucleophilic attack of the carbonyl group of the carboxylate generates an unstable gold alkylidene-γ-lactone **91**, which is protonated to afford the γ-butyrolactone product **92** with regeneration of the gold(I) catalyst.[87]

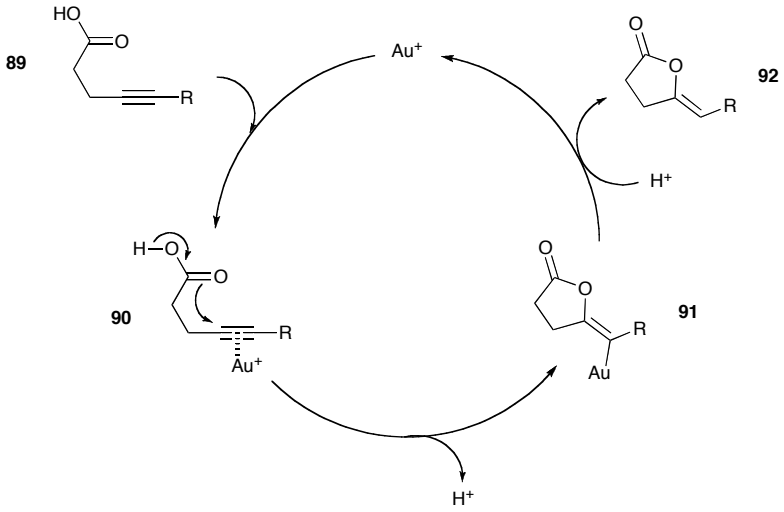
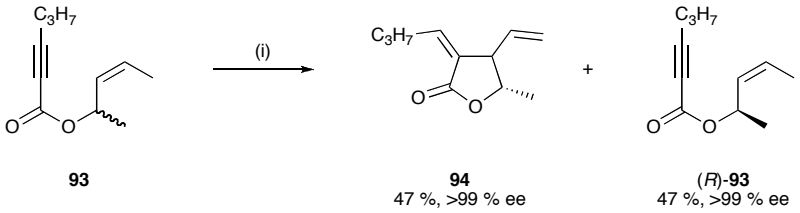


Figure 2.4: Proposed mechanism for the gold catalysed cycloisomerisation of acetylinc acids.

2.6 Carbon-carbon bond forming reactions

Intramolecular reactions of alkynes and alkenes have been demonstrated as effective methods of carbon-carbon bond formation for the generation of γ-butyrolactones.[40,88,89] For example, the intramolecular Alder-ene reaction has been demonstrated as a strategy to access a range of

alkylidene-γ-lactones (Scheme 2.13). Zhang and co-workers demonstrated an effective catalytic kinetic resolution system for the rhodium catalysed Alder-ene reaction of enyn-ester **93** using $[RhCOCCl]_2$/BINAP/$AgSbF_6$ as a catalytic system to enable access to the desired enantiopure alkylidene-γ-lactone (*S*)-**94** and enantioenriched (*R*)-**93**.[40]



Reagents and conditions: (i) $[Rh(COD)Cl]_2$, (*R*)-BINAP, $AgSbF_6$, $ClCH_2CH_2Cl$, RT.

Scheme 2.13: Intramolecular Alder-ene reaction for the synthesis of γ-butyrolactone **94**.

It is postulated that the rhodium complex coordinates to the alkene π system, with subsequent β-hydride elimination to afford an allylic-metal-hydride species 9**6** that results in concomitant intramolecular attack of the alkynyl system to generate the new C-C bond yielding of rhodium-diene **97**. Subsequent hydride shift generates the alkylidene-γ-lactone **94** with regeneration of the rhodium(I) catalyst for further reaction.

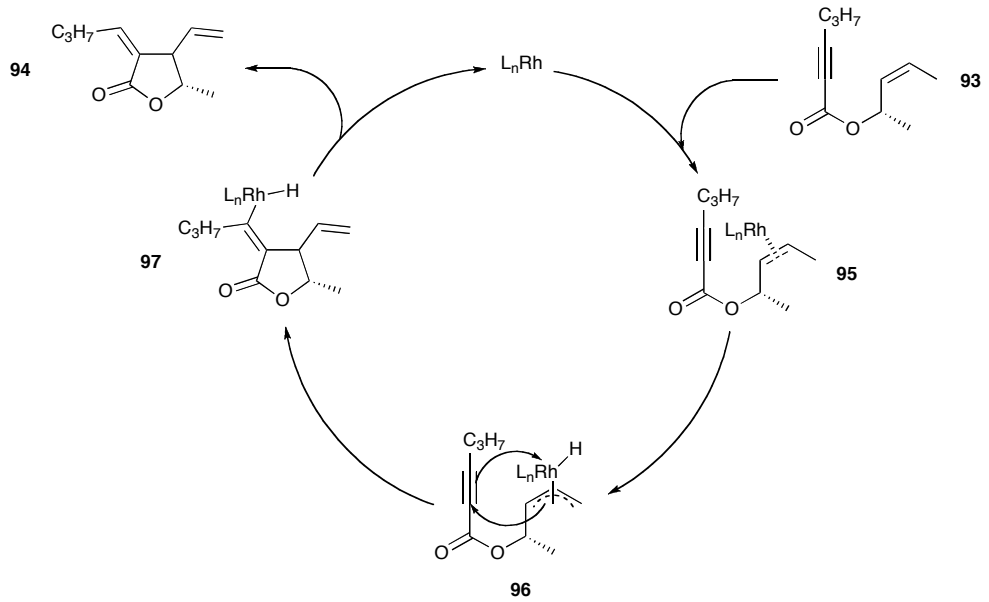
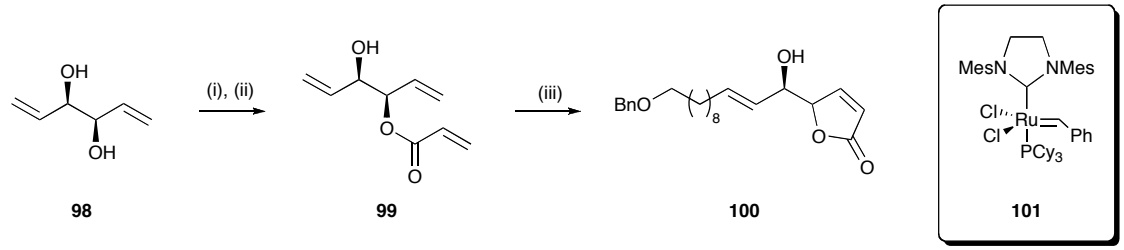


Figure 2.5: Mechanism of the rhodium catalysed intramolecular alderene reaction.

Olefin metathesis reactions are one of the most powerful tools for organic synthesis and the application of this strategy for ring formation is now a well-established protocol for

constructing 5-membered rings of γ-lactone frameworks.[90-94] For example, Quinn and co-workers have demonstrated the power of Grubbs' second generation catalyst in tandem ring-closing/cross metathesis reactions (See Scheme 2.14).[94] Initially, monoester **98** was prepared *via* a two-step mono-silylation/ acryloyl chloride esterification protocol to afford triene **99**, which was treated with Grubbs second-generation catalyst to afford γ-lactone **100**.



98 99 100 101

Reagents and conditions: (i) TBSCl (1.0equiv), imidazole, CH_2Cl_2, 72 %; (ii) Acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, 90%; (iii) **101** (10 mol%), ((undec-10-enyloxy)methyl)benzene (3.0equiv), Benzene, 80 °C , 64%.

Scheme 2.14: Tandem ring-closing/cross metathesis for the formation of α,β-unsaturated-γ-lactone **100**.

Initial intramolecular ring closing metathesis between the alkene of the acryloyl fragment and the proximal alkene occurs to cleanly afford α,β-unsaturated-γ-butyrolactone **102**, with none of the corresponding δ-lactone being formed. Subsequent intermolecular cross metathesis between the terminal alkene functionality of lactone **102** and alkene **103** then results in formation of γ-butyrolactone **100** in 64% yield (See Figure 2.6).[94]

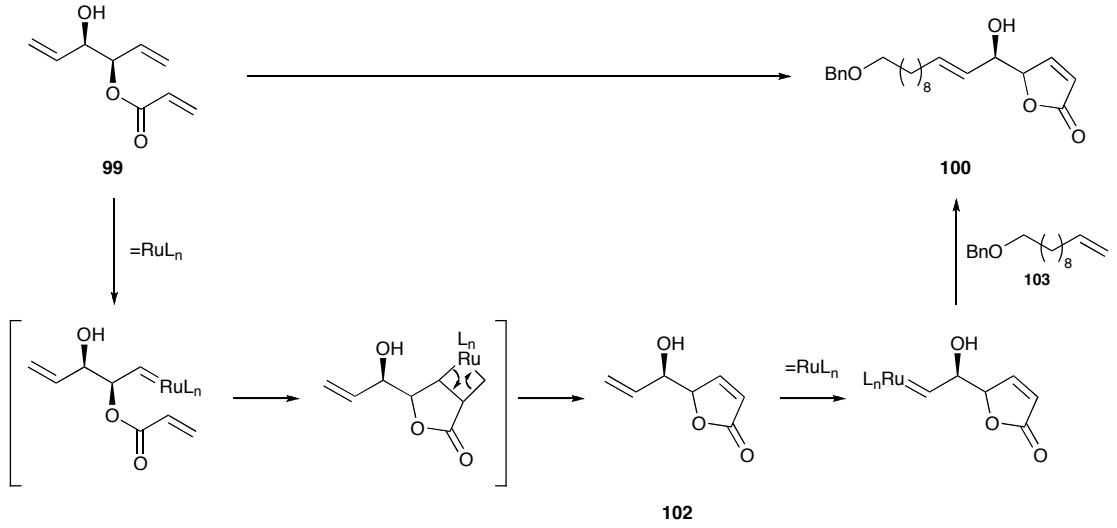
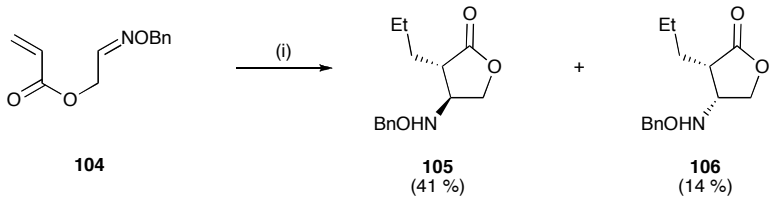


Figure 2.6: Mechanism of tandem ring-closing/cross metathesis.

There are many examples in the literature where radicals have been used to construct lactone functionalities *via* intramolecular cyclisation onto unsaturated functionalities.[95-97,98,99] For example, Naito has described free radical-mediated methodology for cyclisation of oxime ether substrates *via* a conjugate addition-cylisation strategy (Scheme 2.15).[100]

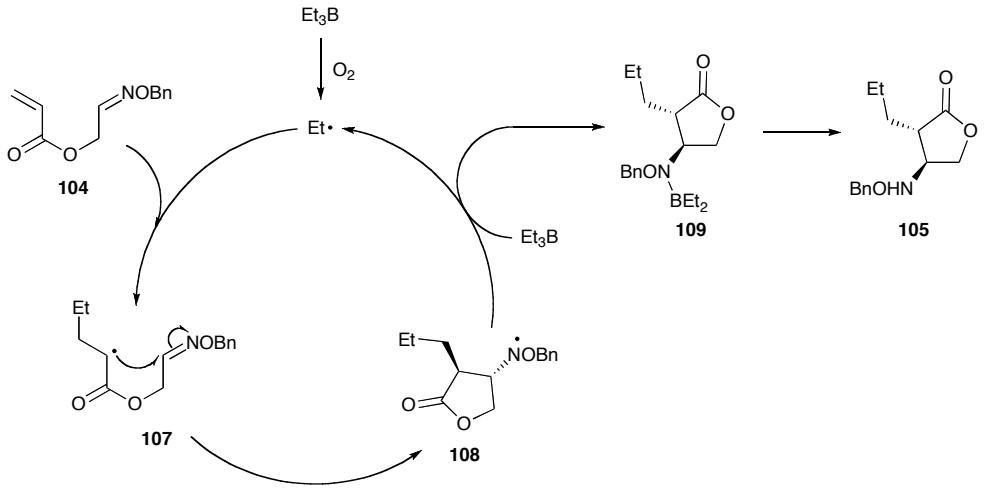


104 **105** (41 %) **106** (14 %)

Reagents and conditions: (i) Et_3B, toluene, reflux, **105**:**106** (3:1).

Scheme 2.15: Radical mediated cyclisation of oxime ether **104**.

Therefore, refluxing triethylborane in toluene generates an ethyl radical, which undergoes conjugate addition to the acrylate functionality of **104** to a carbonyl stabilised α-radical **107**, that then undergoes intramolecular 5-*exo*-trig intramolecular cyclisation onto its oxime functionality. The resulting oxime radical **108** is trapped *via* reaction with a further equivalent of triethylborane to generate an ethyl radical and borane-γ-lactone **109** which on aqueous workup affords the α,β-disubstituted-γ-lactone **105** as the major product.[100]

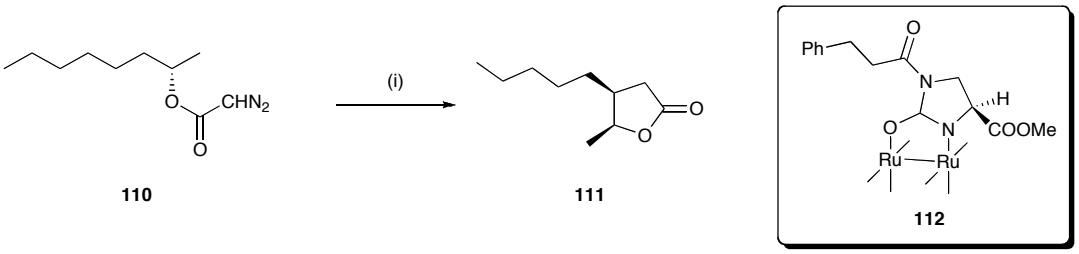


104 **109** **105** **107** **108**

Figure 2.7: Radical mediated cyclisation of oxime-ether **104**.

Another, interesting reaction for the generation of carbon-carbon bonds involves ring formation *via* carbene insertion into an unactivated C-H bond.[101] For example, Doyle *et al* have reported

the synthesis of β,γ-disubstituted-γ-butyrolactone **111** *via* rhodium catalysed intramolecular C-H insertion of diazoacetate **110** (Scheme 2.16).[102]



Reagents and conditions: (i) $Rh_2(4S\text{-MPPIM})_4$ (1 mol%), CH_2Cl_2, reflux, 72% yield

Scheme 2.16: Intramolecular C-H insertion reaction generating β,γ-disubstituted-γ-butyrolactone **110**.

The reaction is envisaged to proceed *via* generation of a rhodium carbenoid species **113** whose *p*-orbital of overlaps with the *σ*-orbital of a suitably orientated C-H bond to initiate C-C bond formation *via* intermediate **114** (Figure 2.8), with hydrogen atom migration to the original carbene center affording the final product **111**.[102]

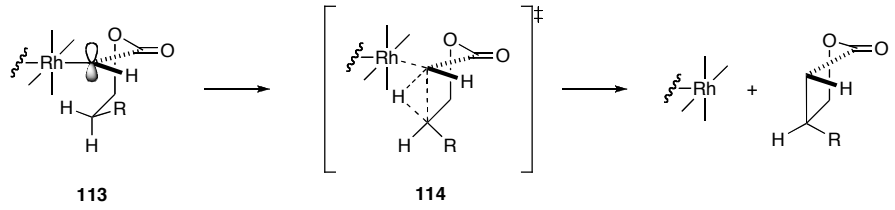
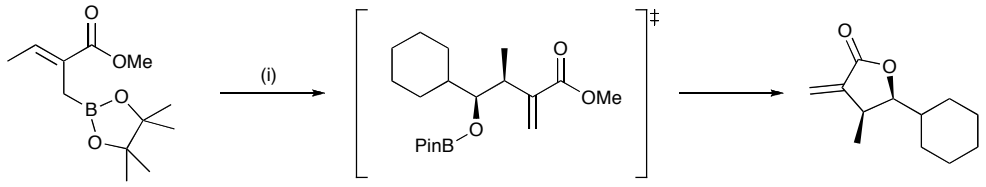


Figure 2.8: Mechanism of rhodium catalysed C-H insertion.

Strategies that utilise carbon-carbon bond forming reactions to access chiral-γ-butyrolactones are not simply limited to intramolecular reactions, with protocols based on Baylis-Hillman and aldol reactions having been used to access chiral starting materials for iterative synthesise of γ-butyrolactones. Therefore, a number of 'one-pot' C-C bond formation/lactonisation reactions have been developed for this purpose, with boron-mediated allylation reactions of aldehydes representing an impressive route to alkylidene-γ-butyrolactones.[103,104] For example, Ramachandran has shown that treatment of *Z*-crotylboronate **115** with cyclohexane carboxaldehyde with ytterbium(III) triflate as a Lewis acid resulted in *cis*-β,γ-disubstituted-α-methylene-γ-butyrolactone **117** in 90 % yield.

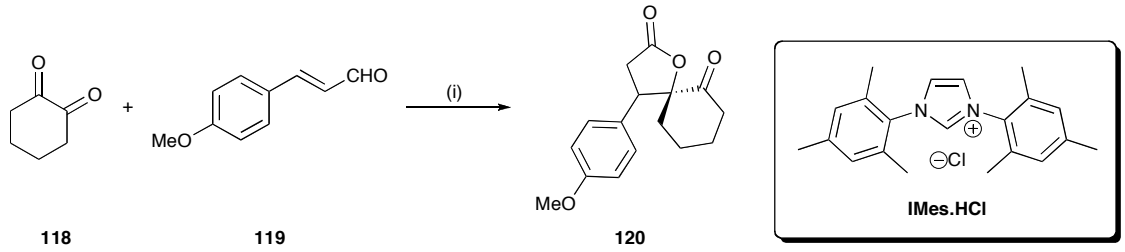


Reagents and conditions: (i) Cyclohexanecarboxaldehyde (1 equiv), $Yb(OTf)_3$ (20 mol%), Toluene, RT, 80 %

Scheme 2.17: Synthesis of β,γ-disubstituted-α-methylene-γ-butyrolactone **117**.

2.7 Organocatalysis

In recent years there has been an ever-increasing interest in organocatalysis and it applications for organic synthesis,[9,105] with its use for the asymmetric synthesis of lactone moieties having attracted much interest.[106] The application of nucleophilic heterocyclic carbenes (NHC) for reaction catalysis has been widely investigated.[107-109] Suresh and co-workers demonstrated the application of the NHC catalysed reaction of enals and 1,2-dicarbonyl species for the synthesis of γ-butyrolactones (Scheme 2.18).



Reagents and conditions: (i) IMes·HCl (6 mol%), DBU (12 mol%), THF, RT, 12 h, 78 %

Scheme 2.18: NHC catalysed annulation of enal **119** and biscarbonyl **118** to generate the spiro-γ-lactone **120**.

Initially the carbene is generated by treatment of IMes·HCl with a base (DBU) to generate catalytic species **121** *in-situ*, with subsequent nucleophilic attack at the carbonyl of aldehyde **119** to generate alkoxide intermediate **122** that then tautomerises to afford diene **123**, which undergoes nucleophilic attack at the carbonyl of acetone to generate a γ-hydroxy-carbonyl **125**, with concomitant cyclisation/elimination to afford the desired γ-butyrolactone.[108]

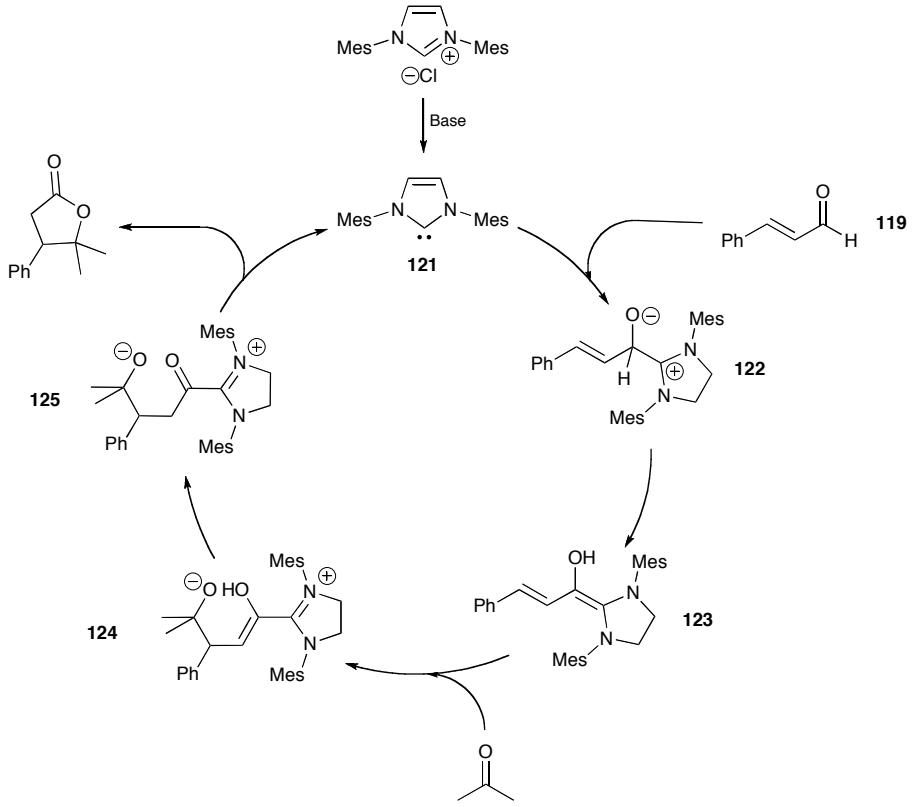


Figure 2.9: Mechanism of NHC catalysed annulation of enals and carbonyl compounds to generate spiro-γ-butyrolactones.

2.8 Conclusions

Clearly, there are a wide range of synthetic strategies available to construct a range of different γ-butyrolactone frameworks; utilising a range of reactions from organocatalysis, electrocyclisation to reduction/oxidation to name but a few. However the synthesis of three or more contiguous stereocentres in a single γ-butyrolactone still remains a challenge with most strategies being target driven aiming at a particular class of γ-butyrolactone natural products. Here in we shall discuss our attempts to access highly functionalised α,β,-substituted-γ-butyrolactones utilising an aldol/epoxidation/lactonisation strategy upon unsaturated-aldol systems.

Chapter 3: An efficient asymmetric synthesis of hydroxy-γ-butyrolactones

3.1 Trisubstituted γ-butyrolactones

Chiral trisubstituted γ-butyrolactones are of particular synthetic and biological interest. They are known to display a wide range of biological activity with the γ-butyrolactone moiety being found in a wide range of natural products. For example, Crassalactone C (**130**) isolated from Asian trees is known to display cytotoxic activity against human tumour cells;[110] *ent*-Clavilactone B (**131**) isolated from the *Clitocybe clavipes* fungus demonstrates antibacterial activity;[111] and peroxylactone Plakortolide **132** (isolated from a Jamaican sponge) has been shown to inhibit protein kinase enzymes.[112]

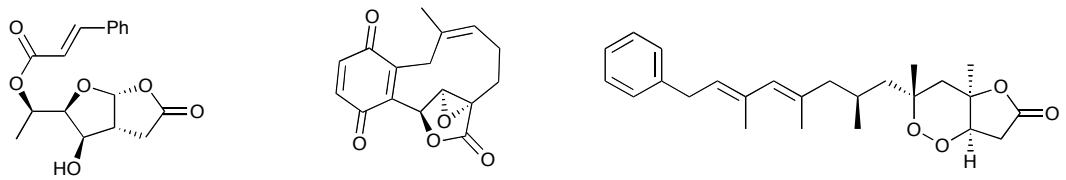
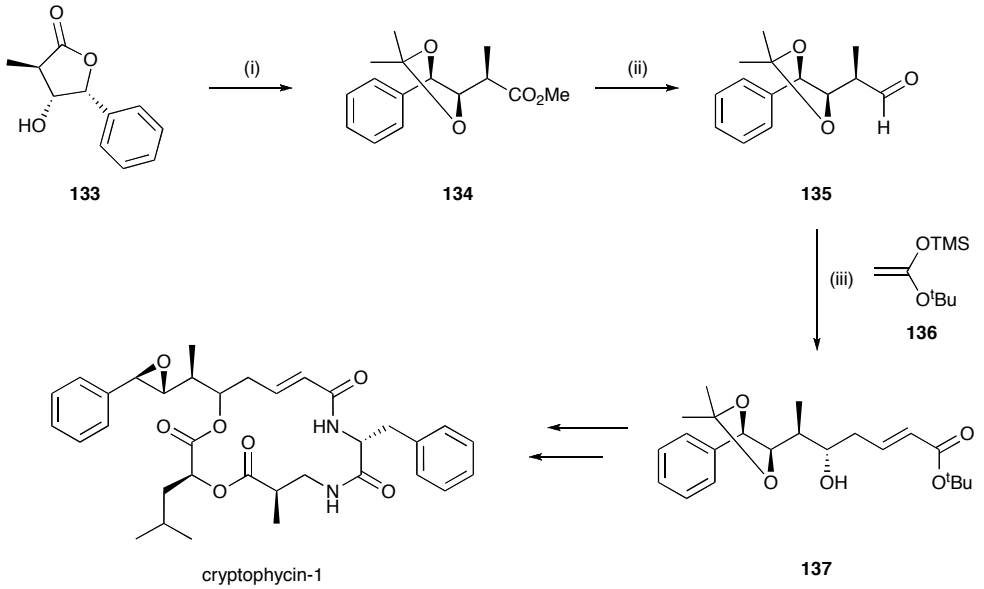


Figure 3.1: Naturally occurring γ-butyrolactones

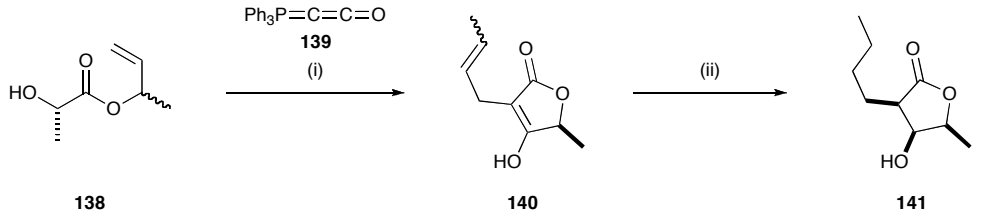
Moreover, trisubstituted γ-butyrolactones have proven to be powerful synthetic precursors, and have been used in many natural product syntheses. [40,113] One such example is in the synthesis of cryptophycin A (Scheme 3.1).[114] Initially (*R*)-α-methyl lactone **133** is esterified and acetal protected using 2,2-dimethoxypropane, methanol and Amberlyst 15 in a one pot procedure. The resulting open chain methyl ester-acetonide **134** is subsequently reduced to the corresponding aldehyde derivative with concomitant Mukaiyama aldol addition/dehydration giving the cryptophycin unit A precursor **137** in 42% yield over two steps.



Reagents and conditions: (i) Amberlyst-15, MeOH, $C(CH_3)_2(OMe)_2$, RT, 2d, 88% yield; (ii)DIBAL-H, CH_2Cl_2, -78 °C, 3h; (iii) **136**, $MgBr_2.Et_2O$, PhMe, -78 °C, 8h, 42% yield.

Scheme 3.1: Synthesis of cryptophycin unit A.

As a consequence of their diverse applications, a wide range of methods have been developed for the synthesis of enantiopure trisubstituted γ-butyrolactones.[115,116] One such example is the synthesis of (-)-*epi*-blastmycinolactol **141**; where Schobert utilised a one-pot Wittig alkenylation/Claisen rearrangement for construction of the lactone moiety.[117] Treatment of methallyl-(*S*)-lactate **138** with (triphenylphosphoranylidene) ketene **139** in toluene under microwave irradiation (sealed vial, 180 °C, 10 min) generated the unsaturated γ-lactone **140** in 65% yield. Subsequent hydrogenation of the alkenyl bonds utilising a rhodium/alumina catalyst and hydrogen gas (50 bar) afforded (-)-*epi*-blastmycinolactol **141** in 70% yield and in 92% ee.



Reagents and conditions: (i) **139**, PhMe, 180 °C, MW, 10 mins; (ii) H_2 (50 bar), Rh/Al_2O_3 (20 mol%), EtOAc, 60 °C, 5d

Scheme 3.2: Synthesis of (-)-*epi*-blastmycinolactol **141**.

Given their potential importance, I now report the development of highly efficient methodology for the asymmetric synthesis of trisubstituted hydroxylated γ-butyrolactones *via* hydroxyl directed epoxidation reactions of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-ones.

3.2 Previous work

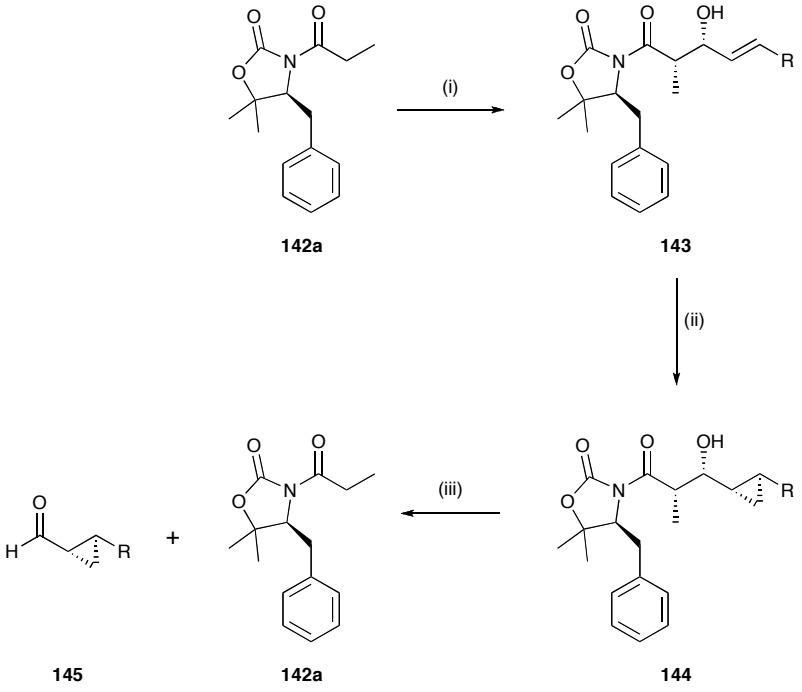
Aldehydes are important building blocks in organic chemistry, with the range of high yielding one-step transformations that the aldehyde synthon can undergo making them highly desirable precursors for organic synthesis. As such, chiral aldehydes (or their equivalents) containing α-stereocentres are widely employed as versatile chiral building blocks for the asymmetric synthesis of complex natural products and drug like molecules.

As a consequence, a wide range of methodology has been developed for their asymmetric synthesis. These include reduction of corresponding chiral amides,[118] Weinreb amides,[119] thioesters and oxazolines that allow direct access to chiral aldehyde motifs.[120,121] Oxidations from chiral primary alcohols are also viable, although often limited by the potential of racemisation of the α-stereocentre.[122] Alternatively, oxidative cleavage of chiral diols and ozonolysis of chiral alkenes or hydrazones have also been widely reported.[123] Further to this, methodologies have also been developed that do not require oxidative or reductive steps to generate the aldehyde functionality, including hydroformylation of alkenes,[124] rearrangement reactions,[125] conjugate addition reactions, cycloadditions, and kinetic resolution of racemic substrates.

A number of chiral auxiliary approaches have been developed for the asymmetric synthesis of chiral aldehydes.[126-128] In these protocols, chiral aldehyde equivalents are stereoselectively transformed into a chiral intermediate containing a new stereocentre in high de, with diastereocontrol being controlled by the attached chiral auxiliary fragment. Subsequent cleavage of the chiral auxiliary fragment from each chiral intermediate then generates a chiral aldehyde product containing an α-stereocentre in high ee.

Previous work in the SDB group has focused around the use of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one substrates as novel synthons for the asymmetric synthesis of chiral aldehydes.[129,130] In these methodologies, a novel 'temporary stereocentre' strategy is employed to relay stereocontrol which enables a chiral auxiliary fragment to be used to create remote stereocentres in high de.

One such example utilises a three-step strategy of stereoselective aldol/directed cyclopropanation/*retro*-aldol reactions for the synthesis of enantiopure cyclopropane carboxaldehydes (See Scheme 3.3). Initially, *N*-acyl-oxazolidin-2-one **142a** was treated under boron mediated aldol conditions to generate a *syn*-aldol product in high de. Treatment of *syn*-aldol **143** with diethyl zinc and diiodomethane in dichloromethane at –10 °C resulted in a highly diastereoselective cyclopropanation reaction to yield cyclopropyl aldol **144** in 99% yield and > 95% de. Subsequent treatment of cyclopropyl-*syn*-aldol **144** with LHMDS in toluene at 0 °C resulted in a clean *retro*-aldol to yield the cyclopropane carboxaldehyde **145** in > 95% de.

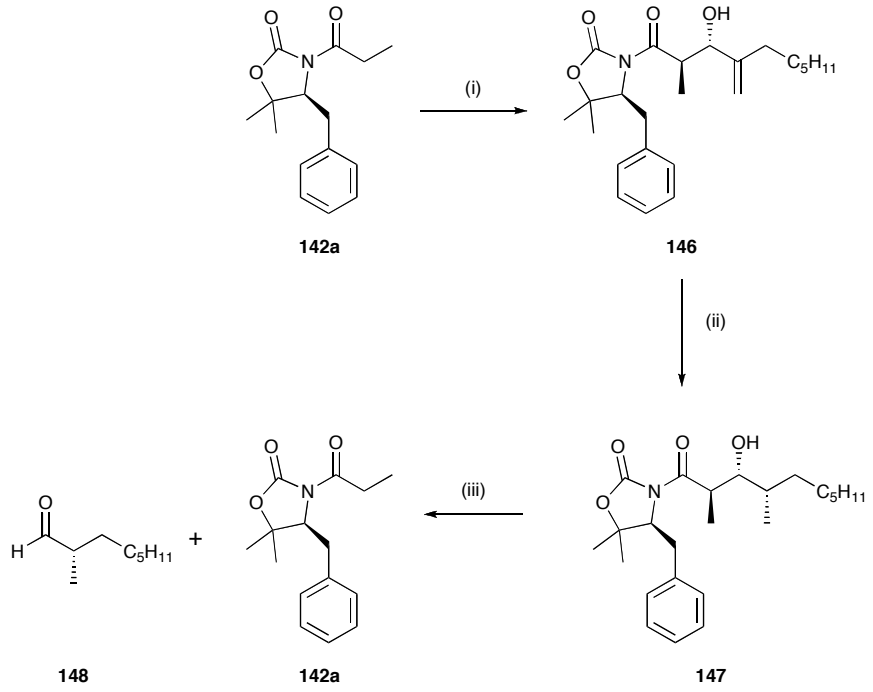


Reagents and conditions: (i) (a) 9-BBN-OTf, DIPEA, CH_2Cl_2, 0 °C; (b) α,β-Unsaturated aldehyde, -78 °C to RT; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0 °C; (iii) LHMDS, toluene, 0 °C.

Scheme 3.3: Temporary stereocentre approach for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

The overall outcome of this three-step protocol was the stereoselective transformation of an achiral α,β-unsaturated aldehyde into chiral cyclopropane carboxaldehyde **145** in high ee, using reversible formation of the temporary β-hydroxyl stereocentre of *syn*-aldol **143** to control the facial selectivity of the cyclopropanation reaction. Further to this the SDB group has also demonstrated that this three-step 'temporary stereocentre' approach is not simply limited to the hydroxyl-directed-cyclopropanation reaction. One example is the asymmetric synthesis of (*S*)-α-methyl octanal, with *anti*-aldol **146** being generated *via* use of the magnesium enolate of **142a** in high levels of diastereocontrol (See Scheme 3.4). Hydrogenation of *anti*-aldol **146** with

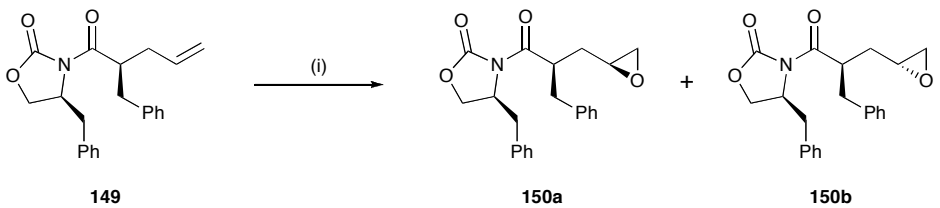
Wilkinson's catalyst in dichloromethane generated the saturated (2*R*,3*R*,4*S*)-*anti*-aldol **147** in 96% de. Subsequent treatment of (2*R*,3*R*,4*S*)-*anti*-aldol **147** with LHMDS at 0 °C, resulted in a clean *retro*-aldol reaction to afford (*S*)-α-methyl-octanal **148** in >95% ee.



Reagents and conditions: (i) (a) $MgCl_2$, Et_3N, Hexylacrolein, TMSOTf, EtOAc; (b) TFA, MeOH; (ii) 17.5 mol% Wilkinson's catalyst, 5 bar H_2, CH_2Cl_2; (iii) LHMDS, toluene, 0 °C

Scheme 3.4: Temporary stereocentre approach for the asymmetric synthesis of (*S*)-methyl-octanal.

γ,δ-Unsaturated-*N*-acyl-oxazolidin-2-ones have previously been shown to undergo epoxidation reactions. For example, Trova *et al* previously demonstrated that epoxidation of γ,δ-unsaturated *N*-acyl-oxazolidin-2-one **149** with *m*CPBA and $NaHCO_3$ in dichloromethane yielded a 50:50 mixture of the diastereomeric epoxides **150a** and **150b** (Scheme 3.5). [131]

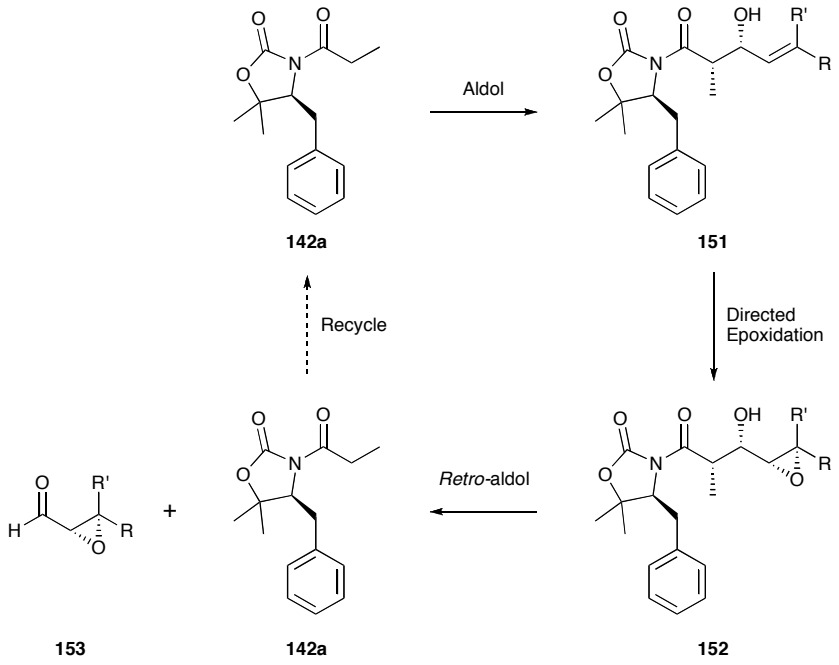


Reactions and conditions: (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2

Scheme 3.5: Synthesis of 50:50 diastereotopic mixture of γ,δ-epoxy *N*-acyl-oxazolidin-2-one **150**.

With this precedent in mind, it was decided to investigate the hydroxyl-directed epoxidation reactions of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-ones, with the aim of developing a 'temporary stereocentre' methodology for the synthesis of chiral α,β-epoxy aldehydes.

Initially, an asymmetric aldol reaction would be used to generate the directing hydroxyl functionality of **151** with high levels of stereocontrol; subsequent reaction of the aldol product **151** under hydroxyl-directed epoxidation conditions would generate the chiral epoxide **152** with *retro*-aldol cleavage affording the desired α,β-*epoxy*-aldehyde **153**.

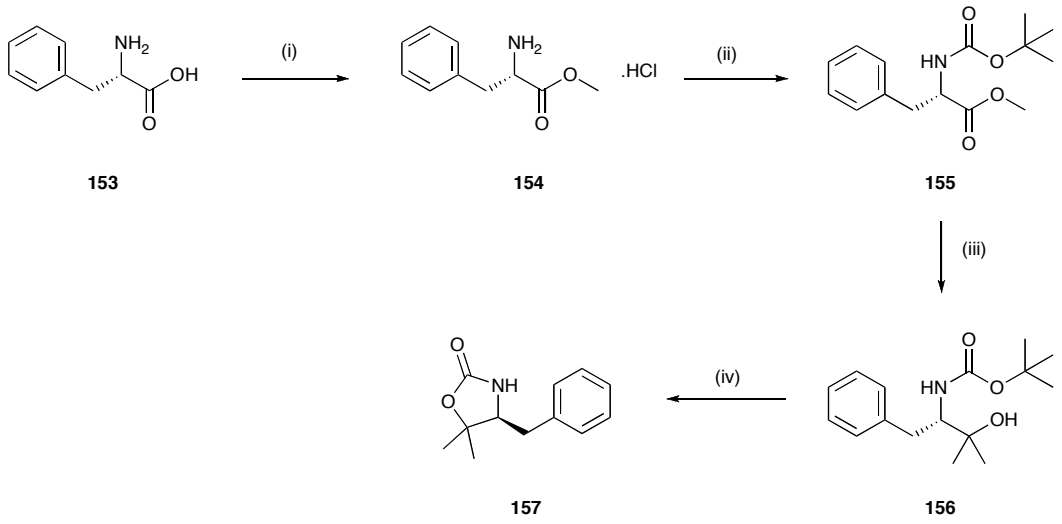


Scheme 3.6: Proposed temporary stereocentre approach for the synthesis of chiral epoxy-aldehydes.

The initial target was therefore the synthesis of gram quantities of SuperQuat auxiliary **157**, the use of which would enable the temporary stereocentre epoxidation protocol to proceed as envisaged.

3.3 Synthesis of SuperQuat auxiliary

The synthesis of the SuperQuat auxiliary was adapted from the original methodology reported by Bull *et al,* starting from naturally occurring (*S*)-Phenylalanine (Scheme 3.7).[132,133]



Reagents and conditions: (i) $SOCl_2$ (1.5 equiv), MeOH; (ii) Boc_2O, $NaHCO_3$, THF, 48 hours; (iii) Mg turnings, CH_3I, THF, 48 hours; (iv) ^tBuOK, THF, 2 hours.

Scheme 3.7: Synthesis of SuperQuat auxiliary **57**.

(*S*)-Phenylalanine was esterified using thionyl chloride at room temperature. Initially, the thionyl chloride reacts with methanol to generate dry HCl which catalyses the esterification reaction with methanol to yield the HCl salt of methyl ester **154** in 98% yield, which was used without further purification.

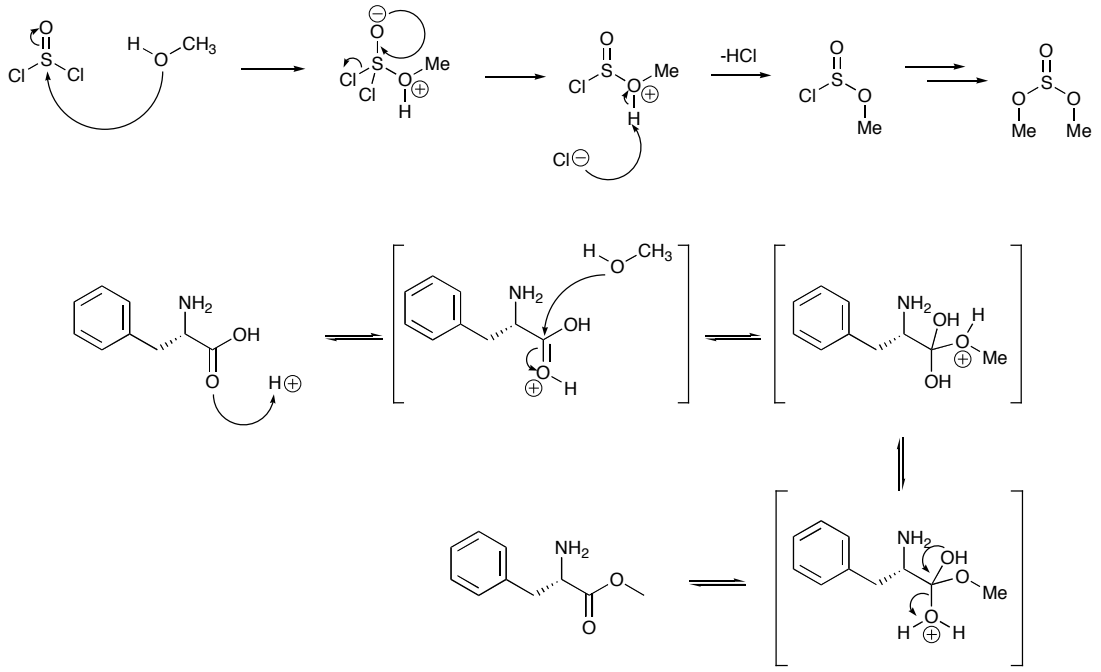


Figure 3.2: Mechanism of thionyl chloride mediated esterification of L-phenyl alanine in methanol.

The next stage was protection of the primary amine of L-phenylalanine methyl ester **154** with a *tert*-butoxycarbonyl (Boc) moiety, which was achieved by reaction with Boc-anhydride and sodium hydrogencarbonate in tetrahydrofuran, affording *N*-Boc-ester **155** in 96% yield without the need for purification.

Reaction of **155** with excess methyl magnesium iodide (generated *in situ* from Mg turnings and methyl iodide) resulted in formation of the *gem*-dimethyl alcohol **156** in 74% yield without the need for further purification. The acidic proton of the *N*-Boc functionality is also deprotonated in this reaction, which prevents racemisation of the α-stereocentre of the ketone intermediate formed during the Grignard reaction.

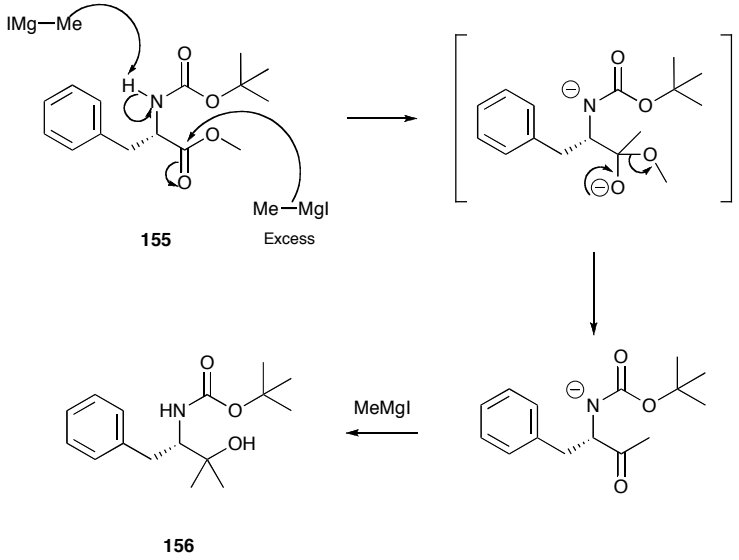


Figure 3.3: Mechanism of Grignard addition to the methyl ester 1**55** to generate the *gem*-dimethyl alcohol **156** *via* a ketone intermediate.

Treatment of the *gem*-dimethyl alcohol **156** with potassium *tert*-butoxide in tetrahydrofuran generated a potassium alkoxide intermediate, which underwent intramolecular cyclisation elimination to yield the desired SuperQuat auxiliary **157** in overall 65% yield. Therefore, the *N*-Boc functionality not only serves as a protecting group but also acts as a sacrificial carbonyl group in the oxazolidin-2-one cyclisation step.

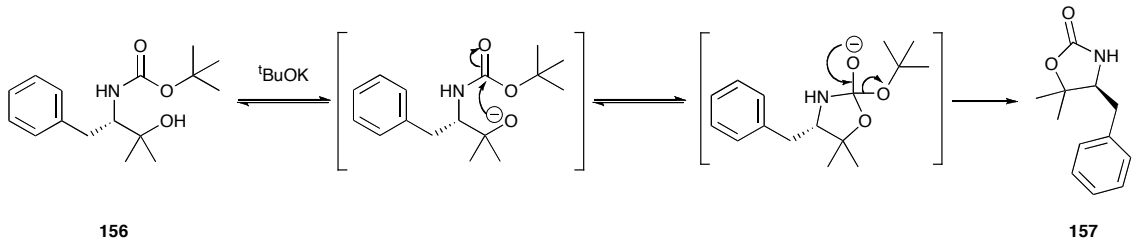
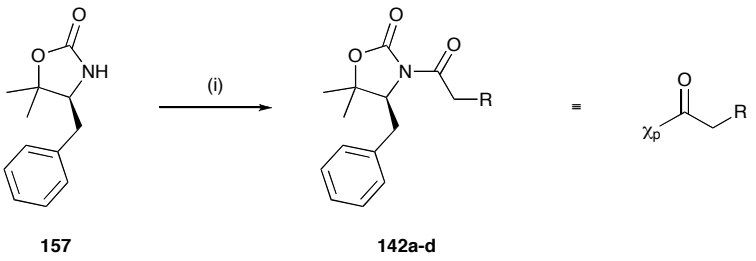


Figure 3.4: Mechanism of intramolecular cyclisation elimination reaction for formation of SuperQuat oxazolidin-2-one **157**.

A range of *N*- acylated oxazolidin-2-ones were then synthesised (See Table 3-1). The parent oxazolidin-2-one **157** was treated with *n*-butyllithium (2.5M in hexanes) at –78 ^{o}C, followed by addition of the appropriate acid-chloride and the resulting reaction mixture allowed to warm to room temperature over 2 hours. The reaction was quenched with saturated ammonium chloride solution before work up, yielding the desired product in good yield (See Scheme 3.8 and Table 3-1).



Reagents and conditions: (i) ^{n}BuLi, acid chloride, CH_2Cl_2, -78 ^{o}C to RT, 2 hours.

Scheme 3.8: Acylation of *N*-H SuperQuat auxiliary **157**.

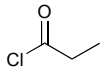
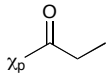
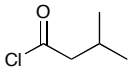
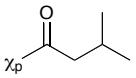
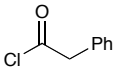
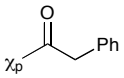
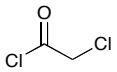
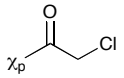
Entry	*Acid Chloride*	*Product*	*Yield (%)*
1		 **142a**	93% [a]
2		 **142b**	75% [a]
3		 **142c**	71% [b]
4		 **142d**	69% [b]

Table 3-1: Acylation of SuperQuat auxiliary **157** with various acid chlorides; [a] Isolated yield after recrystallisation from Et_2O:Petroleum ether; [b] Isolated yield after column chromatography**.**

3.3.1 Aldol reaction

The aldol reaction is one of the most powerful and widely documented methodology for stereoselective carbon-carbon bond formation, which involves reaction of an enol/enolate with an aldehyde to generate a β-hydroxy-carbonyl compound.

It is important to note that this reaction, can potentially afford four diastereomeric products, and as a consequence it is necessary to control both the diastereoselectivity (S_1 and S_2 *vs.* A_1 and A_2) and the enantioselectivity (S_1 *vs.* S_2 or A_1 *vs.* A_2) of the reaction.[134]

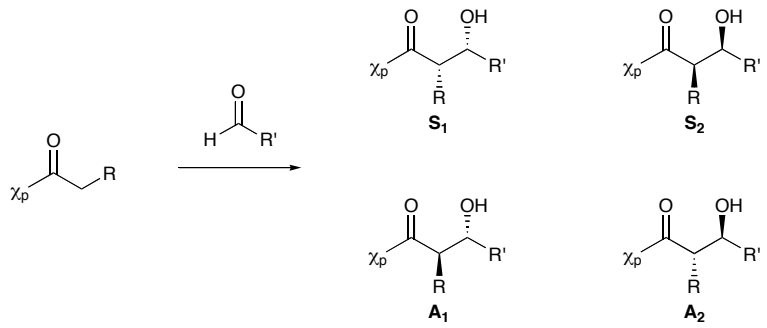


Figure 3.5: Potential diastereomeric products of the aldol reaction formed from reaction of *N*-acetyl-oxazolidin-2-one **142** with an aldehyde (R′CHO).

The diastereoselectivity of the aldol reaction is dependent on the geometry (*cis* or *trans*) of the enol or enolate generated. Lewis acid mediated enantioselective aldol reactions proceed *via* a concerted pericyclic process, that can generate two diastereotopic transition states for each enolate geometry (See Figure 3.6).[135] The resultant rigid Zimmerman-Traxler transition states allow us to rationalise the stereochemical outcome of the Lewis acid mediated aldol reaction.

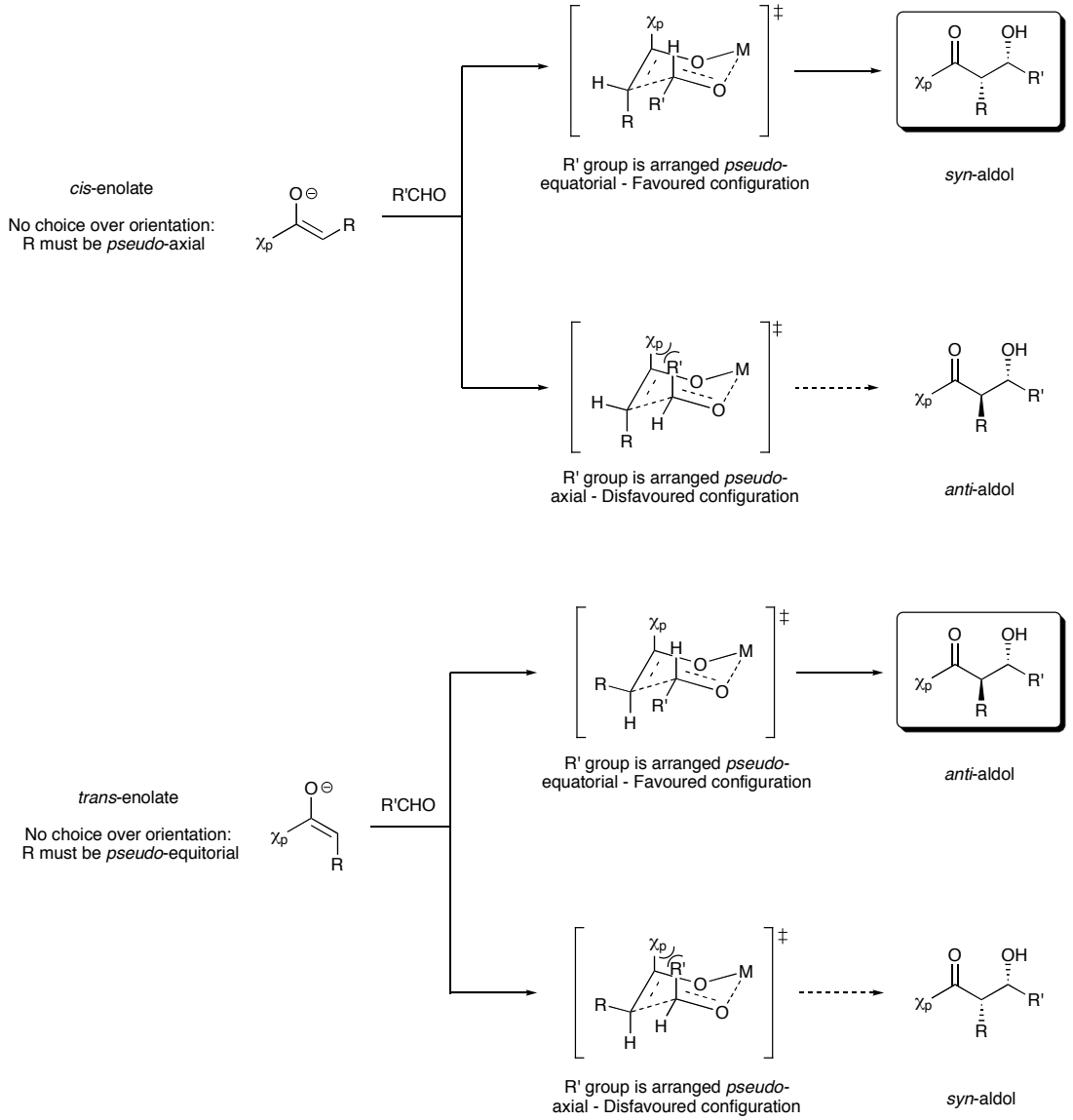


Figure 3.6: Zimmerman-Traxler transition model to explain the stereoselectivity of the aldol reaction.

For lithium enolates the geometry of the enolate is solely dependent on the size of the non-enolisable group, with large groups forcing the enolate to adopt a *cis*-geometry and smaller groups allowing for a *trans*-geometry. However, softer boron enolisation allows for greater stereocontrol with the groups attached to the boron serving to control the geometry of the enolate. The boron atom of 9-BBN-OTf is relatively unhindered, allowing the R group to orientate itself *cis* to the oxygen, favouring the *cis*-geometry and hence a *syn*-aldol product predominates.

3.3.2 Evans' *syn*-aldols

The previous models allow us to predict the relative stereochemistry of the aldol reaction, with the stereochemical outcome being dependent on the enolate geometry. Unhindered boron Lewis acids generate *cis*-enolates and the above models predict that potentially two *syn* diastereomers could be formed.[136] However, using a chiral auxiliary it is possible to access a single diastereomer, since the stereogenic centre located on the auxiliary introduces a steric bias between the two faces of the *cis*-enolate (See Figure 3.7). Upon addition of an aldehyde to a *cis*-boron enolate, the boron centre coordinates to the carbonyl of the aldehyde. In the absence of chelation, the auxiliary is free to rotate about the carbon-nitrogen bond and arranges itself so that the oxazolidin-2-one carbonyl is positioned *syn*-periplanar to the alkene functionality of the *cis*-enolate. In this conformation the bulky R group of the oxazolidin-2-one projects downward (according to Scheme 3.7) and the aldehyde is delivered preferentially from the opposite face to afford what is described as an Evans'-*syn*-aldol diastereomer **158b**.

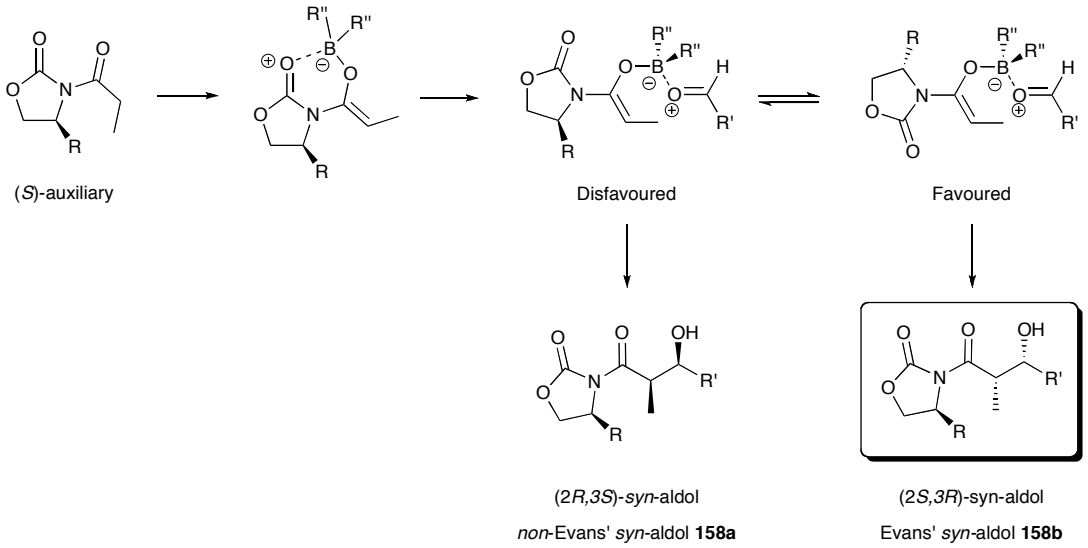
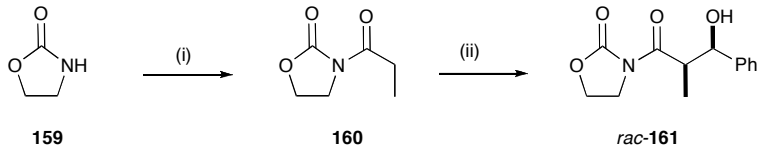


Figure 3.7: Directing effect of the chiral auxiliary the aldol reaction.

The SDB group has previously optimised Caddick's conditions for the synthesis of racemic Evans' *syn*-aldol products.[130,137-140] For example generation of the boron enolate of **160** *via* treatment with 9-BBNOTf and DIPEA in dichloromethane, followed by reaction with an aldehyde to afford a racemic *syn*-*β*-hydroxy-*N*-acyloxazolidin-2-one **161** in >95% de.[139]

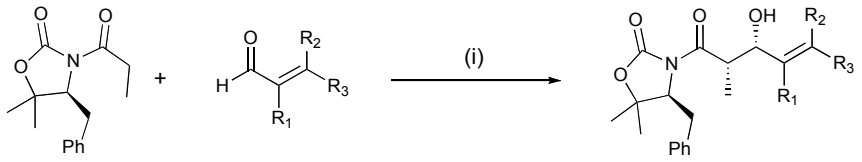


159 **160** ***rac*-161**

Reagents and conditions: (i) ^{n}BuLi, THF, -78 °C; CH_3CH_2COCl; (ii) 9-BBN-OTf, DIPEA, CH_2Cl_2, 0 to -78 °C; PhCHO, CH_2Cl_2.

Scheme 3.9: Synthesis of racemic aldol **161**.

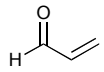
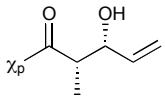
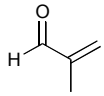
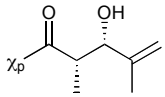
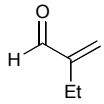
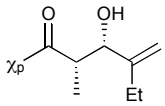
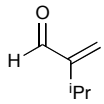
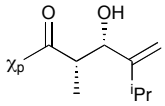
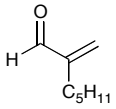
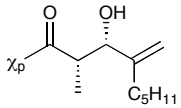
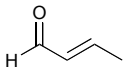
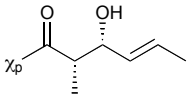
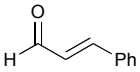
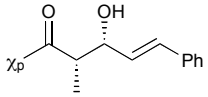
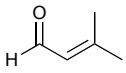
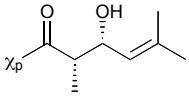
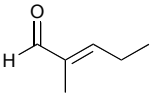
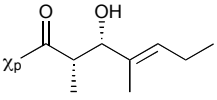
As such, it was decided to apply these conditions to the synthesis of unsaturated *syn*-aldol products.[141] *N*-propionyl-'SuperQuat' oxazolidin-2-one **157** was initially treated with 9-BBN-OTf (1.1 equiv) and DIPEA (1.3 equiv) to generate the *cis*-boron enolate. Subsequent addition of the appropriate aldehyde (1.3 equiv) yielded the desired *syn*-aldol products in >95% de. This methodology has been applied to a range of α,β-unsaturated aldehydes for the synthesis of unsaturated *syn*-aldol products **163a-i** (See Scheme 3.10), with the *syn* stereochemistry of the resulting products confirmed from their small $J_{2,3}$ coupling constants of between 4.0 and 5.0 Hz.



142a **162** **163a-i**

Reagents and conditions: (i) 9-BBN-OTf, DIPEA, α,β-unsaturated aldehyde, CH_2Cl_2, 0 to –78 °C, warm to RT overnight.

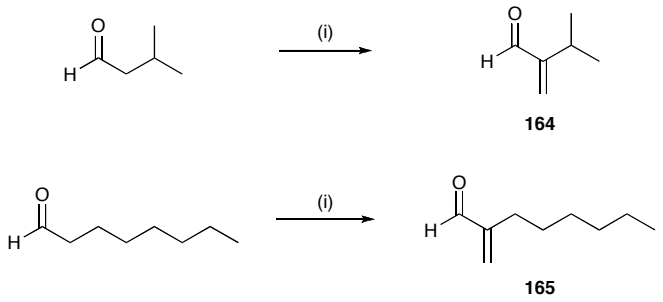
Scheme 3.10: Synthesis of *syn*-aldol products from *N*-propionyl SuperQuat **142a**.

Entry	*Aldehyde*	*Product*	*Yield* [a]	*de* [b]
1		 **163a**	71%	>95%
2		 **163b**	81%	>95%
3		 **163c**	82%	>95%
4		 **163d**	79%	>95%
5		 **163e**	83%	>95%
6		 **163f**	93%	>95%
7		 **163g**	88%	>95%
8		 **163h**	83%	>95%
9		 **163i**	86%	>95%

χ_p is equivalent to the SuperQuat auxiliary; [a] Isolated yield after column chromatography eluting with CH_2Cl_2; [b] de determined from examination of crude 300 MHz ^{1}H NMR spectra.

Table 3-2: *Syn*-aldol reactions on *N*-propionyl auxiliary **142a**.

The *syn*-aldol products (Entries 1 to 3 and 6 to 9) were all synthesised from their commercially available aldehydes in greater than 95% de and good to excellent yields. Entries 4 and 5, were synthesised using a non-commercially available aldehydes **164** and **165** respectively, whose synthesis was simple and readily achieved in one step.[142]



Reagents and conditions: (i) Formaldehyde (37% solution in water), Me_2NH.

Scheme 3.11: Synthesis of acrolein derivatives.

Therefore, aldehydes **164** and **165** were prepared *via* Mannich-type reactions involving treatment of *iso*-valeroaldehyde or octanal with formaldehyde (37% solution in water) and dimethylamine over a 24 hour period. Initially formaldehyde reacts with dimethylamine to generate a reactive imminium species **166**, with a second equivalent of dimethylamine generating an enolate **167** (or enamine equivalent) of the aldehyde. Subsequent reaction of the enolate **167** and imminium species **166** generates the tertiary amine **167**. This is concomitantly enolised (**168**) and dimethylamine eliminated to generate the desired 1,1-disubstituted aldehyde (See Figure 3.8).

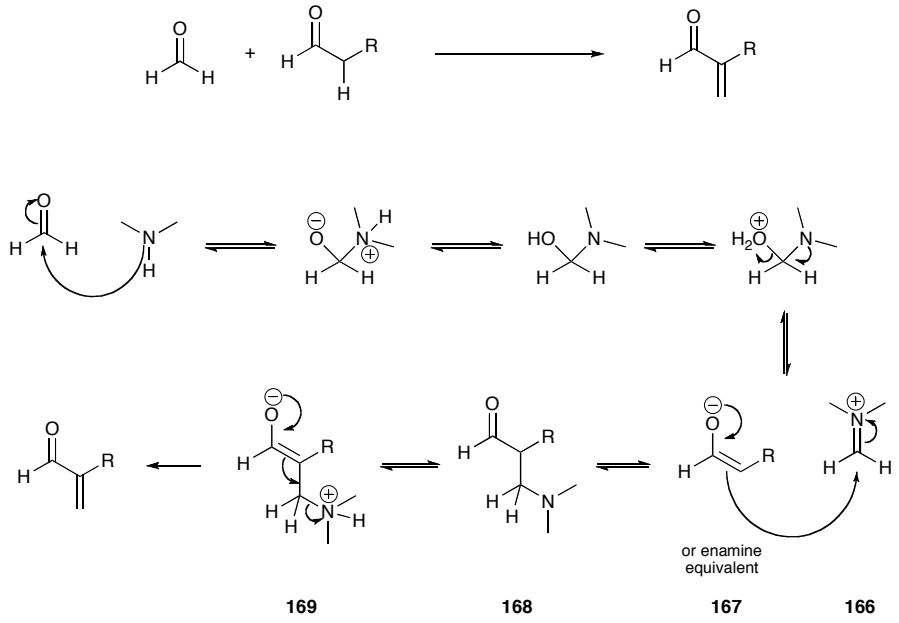
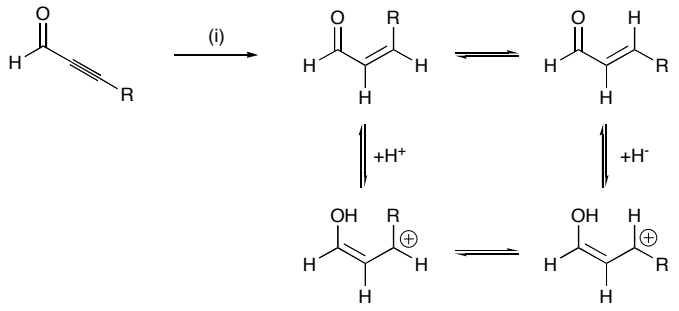


Figure 3.8: Mechanism for the formation of 1,1-disubstituted aldehydes *via* a Mannich reaction.

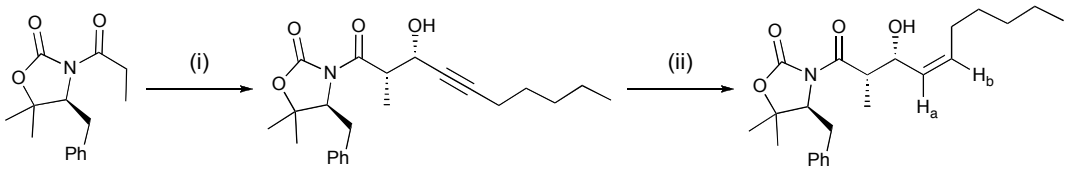
The *cis*-octenal aldol derivative (**163j**) had to be indirectly synthesised *via* its corresponding alkyne derivative **170**, because *cis*-alkenes are known to be notoriously unstable under Lewis acidic conditions and readily isomerise to generate inseparable mixtures of *cis* and *trans* isomers (See Scheme 3.12).



Reagents and conditions: (i) Lindlar's catalyst, H_2 (1 atm), MeOH.

Scheme 3.12: Potential isomerization of *cis*-α,β-unsaturated aldehydes under Lewis acidic conditions.

As a result, aldol **163j** was synthesised by treatment of octynal under the standard aldol conditions to yield the alkynyl-aldol derivative **170** (See Scheme 3.13). Subsequent reduction under hydrogen over Lindlar's catalyst gave the desired *cis*-α,β-unsaturated aldol **170** in 79% yield and >95% de.



142a **170** **163j**

Reagents and conditions: (i) 9-BBN-OTf, DIPEA, octynal, CH_2Cl_2, 0 °C to -78 °C; warm to RT overnight; (ii) Lindlar's catalyst, H_2 (1 atm), CH_2Cl_2.

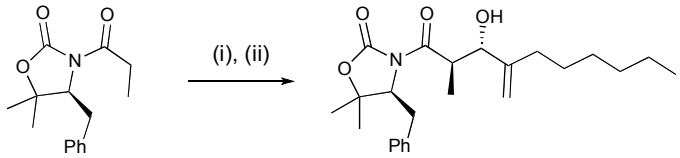
Scheme 3.13: Synthesis of *cis*-α,β-unsaturated aldol **163j**.

The *cis*-stereochemistry was confirmed from its ^{1}H NMR spectrum, the vicinal coupling ($J_{a,b}$) of the alkenyl protons was shown to be 11.0 Hz which is consistent with literature precedent, where small coupling constants between 7-11 Hz are indicative of a small dihedral angle found within *cis*-alkenyl systems.

3.3.3 Non-Evans' *anti*-aldols

For completeness, an *anti*-aldol substrate was synthesised to investigate the effect of the α-stereocentre upon diastereoselectivity in the future epoxidation reactions.

Therefore, non-Evans' *anti*-aldol **146** was prepared *via* treatment of *N*-acylated oxazolidin-2-one **142a** with 1,1-disubstituted aldehyde **165**, magnesium chloride (10 mol%), triethylamine (2 equiv), chlorotrimethylsilane (1.5 equiv) and sodium hexafluoroantimonate (30 mol%) in ethyl acetate for 48 hours to afford the desired aldol **146** in 60% yield and >95% de.



142a **146**

Reagents and conditions: (i) Hexylacrolein (1.2 equiv), $MgCl_2$ (10 mol%), Et_3N (2.0 equiv), $NaSbF_6$ (0.3 equiv) TMSCl (1.5 equiv), EtOAc; (ii) MeOH, TFA.

Scheme 3.14: Synthesis of non-Evans' *anti*-aldol **146**.

In this reaction there appears to be a delicate balance between metal mediated silylation and reversible *retro*-aldol fragmentation, with silylation trapping the "unstable" *trans*-aldolate, thus preventing epimerization to a mixture of *syn*- and *anti*-products. Clearly, this aldol reaction

does not follow the "traditional" auxiliary mediated process (*vide supra*); since the alpha substituent is *syn* to the chiral auxiliary's R group in the final product. This unexpected *anti*-aldol product can be rationalized by consideration of the transition state of this reaction. In this case the previous Zimmerman-Traxler models are precluded with a 6-coordinate magnesium species being invoked, that results in a twisted boat transition state for the carbon-carbon bond forming step.[143] This results in coordination of the oxazolidin-2-one carbonyl to the magnesium counterion throughout the course of the reaction, with the aldehyde approaching the *trans*-enolate from the (*si*)-face to afford non-Evans' *anti*-aldol (See Figure 3.9).

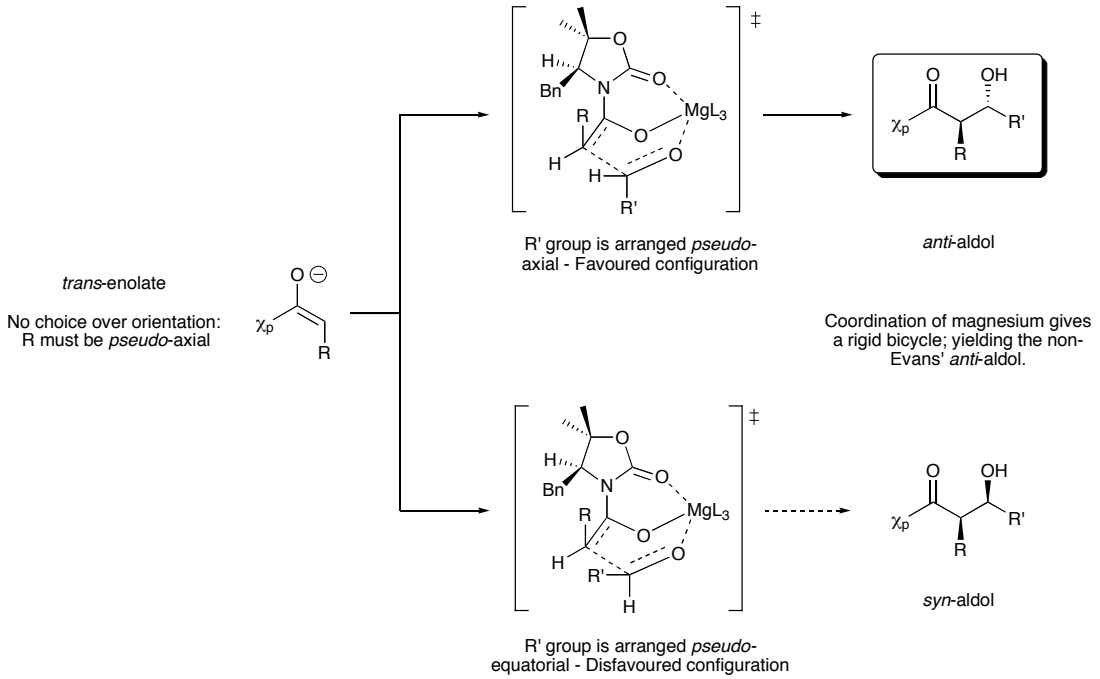


Figure 3.9: Magnesium catalysed aldol reaction, including rationale for non-Evans selectivity.

3.4 Directed epoxidation reactions

In the epoxidation reactions of allylic alcohols the oxidant can deliver oxygen to either of the two diastereotopic faces of the alkene functionality, generating either *threo*- or *erythro*-epoxy alcohols (See Figure 3.10). The terms *threo* and *erythro* are used in acyclic systems as descriptors for relative stereochemistry and are specifically used to describe two contiguous stereocentres where two of the groups on the asymmetric carbons are the same and one is different.[144] *Erythro* describes how the identical groups are on the same side (when drawn in the Fischer convention), i.e. in the case of *erythro*-**171a** the two oxygen atoms are on identical faces. In the case of *threo*, the two identical groups are on opposite sides, for example, in *threo*-**171b** the directing hydroxyl group and the epoxide oxygen are on opposite sides.

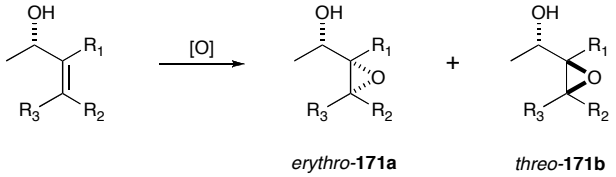


Figure 3.10: Possible stereochemical outcomes from epoxidation of allylic alcohols.

Epoxidation of allylic alcohols has been widely reported in the literature, and methodologies available to exist to access both the *threo*- and *erythro*-epoxy products in high levels of diastereocontrol. These include the use of metal catalysed approaches such as $VO(acac)_2$, $Ti(O^iPr)_4$ or $Mo(CO)_6$ activation of *tert*-butylhydroperoxide, MTO/UHP (Methyl trioxo-rhenium/Urea hydrogen peroxide) and non metal peroxides such as *m*CPBA and DMD (Dimethyl-dioxirane).[145]

The stereoselectivity of these epoxidations relies on a delicate balance between conformational control and substrate-reagent interactions. Of these interactions, there are two distinct mechanisms or intermediates that must be considered, involving either alkoxide coordination and/or hydrogen bonding. This area has been widely investigated by Adam *et al* who have experimentally investigated the selectivity of a range of epoxidation methods and the relationship of their epoxidation diastereoselectivity to their transition states (See Figure 3.11 and Table 3.3).[145-148]

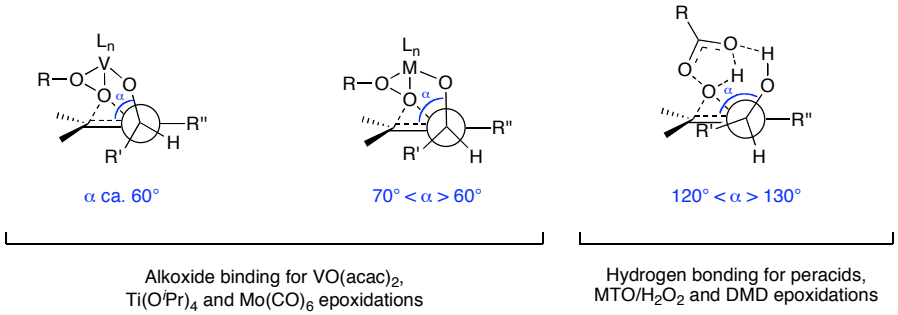


Figure 3.11: Proposed transition-state structures for the epoxidation of chiral allylic alcohols by various oxidants.

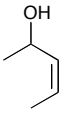
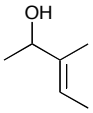
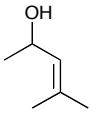
				Erythro/Threo diastereoselectivity			
Entry	*Oxidant*	*Solvent*	*Transition State*				
1	$VO(acac)_2$, ^tBuOOH	C_6H_6	Alkoxide	95:05	29:71	90:10	14:86
2	$Mo(CO)_6$, ^tBuOOH	CH_2Cl_2	Alkoxide	84:16	16:84	71:29	05:95
3	$Ti(O^iPr)_4$, ^tBuOOH	CH_2Cl_2	Alkoxide	78:22	09:91	76:24	05:95
4	*m*CPBA	CH_2Cl_2	H-bonding	55:45	05:95	52:48	05:95
5	DMD	Acetone	H-bonding	43:57	33:67	49:51	24:76
6	MTO, UHP	$CHCl_3$	H-bonding	50:50	18:82	44:56	17:83

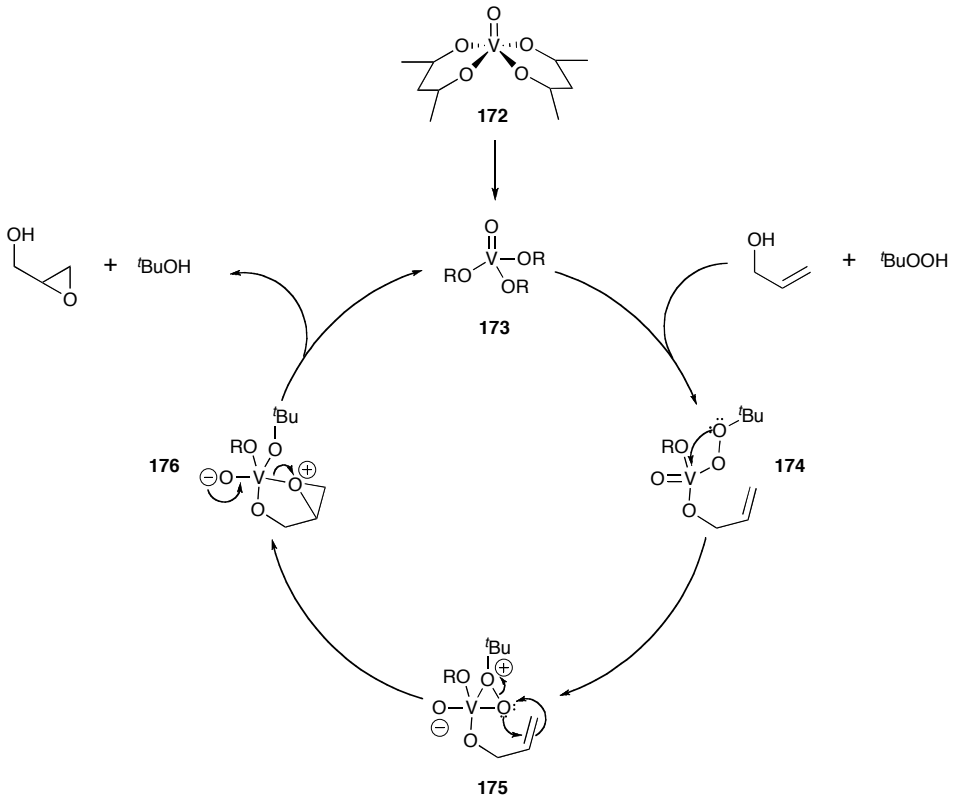
Table 3-3: Observed stereoselectivity of selected epoxidation reaction conditions.

Adam demonstrated that the facial selectivity for epoxidation is generally the same for both metal alkoxide or hydrogen bond coordinated intermediates. However, alkoxide intermediates gave an overall higher level of stereocontrol, with vanadium-mediated epoxidations (Entry 1) proceeding with the most consistent levels of control over all of the above alkene substitution patterns.

3.4.1 Vanadium catalysed epoxidation reactions

Consequently, it was decided to attempt epoxidation reactions on our β-vinyl-aldol substrates utilising the homogenous vanadium oxidation system that employs vanadyl acetylacetonate and *tert*-butyl hydroperoxide. Mechanistically, *tert*-butyl hydroperoxide oxidises the vanadyl acetylacetonate from the inactive d^1 complex **172** to the catalytically active d^0 vanadate ester **173**.[149] Rapid ligand exchange generates alkoxy-intermediate **174**, which rearranges to activate

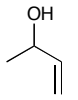
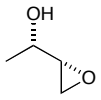
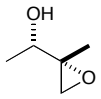
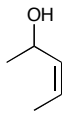
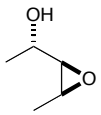
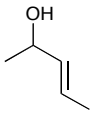
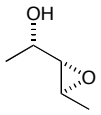
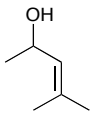
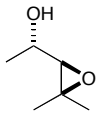
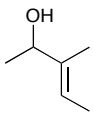
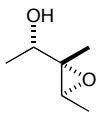
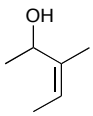
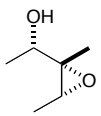
the alkyl peroxide by bidentate coordination to the vanadium centre generating species **175**. Subsequent intramolecular nucleophilic attack on the allylic functionality yields the epoxy-alcohol and regenerates the catalyst **173** for further use.[150]



Scheme 3.15: Mechanism of the $VO(acac)_2/^tBuOOH$ epoxidation of allylic alcohols.

Both Sharpless and Adam have investigated the stereoselectivity of the homogenous vanadium catalysed epoxidation of allylic alcohols.[146,147] They have shown that provided efficient coordination operates between the reagent and the substrate, high diastereoselectivity can be observed, whose final selectivity can be rationalised by consideration of allylic strain.

Experimental observations by Adam *et al* have shown that the presence of an α-substituent favours an *erythro*-epoxy alcohol, whilst the presence of a *cis*-β-substituent results in a *threo*-epoxy alcohol being formed as the favoured product (See Table 3.4).

Entry	*Allylic alcohol*	*Major epoxy-alcohol product*	*Erythro/threo selectivity*
1			80:20
2			95:05
3			29:71
4			71:29
5			14:86
6			90:10
7			67:33

Reagents and conditions: $VO(acac)_2$, ^tBuOOH, benzene, RT.

Table 3-4: Stereochemical outcome of the vanadium catalysed epoxidation reaction of allylic alcohols.

This stereochemical outcome can be rationalised by consideration of the allylic strain of the intermediate transition state. For 3-methylbut-3-en-2-ol (Entry 2), the oxidant is delivered to the one face of the alkene due to minimisation of $A^{1,2}$ strain. In this example there is no sterically demanding group in the *cis*-β-position and as a consequence $A^{1,3}$ strain is negligible. Thus, for 1,1-disubstituted alkenes $A^{1,2}$ strain is dominant and an *erythro*-epoxy alcohol **177a** is favoured. Conversely, for the case of 4-methyl-pent-3-en-2-ol (Entry 5) the lack of a sterically demanding group at its α-position means that $A^{1,2}$ strain can be considered negligible, and as a consequence

$A^{1,3}$ becomes dominant due to the presence of its *cis*-β-substituent, with a *threo*-epoxy alcohol **178b** being formed as the favoured product.

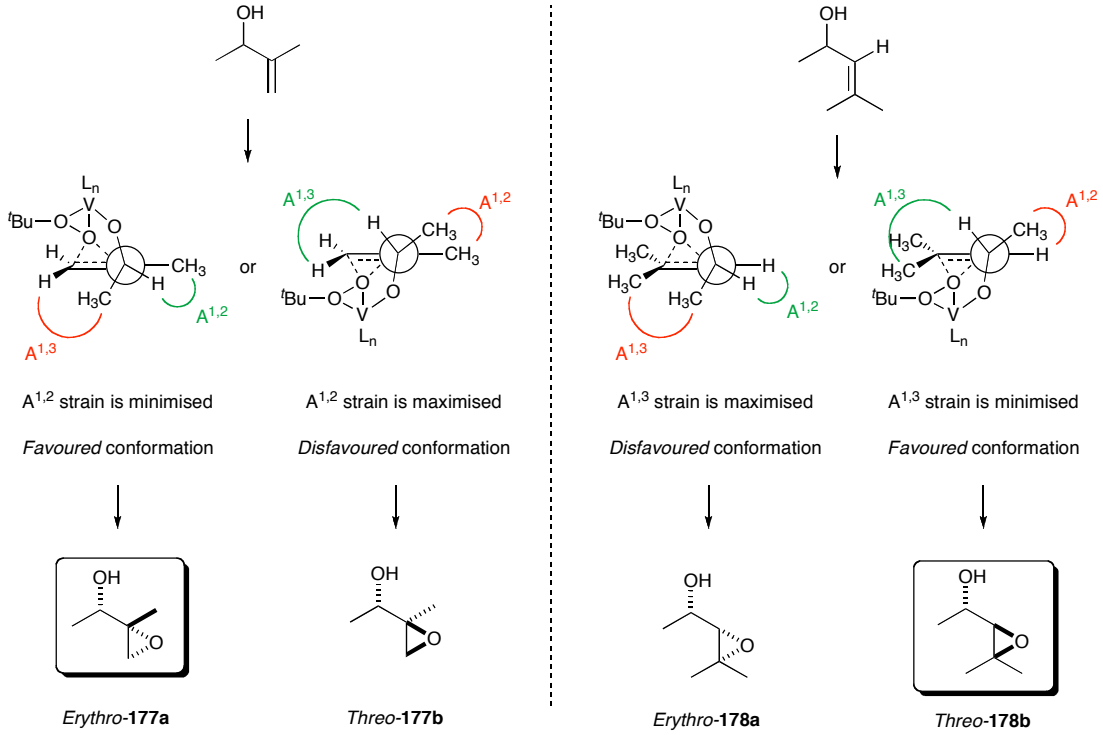


Figure 3.12: Allylic strain models that explain diastereoselectivity of epoxidation of 3-methylbut-3-en-2-ol and 4-methyl-pent-3-en-2-ol.

Adam observed that *cis*-β-functionalities are more sterically dominant than *trans*-β-substituents. This can be observed by comparison of the epoxidation selectivities of *trans*- and *cis*-3-methyl-pent-3-en-2-ol (Entries 6 and 7 respectively), with a *cis*-substituent decreasing selectivity to 33% de due to increased $A^{1,3}$ strain. This is further supported by consideration of the geometric isomers of pent-3-en-2-ol (Entries 3 and 4). Here the stereochemical outcome is fully inverted, with epoxidation of *cis*-pent-3-en-2-ol being dominated by $A^{1,3}$ strain to favour the *threo*-epoxy alcohol, and *trans*-pent-3-en-2-ol being dominated by $A^{1,2}$ strain to favour the *erythro*-epoxy alcohol. Furthermore, the poor levels of diastereocontrol for epoxidation of simple *trans*-β-allylic alcohols may also be rationalised by consideration of the transition states shown in Figure 3.3.

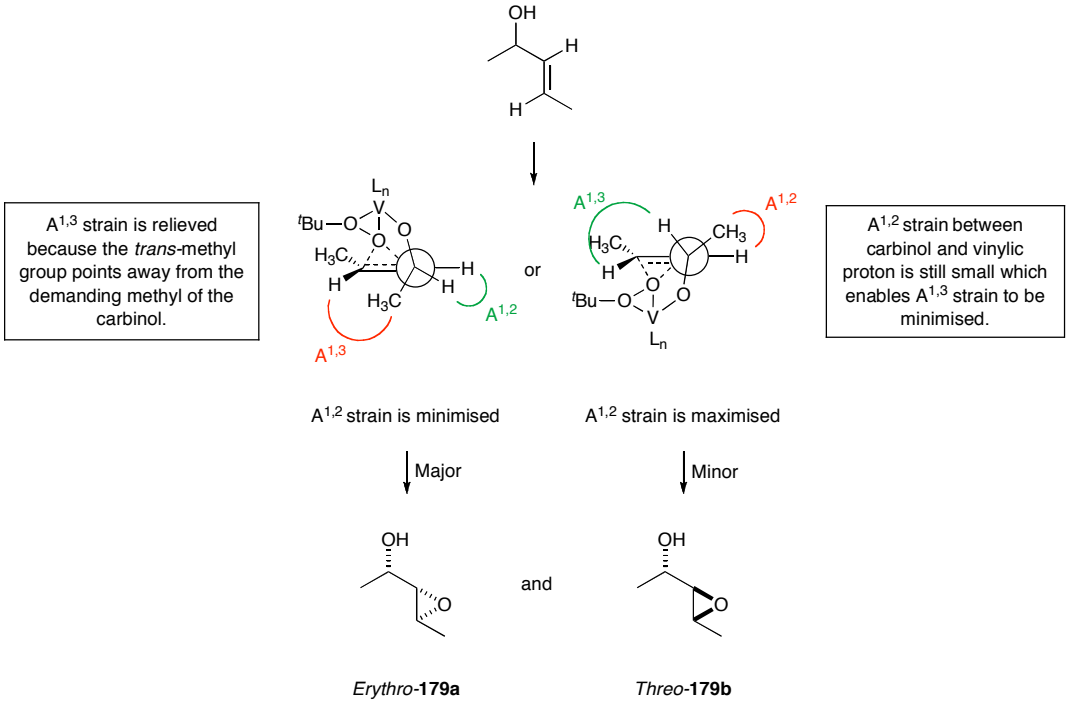
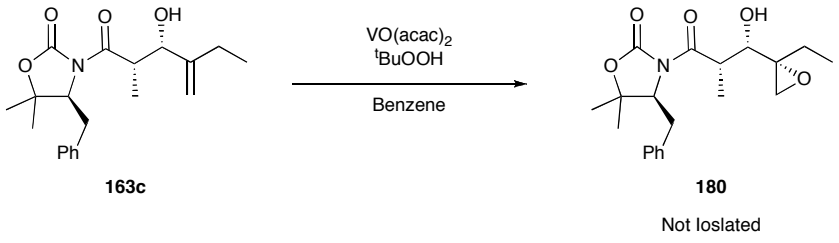


Figure 3.13: Allylic strain models that explain diastereoselectivity of epoxidation of *trans*-pent-3-en-ol.

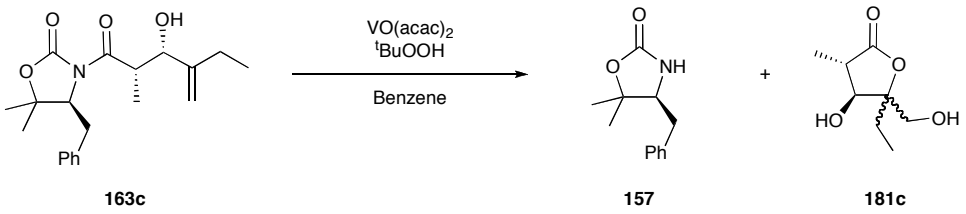
Considering this literature precedent, it was decided to attempt the directed epoxidation of 1,1-disubstituted unsaturated aldol **163c**, which we expected to proceed in very high de. Aldol **163c** was dissolved in benzene and vanadyl acetylacetonate (10 mol%) added, with *tert*-butyl hydroperoxide (1.1 equiv.) after 5 minutes added in one portion and the reaction was stirred for 24 hours. ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed that the starting material had been consumed, however none of the desired epoxide **180** was present in the crude reaction product.



Scheme 3.16: Proposed epoxidation of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one **163c**.

The ^{1}H NMR spectrum indicated that only *N*-*H* oxazolidin-2-one **157** was present in the organic layer, with no product derived from the aldol side chain present. However, saturation of the aqueous layer with sodium chloride and extraction with ethyl acetate yielded a γ-butyrolactone **181c**, in high de. The gross structure of this γ-butyrolactone was determined using several analytical techniques. Firstly, FTIR indicated a compound with a single carbonyl group at 1740

cm^{-1}, which is consistent for a cyclic ester, a broad signal was observed at 3504 cm^{-1} which represents the presence of hydroxyl functionality. The ^{1}H NMR spectra indicated a dq at 2.79 ppm that integrated to one proton, this is indicative of a CH adjacent to an ester functionality with a methyl group attached. The ^{13}C NMR spectra indicated the presence of 3 carbon centres attached to oxygen centres, as such it was inferred that a γ-lactone was generated which is derived form the aldol side chain. This was further confirmed by HRMS, which confirmed the presence of a compound with the formula $C_8H_{14}O_4$.



163c **157** **181c**

Scheme 3.17: Synthesis of γ-lactone **181c** *via* epoxidation of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one **163c**.

The stereochemical determination of five-membered cyclic systems is more complicated than their six-membered counterparts. Normally, ^{1}H NMR spectroscopy can be used to assign relative stereochemistry to vicinal chiral centres because of the correlation of coupling constants to the dihedral angle.[151] However, in five membered lactones this is known to be difficult, the ring system is puckered, not flat, and two potential conformers exist for the 'envelope' structure. The ring system rapidly interconverts between the two conformers with similar energies (pseudorotation), which makes structural elucidation limited (See Figure 3.17).[152] Addition of functionality to the ring system alters the puckering of the ring, and leads to some conformations being more stable than others.

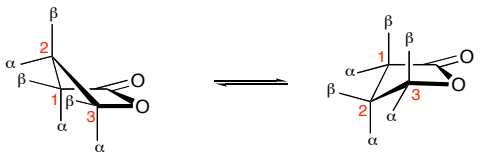


Figure 3.14: Two potential conformers for γ-lactone ring systems.

The more functionalised the ring system then the more favoured one conformer becomes, as such it was hoped that use of NOE spectroscopy could help to assign the relative stereochemistry of our tetra-substituted lactone **181c**.

To define the stereochemical outcome, the key interactions to consider are those about the newly formed stereocentre at the C_5 position. The C_3 hydrogen is shown to strongly interact

with the CH_2OH hydrogens (Figure 3.15), which indicates a *syn* relationship for these substituents. Further to this the C_3 methyl group was shown to be close in space to the C_4 hydrogen, which in turn strongly interacts with the C_6 hydrogens indicating that these functionalities are all on the same face of the ring system. Given the known 2*S*,3*S* configuration of the precursor *syn*-aldol **163c** that was epoxidised this is indicative of an *S* geometry at the newly formed C_5 stereocentre centre.

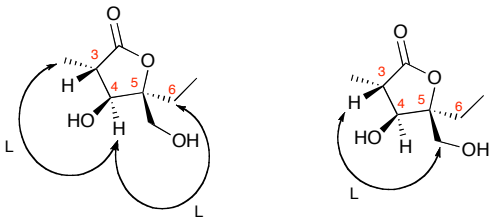


Figure 3.15: Observed interactions for γ-lactone **181c** using NOE spectroscopy.

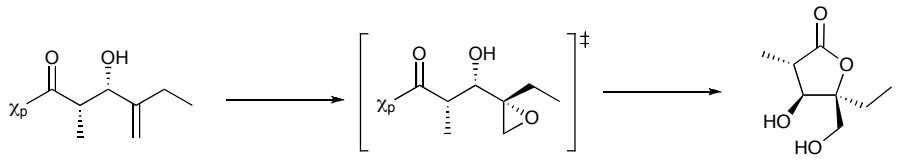
Lactone **181c** was recrystallised from diethyl ether and petroleum ether, X-ray crystallography further confirmed an *S* geometry at the newly formed quaternary centre in the γ-position.

181c

Colour code: grey, C = Grey, O = Red, H = White; selected hydrogens omitted for clarity.

Figure 3.16: X-ray crystal structure of (3*S*,4*S*,5*S*)-**181c**.

Therefore, when all this spectroscopic information is considered, it is clear that treatment of 1,1-disubstituted unsaturated aldol **163c** under vanadium mediated epoxidation conditions yields the γ-lactone **181c** with an *S* geometry at the newly formed γ-stereocentre.



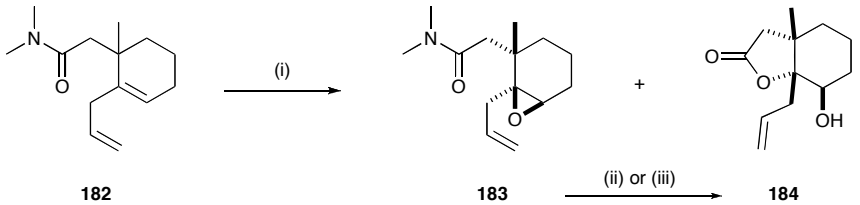
163c **180** **181c**

Reagents and conditions: (i) ^{t}BuOOH, $VO(acac)_2$, Benzene

Scheme 3.18: Treatment of 1,1-disubstituted-unsaturated aldol **163c** under vanadium mediated epoxidation conditions.

3.4.2 Mechanism of lactonisation

Before we can rationalise the stereochemical outcome for this epoxidation/lactonisation reaction we must consider the potential mechanism that is operating under these epoxidation conditions. There are many examples of stable epoxides of 1,1-disubstituted allylic alcohols having been reported in the literature. Therefore, if the observed lactonisation of unsaturated-*syn*-aldol **163c** proceeds *via* epoxidation, then there must be something about the epoxide intermediate that makes it so reactive. A review of the literature revealed that similar γ,δ-epoxy-amides had been reported previously to be unstable, also ring opening to afford γ-butyrolactones.[153,154] For example, Jenkins *et al* showed that treatment of amide-diene **182** with *meta*-chloroperbenzoic acid in acetonitrile and water yielded a mixture of both the epoxide **183** and hydroxy lactone **184**. The yield of the hydroxy lactone **184** could be further improved by treatment of the epoxide **183** under either acidic (H_2SO_4) or basic (NaOH) conditions according to the mechanism shown in Figure 3.19.



182 **183** **184**

Reagents and conditions: (i) (a) mCPBA, MeCN, H_2O; (b) saturated Na_2SO_3, then saturated $NaHCO_3$; (ii) H_2SO_4, H_2O, H_2SO_4; (iii) 0.5 M NaOH, ^{t}BuOH, heat, then H_2SO_4, H_2O.

Scheme 3.19: Synthesis of hydroxy-γ-lactone **184** *via* epoxidation of amide diene **182**.

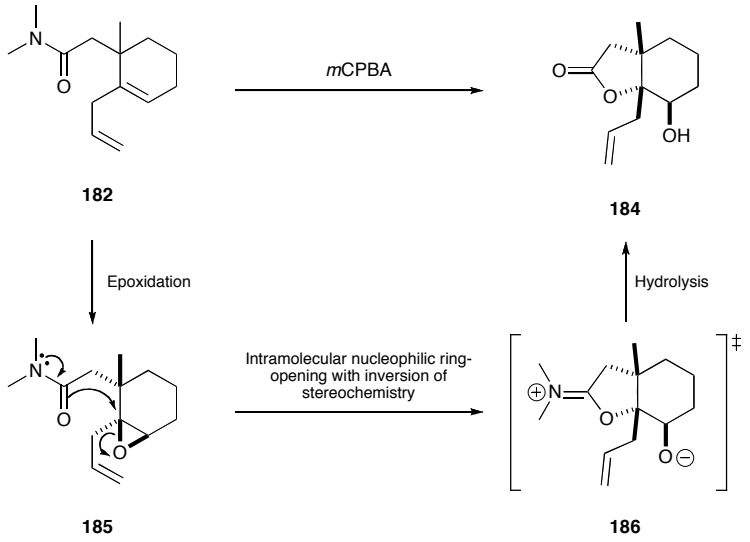
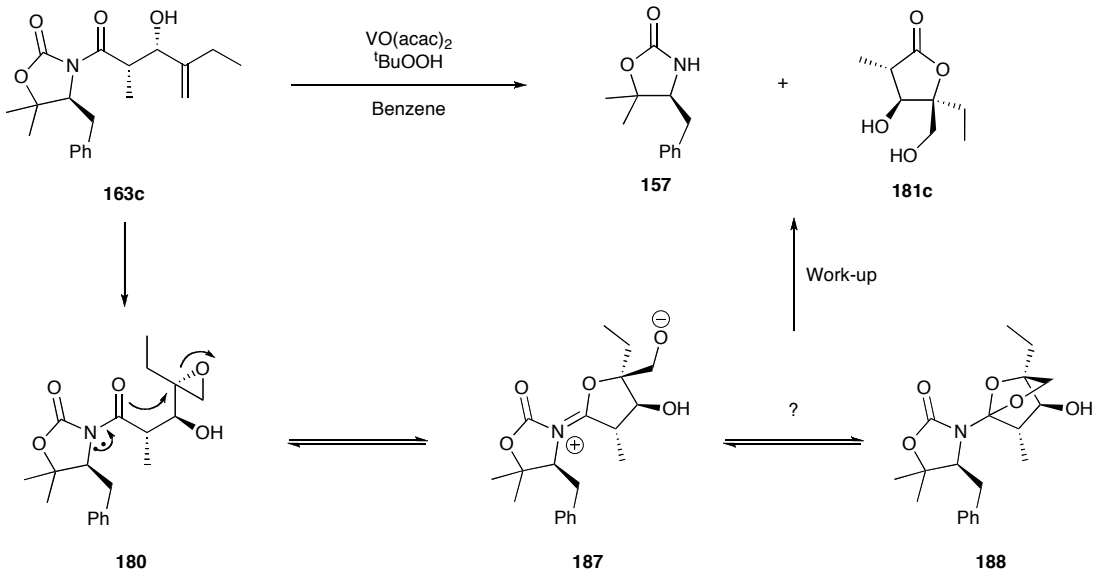


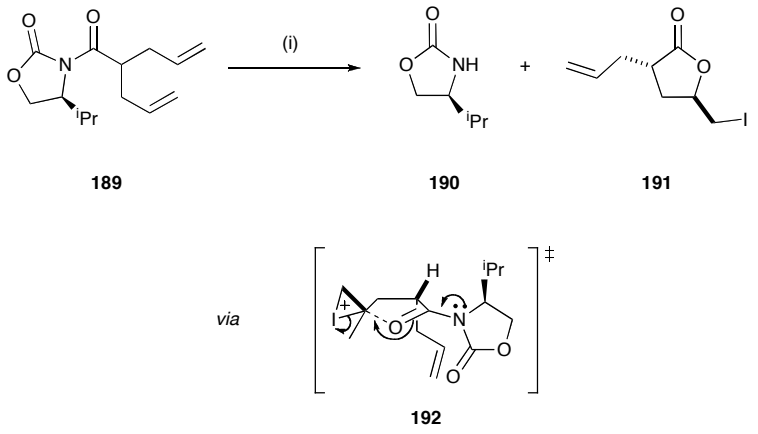
Figure 3.17: Proposed mechanism of lactonisation of epoxide **182**.

Applying this mechanistic rationale to our substrate, it is proposed that aldol **163c** is stereoselectively epoxidised to generate an unstable (2*S*,3*S*,4*R*)-γ,δ-*erythro*-epoxy-*N*-acyl-oxazolidin-2-one **180** in high de as predicted for directed epoxidation of this class of 1,1-disubstituted alkene. Concomitant nucleophilic ring opening of the epoxide at its γ-centre *via* a neighbouring group participation mechanism involving intramolecular nucleophilic attack of the *exo*-cyclic carbonyl of its *N*-acyl fragment, would result in inversion of the stereocentre at the C_5 position, affords the unstable imminium intermediate **187**. It is proposed that this imminium species may be potentially stabilised by the reversible formation of *NOO*-intermediate **188**. The imminium intermediate is then hydrolysed on workup to yield the parent *N-H* auxiliary **157** and the desired lactone **181c**.



Scheme 3.20: Proposed neighbouring group participation mechanism for the epoxidation/lactonisation of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one **163c**.

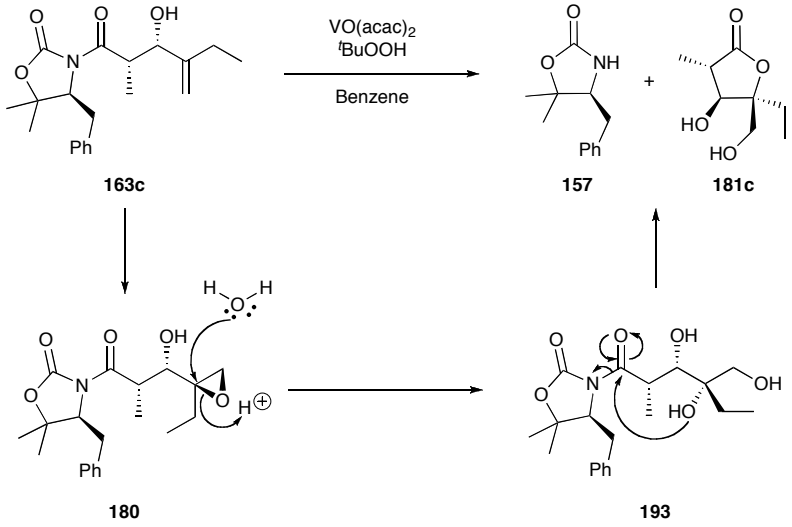
A similar mechanism has been proposed for the iodolactonisation of γ,δ-unsaturated oxazolidin-2-one functionalities which aldol afforded γ-butyrolactones.[155] Shibuya *et al* showed that treatment of bis-γ,δ-unsaturated oxazolidin-2-one **189** with *N*-iodo-succinimide in tetrahydrofuran and water, generated a key iodonium intermediate **192** that underwent a neighbouring group ring opening where by its *exo*-cyclic carbonyl also acts as an internal nucleophile to open the iodonium species with inversion of configuration at the γ-stereocentre.



Reagents and conditions: (i) NIS (1.5 equiv), THF:H_2O (1:1), 0 to 25 °C, 36 hours, 30 % yield, 54 % ee

Scheme 3.21: Iodolactonisation of bis-γ,δ-unsaturated oxazolidin-2-one **189** *via* a neighbouring group participation mechanism to afford iodo-γ-butyrolactone **191**.

It was considered that an alternative mechanism might be operating in which an external water nucleophile was responsible for hydrolysing the unstable epoxide followed by cyclisation of the resultant diol **193** to afford the lactone **181c** (See Scheme 3.22).



Scheme 3.22: Alternative mechanism for the epoxidation/lactonisation of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one **163c**.

Although this mechanism seemed unlikely, since numerous stable epoxides of this type had been isolated previously from these types of epoxidation reactions, it was decided to investigate whether the epoxide intermediate **180** could be intercepted by powerful nucleophiles such as ethane thiol or azide. Therefore, unsaturated aldol **163c**, was treated under standard epoxidation conditions, with the reaction being subsequently quenched with ethanethiol or a solution of aqueous sodium azide. Subsequent inspection of the resultant crude ^{1}H NMR spectra indicated that none of the lactone derivatives **194/195** or **196/197** were present in the crude reaction mixture, with only the *N-H* auxiliary **153c** and the dihydroxy-γ-lactone being present.

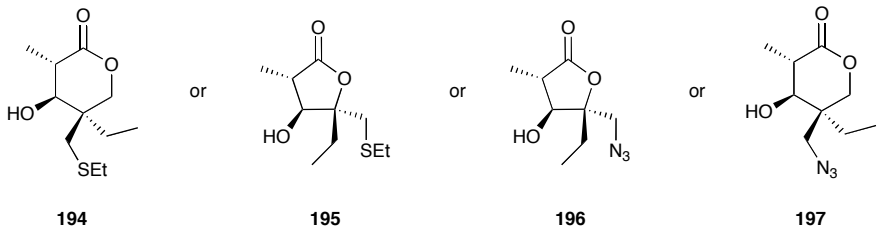
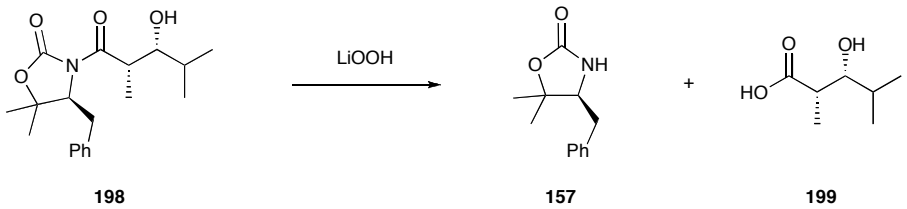


Figure 3.18: Potential γ- or δ-lactones not formed from treatment of aldol **163c** under epoxidation conditions followed by work-up using ethanethiol or sodium azide.

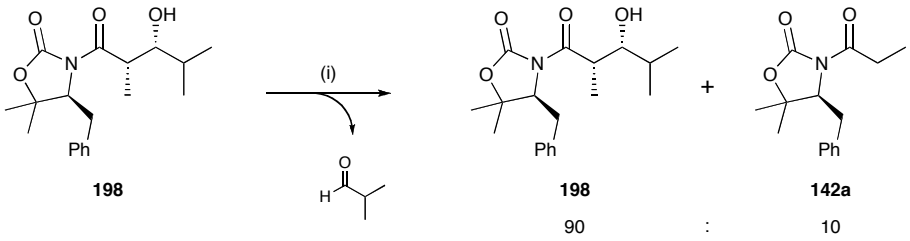
A second consideration was that peroxide mediated *exo*-cyclic cleavage of the oxazolidin-2-one fragment of the intermediate epoxide **180** had occurred, since lithium alkyl-hydroperoxides

were known to cleave *N*-acyl-oxazolidin-2-ones to afford their corresponding carboxylic acid derivatives (Scheme 3.23).[156]



Scheme 3.23: Cleavage of *N*-H oxazolidin-2one **157**.

It was proposed that vanadium peroxides could potentially act in a similar fashion, with the resulting carboxylic acid derivative acting as a nucleophile in the intramolecular cyclisation reaction. To further investigate whether this potential cleavage mechanism could occur, a saturated *syn*-aldol **198** was prepared *via* reaction of the boron enolate of *N*-propionyl oxazolidin-2-one **142a** with *iso*-valeroaldehyde in 81% yield and >95% de. Subsequent treatment of aldol **198** with vanadyl acetylacetonate and *tert*-butyl hydroperoxide resulted in >90% starting material being recovered, with 10% of the *N*-acylated auxiliary **142a** being observed. This indicates that *N*-acyl-oxazolidin-2-one derived aldol products do not undergo *exo*-cyclic cleavage of their oxazolidin-2-one fragments under these epoxidation conditions, however their vanadium alkoxides do appear to have a slight propensity to undergo *retro*-aldol cleavage (*vide supra*).

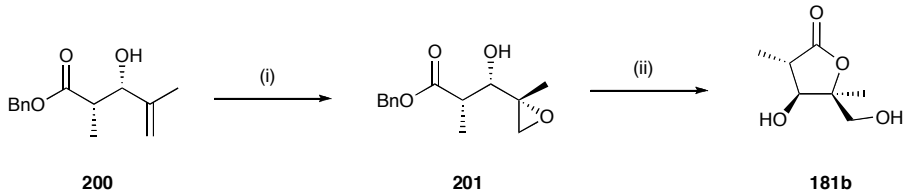


Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, benzene, RT

Scheme 3.24: Investigation into the stability of oxazolidin-2-one derived aldol product **198**.

To further confirm our mechanism, it was decided to attempt the epoxidation of *syn*-aldol esters, which should allow access to a stable epoxy-aldol product so that we could confirm the stereochemical outcome of the epoxidation reaction. Lactonisation of related *syn*-aldol esters *via* an epoxide intermediate has been reported previously in the literature.[157,158] For example, Nakata had reported that epoxidation of *syn*-aldol benzyl ester **200** gave an epoxide intermediate that was stable, with subsequent hydrogenation of the benzyl group yielding a carboxylic acid

that immediately underwent intramolecular cyclisation ring-opening onto the epoxide to yield a γ-lactone **181b**.

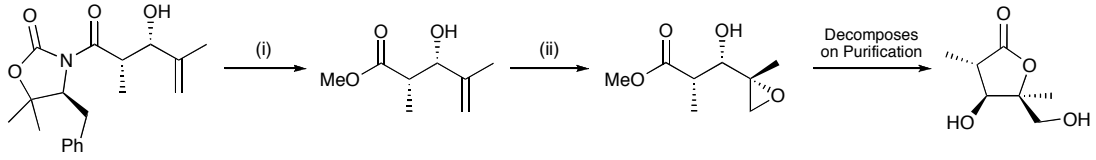


200 **201** **181b**

Reagents and conditions: (i) ^{t}BuOOH, $VO(acac)_2$, benzene; (ii) H_2, Pd/C, MeOH, RT, 2 hours

Scheme 3.25: Synthesis of γ-butyrolactone **181b** *via* epoxidation of benzyl ester **200**.

Unsaturated *syn*-aldol **163b** was treated with sodium methoxide solution for five minutes and the resulting methyl ester isolated in quantitative yield with no racemisation of the α-stereocentre being observed in the crude ^{1}H NMR spectra. Methyl ester **202** was subsequently treated with vanadyl acetylacentonate and *tert*-butyl hydroperoxide in benzene, which after one hour resulted in complete consumption of the starting material as observed by thin layer chromatography. The resulting reaction mixture was concentrated under reduced pressure and the crude ^{1}H NMR spectra indicated complete consumption of the starting material and the presence of two distinct doublets observed at 2.92 and 2.59 ppm, which were indicative of the chemical shifts expected for epoxide protons. However, attempts to purify this unstable epoxide proved unsuccessful, with chromatography and distillation both resulting in conversion to the corresponding γ-butyrolactone **181b**.



163b **202** **203** **181b**

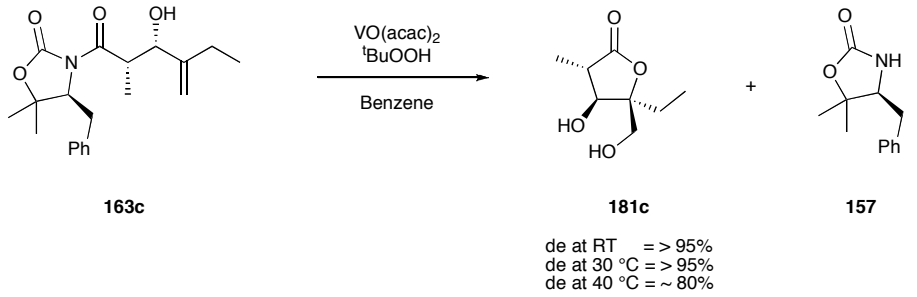
Reagents and conditions: (i) NaOMe, CH_2Cl_2, 5 minutes; (ii) ^{t}BuOOH, $VO(acac)_2$, benzene

Scheme 3.26: Attempted synthesis of stable epoxy-aldol methyl ester **203**.

With this in mind, it is inferred that the lactonisation reaction proceeds *via* the predicted 5-*exo* reaction, where a neighbouring group participation mechanism operates with inversion of stereochemistry at the γ-position. With this considered, optimisation of the reaction conditions was investigated.

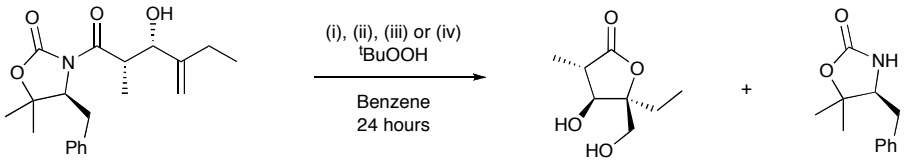
3.4.3 Reaction optimisation

In an attempt to decrease the reaction time, it was initially decided to consider the effect of temperature upon reaction rate. The reaction was repeated at room temperature, 25 °C, 30 °C and 40 °C. Increases in temperature were found to have no effect on the consumption of starting material, according to thin layer chromatography, which indicated the presence of epoxide **180**, some of the desired lactone **181c** and *N*-H oxazolidin-2-one **157**. After 24 hours, thin layer chromatography indicated the reactions had reached completion, with complete consumption of the epoxide intermediate having occured. Increases in temperature were shown to have a limited effect on the rate of lactonisation, however the diastereocontrol of **181c** was shown to decrease from >95% de to 80% de when the epoxidation reaction was carried out at 40 °C.



Scheme 3.27: Effect of temperature up the epoxidation/lactonisation reactions of *syn*-aldol **163c**.

It was subsequently decided to investigate the effect of catalyst loading upon the epoxidation/lactonisation reactions. Increases in the loading of $VO(acac)_2$ did not affect the overall rate of reaction, with comparable rates of consumption of the starting material observed by thin layer chromatography analysis. However, decreasing the loading to 1 mol% did effect the epoxidation reaction significantly, with some starting material still present in the reaction mixture. Use of 5 mol% vanadyl acetylacetonate also showed a decrease in the rate of epoxidation, however γ-lactone **181c** was isolated in comparable yields and de after 24 hours.

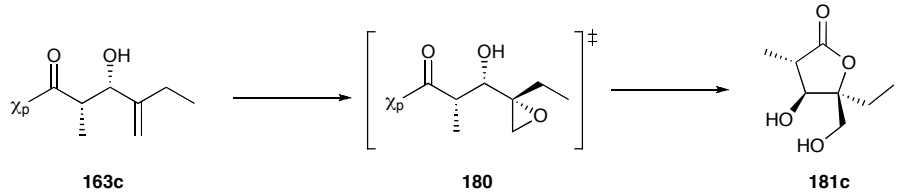


163c 181c 157

	VO(acac)₂	*Conversion*
(i)	1 mol%	95%
(ii)	5 mol%	100%
(iii)	10 mol%	100%
(iv)	20 mol%	100%

Table 3-5: Effect of catalyst loading on consumption of starting material and generation of product.

The reaction work-up was then modified to maximise the yield of γ-butyrolactone **181c** from the yield of epoxidation/lactonisation reaction. It was found that γ-butyrolactone **181c** was readily soluble in water, which resulted in it being partitioned between the organic/aqueous layers during work-up. Therefore, the reaction work-up was modified to limit the amount of water added to the reaction media. Therefore, 0.1 mL of water was added to an epoxidation/lactonisation reaction after 24 hours and the solvent was removed in vacuo to afford the crude product that was analysed by 1H NMR spectroscopy, which indicated the presence of the *N*-H oxazolidin-2-one **157** and the γ-lactone **181c** in a 1:1 ratio. This crude mixture was purified by chromatography over silica eluting with a mixture of ethyl acetate and dichloromethane to afford γ-butyrolactone **181c** in 79% isolated yield and >95% de.



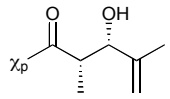
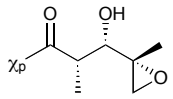
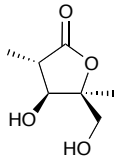
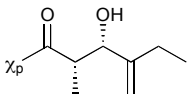
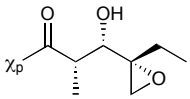
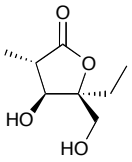
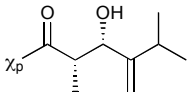
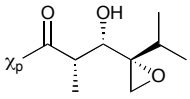
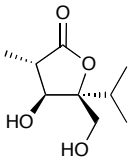
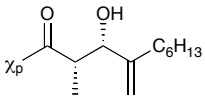
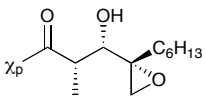
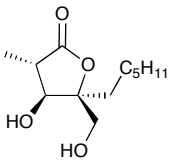
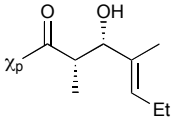
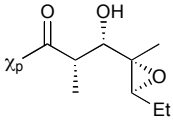
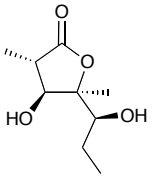
163c 180 181c

Reagents and conditions: (i) ^{t}BuOOH (1.1 equiv), $VO(acac)_2$ (10 mol%), benzene, 1 hour; (ii) 0.1 mL H_2O, 24 hours.

Scheme 3.28: Optimised conditions for epoxidation/lactonisation reactions of unsaturated-*syn*-aldol **163c**.

3.4.4 *Erythro*-selective lactonisation reactions

It was then decided to investigate the scope and limitation of the developed methodology for the epoxidation of a range of *syn*-aldol products, which were predicted to be epoxidised with *erythro*-selectivity in high de.

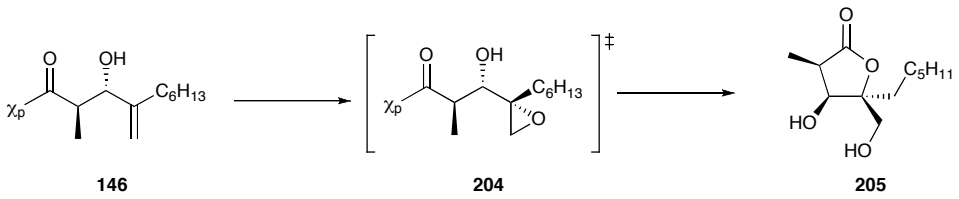
Entry	*syn-Aldol*	*Unstable erythro-epoxide intermediate*	*γ-butyrolactone*	*Yield*[a] *(de)*[b]
1	 **163b**	 **180b**	 **181b**	76%, (>95%)
2	 **163c**	 **180**	 **181c**	78%, (>95%)
3	 **163d**	 **180d**	 **181d**	78%, (>95%)
4	 **163e**	 **180e**	 **181e**	74%, (>95%)
5	 **163i**	 **180i**	 **181i**	83%, (>95%)

Reagents and Conditions: 10 mol% $VO(acac)_2$, 1 equiv ^tBuOOH, Benzene, 24 hrs, RT; [a] All reported yields are after column chromatography eluting with CH_2Cl_2:EtOAc (7:3); [b] Determined from ^1H NMR of crude reaction products.

Table 3-6: Epoxidation/lactonisation of unsaturated *syn*-aldols to afford γ-butyrolactones.

Epoxidation of *syn*-aldol **163b-e,i** under optimal epoxidation-lactonisation conditions resulted in the formation of γ-butyrolactones **181b-e,i** (*via* the *erythro*-epoxy aldols **180b-e,i**) in good to excellent yields and >95% diastereoselectivity (Entries 2-6). The configuration of the C_5 stereocentres of the γ-butyrolactones **181b-e,i** were assigned according to the proposed neighbouring group participation mechanism with (*S*)-configuration of the C_6-hydroxy following from the stereochemistry of the *erythro*-epoxide intermediate **180b-e,i**.

It was then decided to investigate the effect of the α-stereocentre on the diastereocontrol of these tandem epoxidation/lactonisation reactions. Consequently, non-Evans' *anti*-aldol was treated under standard epoxidation/lactonisation conditions (See Scheme 3.29), which gave the desired lactone with equally high diastereoselectivity to that observed for the corresponding *syn*-aldol derivative **163e** (Entry 5, Table 3-6).



Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, benzene, H_2O

Scheme 3.29: Epoxidation/Lactonisation of *anti*-aldol **146**.

The (*S*)-configuration of the C_5 position was confirmed from examination of its NOESY spectra. A favoured conformation is shown in Figure 3.28, which positions the vicinal C_4OH and C_5-alkyl groups in axial positions on opposite faces of the lactone ring.. With this in mind, the C_3 proton gave a strong correlation to the proton on C_4, which in turn gave a strong interaction with the protons on C_6. Further to this, the C_3 proton and the C_5 hexyl-substituent are both arranged axially on the same face of the ring systems, hence a strong interaction is observed.

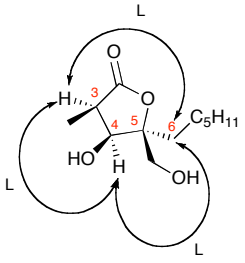
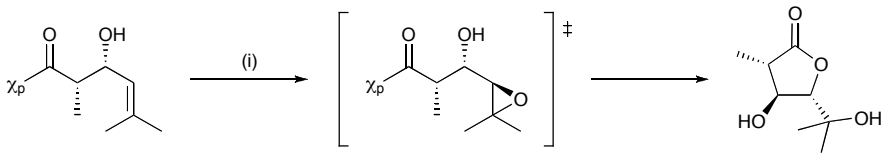


Figure 3.19: Observed interactions from NOE spectroscopy of γ-lactone **146**.

The success of the epoxidation/lactonisation upon 1,1-disubstituted allylic alcohols then led us to investigate the suitability of highly *threo*-selective epoxidation motifs.

3.4.5 *Threo*-selective lactones

The next study was focussed around the lactonisation of various unsaturated aldols containing β-*cis* substituents that were predicted to proceed with *threo* selectivity. Initially, unsaturated aldol **163h** was treated under the optimised oxidation conditions to yield a γ-butyrolactone in >95% de, which from literature precedent was predicted to derived from the *threo*-epoxy aldol **180h** to give a γ-butyrolactone **181h** with a 5*S* stereocentre.

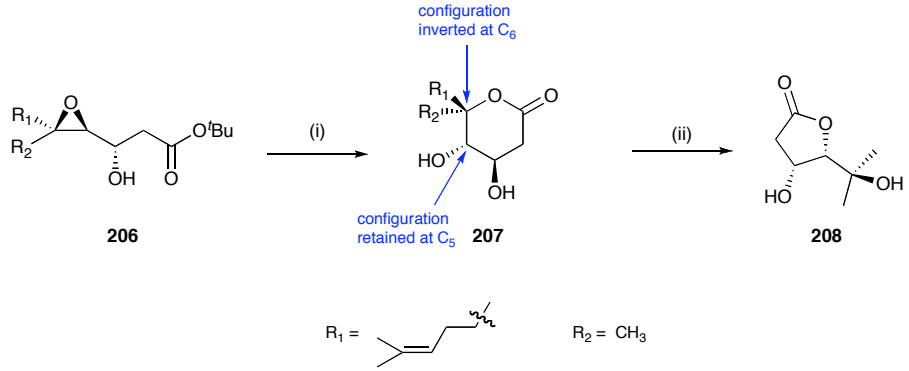


163h **180h** **181h**

Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, Benzene, H_2O

Scheme 3.30: Synthesis of γ-lactone **181h** *via threo*-epoxy aldol **180h**.

Analysis of the crude ^1H NMR spectra indicated a high level of diastereo-control, however, in the absence of a crystal structure we needed to confirm the configuration of its C_5-stereocentre. This was complicated by the fact that Baltas *et al* had previously reported the potential for 2,2-disubstituted-epoxy-β-hydroxy-*tert*-butyl esters to undergo a competitive *endo*-cyclisation mechanism during the formation of γ-lactones.[159,160] They reported that treatment of epoxy ester **206** with a Lewis acid resulted in a neighbouring group participation mechanism occurring *via* a competing endocyclic cyclisation manifold to yield a δ-lactone **207**. This δ-lactone was shown to be unstable and readily rearranged under mild conditions, to its more stable γ-lactone **208** under acidic or basic conditions (Scheme 3.31).



Reagents and conditions: (i) $ZnCl_2$, CH_2Cl_2 (if anhydrous the second step is not required); (ii) $^iPr_2NH$ or TFA.

Scheme 3.31: Synthesis of γ-lactone **208** *via* δ-lactone **207**.

We reasoned that unsaturated aldol **180h** might have an increased potential to undergo this type of competitive 6-*endo*-cyclisation rearrangement pathway, because the 2,2-disubstituted methyl groups would stabilise a carbocation at its C_5 position thus potentially favouring endocyclic attack. This raised concerns over the stereochemical outcome of lactonisation since 6-*endo* lactonisation would not result in inversion of the C_5 stereocentre, whereas 5-*exo* cyclisation manifold would proceed with inversion of configuration at C_5 (See Figure 3.20).

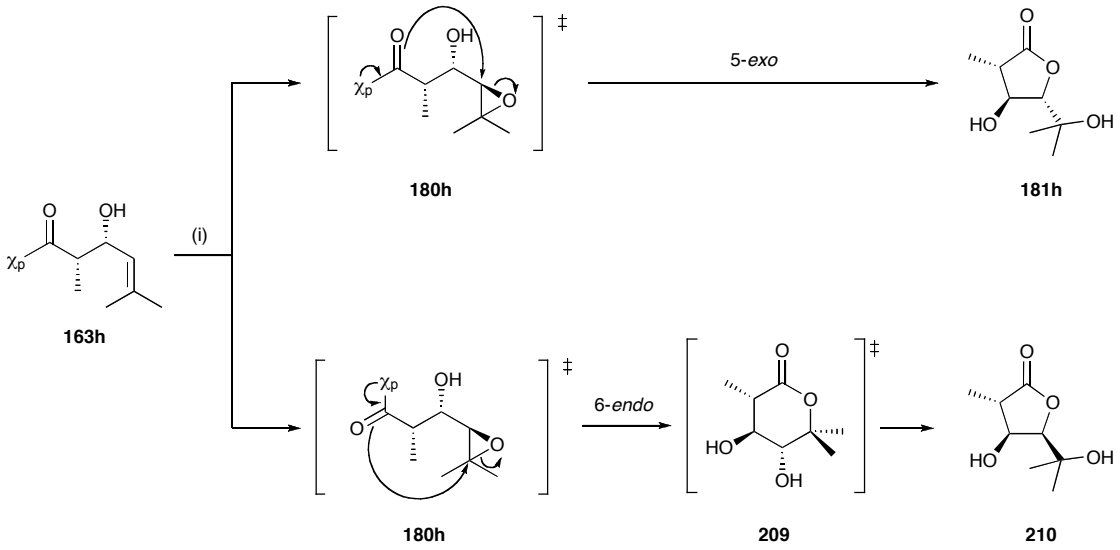


Figure 3.20: Potential competing 5-*exo* and 6-*endo* mechanisms for the synthesis of γ-lactones **181h** and **210**.

NOE spectroscopy of the purified γ-lactone **181h** showed a strong interaction between the C_3 methyl group interacting with the C_6-dimethyl functionality, and further strong interactions between the C_3 and C_5 hydrogens (*vide infra)*. These strong interactions were indicative of the stereochemistry assigned for the 5-*exo* cyclisation of the *threo*-epoxy aldol **180h** and that the

potential 6-*endo* lactonisation pathway was not occurring. This was confirmed by comparison with the NOESY of the diastereomeric 5*R* lactone **210**, which will be discussed in the following chapter (See Section 4.5.6).

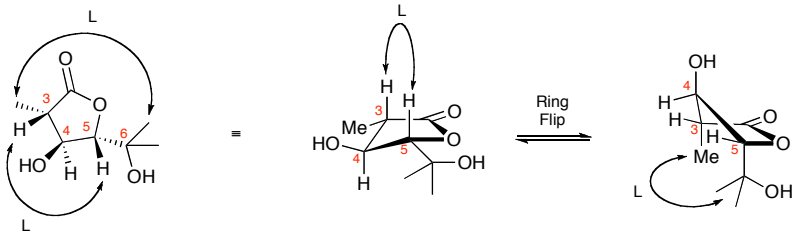
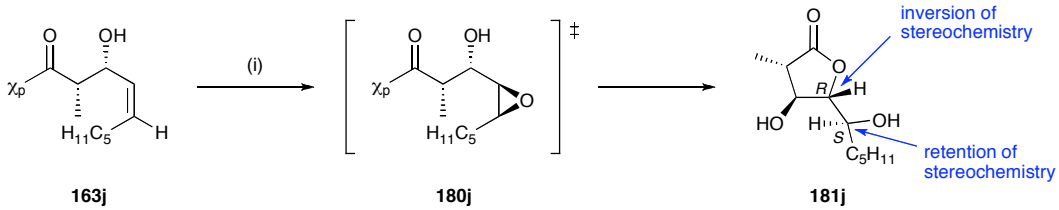


Figure 3.21: Observed interactions from NOE spectroscopy of γ-lactone **181h**.

Further to this stereochemical analysis, *cis*-octene aldol derivative **163j** was treated with vanadyl acetylacetonate and *tert*-butyl hydroperoxide, with the γ-butyrolactone **181j** being generated in 84% yield and in >95% de. Once again, the stereochemistry of the lactone was inferred from the predicted *threo*-epoxide intermediate with inversion occurring at the C_5 position to afford the lactone **181j**.

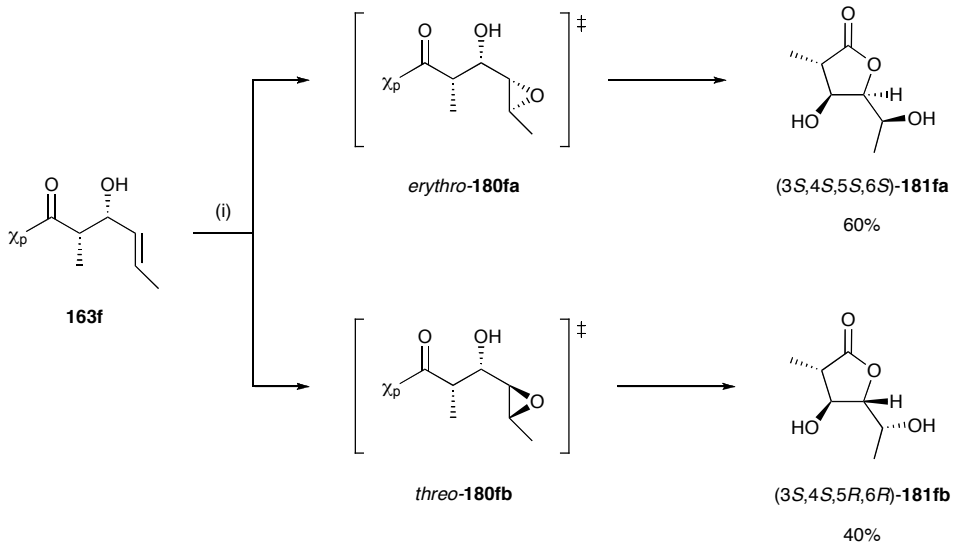


163j **180j** **181j**

Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, Benzene, H_2O

Scheme 3.32: Synthesis of γ-lactone **181j** *via threo*-epoxy alcohol **180j**.

It was then decided for completeness to investigate epoxidation/lactonisation of *trans*-allylic-*syn*-aldol **163f**, which, if our epoxidation/lactonisation mechanism was correct, would be predicted to proceed with poor levels of *erythro*-diastereocontrol. Initially, aldol **163f** was treated under the standard epoxidation conditions, with the analysis showing that all of the starting material had been consumed after 24 hours. ^1H NMR spectroscopic analysis of the crude reaction product revealed that two diastereoisomeric γ-butyrolactones **181fa** and **181fb** in 33% de. These diastereoisomeric lactones were then separated by chromatography to afford (3*S*,4*S*,5*S*)-**181fa** and (3*S*,4*S*,5*R*)-**181fb** respectively.



Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, Benzene, H_2O

Scheme 3.33: Epoxidation/lactonisation reaction of *trans*-aldol **163f** *via* the epoxy alcohol intermediates.

The configuration of the (3*S*,4*S*,5*S*,6*S*)-γ-butyrolactone **181fa** and (3*S*,4*S*,5*R*,6*R*)-γ-butyrolactone **181fb** were assigned from comparison of their ^1H NMR and NOESY spectra. One key difference in the ^1H NMR spectra was the C_3 proton signal, which in the *erythro*-product **181fa** was observed as a quartet of doublets, however in the *threo*-product **181fb** a quartet of doublets is observed. Distinguishing between the two diastereomers was achieved using NOE spectroscopy, which could clearly differentiate between the interactions of the C_3 proton with the rest of the ring.

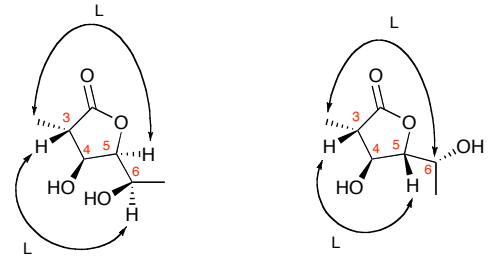


Figure 3.22: Observed interactions from NOESY of both *erythro*-**181fa** and *threo*-**181fb**.

3.5 Polymer support strategy ♦

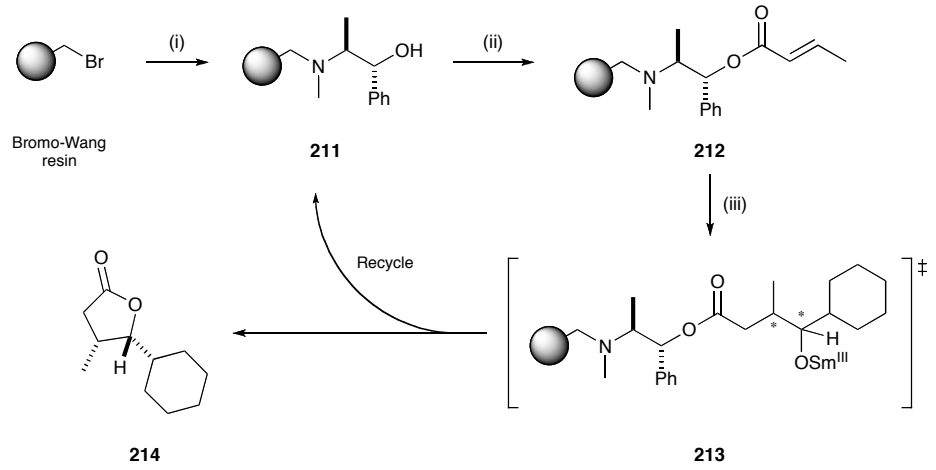
In recent years, the use of solid supported reagents, catalysts and scavengers for synthesis has increased widely. This is particularly true within the pharmaceutical industry where there is a need to synthesise focussed libraries of compounds in >90% purity, for high throughput screening against different biological targets. [161]

The use of solid supported reagents has many advantages over their homogeneous equivalents. Excess reagents can be employed to drive reactions to completion, with simplified purification procedures involving washing of the solid phase, thus allowing for removal of impurities or excess reagents. This allows solid phase synthesis to be used to rapidly prepare libraries of compounds in high yields and purities, without the need for complicated work-ups or purification.

However, solid phase synthesis does have its limitations, with extra steps required to attach starting materials and remove products from solid support. Also monitoring reactions on solid support is difficult, because the range of available analytical techniques is often limited. This often results in existing solution phase reactions needing to be reoptimised for use with solid supported systems, with rates of reaction often much slower on polymer support.

Previously, polymer-supported chiral auxiliaries have been used for the asymmetric synthesis of chiral γ-lactones on solid supports. Procter *et al* reported the use of a solid supported chiral ephedrine **211** for use in asymmetric radical reactions of alkenes with aldehydes using samarium iodide as a reductive catalyst.[161,162] In this case, the chiral ephedrine resin was readily esterified with crotonyl chloride and the resultant unsaturated *O*-acyl resin **212** was treated with samarium iodide and cyclohexanecarboxaldehyde, resulting in an asymmetric radical reaction with self-cleavage to afford the disubstituted γ-lactone **214** in 66% yield and 96% ee.

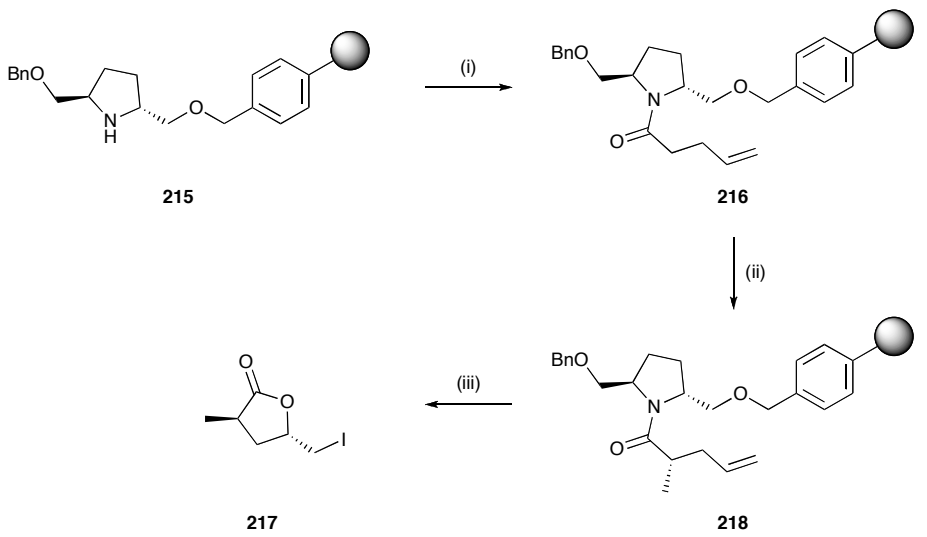
♦ This work was carried out in collaboration with Rachel Green, whose PhD focussed around novel applications of solid supported chiral auxiliaries for organic synthesis.



Reagents and conditions: (i) (1*R*,2*S*)-ephedrine, DMF, 85 °C; (ii) Crotonyl chloride, NEt_3, Et_2O, RT; (iii) Cyclohexanecarboxaldehyde, ^tBuOH, RT to -15 °C, then SmI_2.

Scheme 3.34: Polymer supported synthesis of disubstituted-γ-lactone **214** *via* samarium iodide mediated radical addition of aldehydes to alkenes.

Schore *et al* reported that iodolactonisation of polymer supported γ,δ-unsaturated chiral pyrrolidine derivative **215**.[163,164] Initially, polymer supported pyrrolidine derivative **215** was treated with pentenyl chloride to afford *N*-acyl-polymer **216** whose lithium enolate was alkylated by methyl iodide to afford a chiral α-methyl-γ,δ-unsaturated pyrrolidine derivative **217**. Subsequent treatment with iodine generates an iodonium ion, with concomitant nucleophilic attack by the amide moiety which results in cleavage to afford the monosubstituted iodolactone **218** in 81% ee and 35% overall yield from polymer **215**.

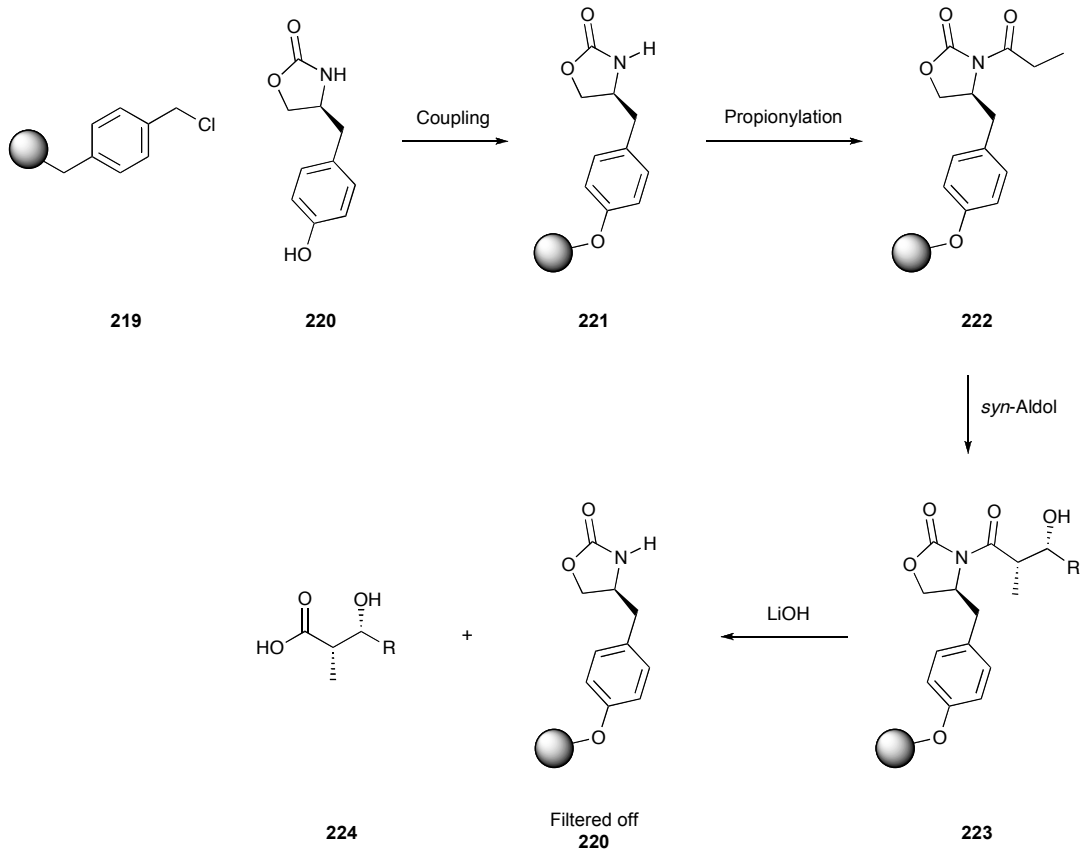


Reagents and conditions: (i) Pentenyl chloride, THF, Et_3N; (ii) (a) LDA, THF, 0 °C; (b) CH_3I; (iii) I_2, THF/H_2O (1.5:1).

Scheme 3.35: Solid supported chiral iodolactonisation.

The high levels of diastereocontrol observed for our solution phase epoxidation/lactonisation protocol, and the successful literature applications of solid supports to the synthesis of chiral lactones, led us to consider transferring our methodology to polymer support.

Previously, the SDB group has developed conditions for the solid supported synthesis of *syn*-aldol products using an L-tyrosine derived oxazolidn-2-one.[165] Initially, L-tyrosine derived oxazolidin-2one **220** is coupled to a Merrifield resin through its phenolic oxygen, followed by *N*-propionylation to afford polymer-supported *N*-acyl-oxazolidin-2-one **222**. Subsequent treatment of this polymer with 9-BBN-OTf under our modified aldol conditions enabled a small series of polymer supported *syn*-aldol products to be formed.[166] These polymers were then cleaved *via* treatment with LiOH to afford the corresponding chiral β-hydroxy acids **224** in high de.

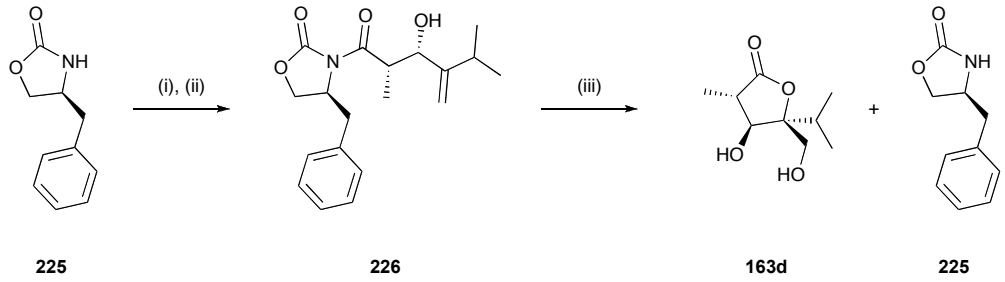


Scheme 3.36: Previously reported synthesis of solid supported ozaxolidin-2-one-*syn*-aldols.

It was proposed that this methodology could be applied to the synthesis of β-vinyl-aldols, which could then be subjected to our epoxidation/lactonisation conditions. The advantage of applying our strategy to solid support was that the methodology would incorporate a self-cleaving

auxiliary fragment that could be removed by filtration at the end of the reaction, thus simplifying the purification process.

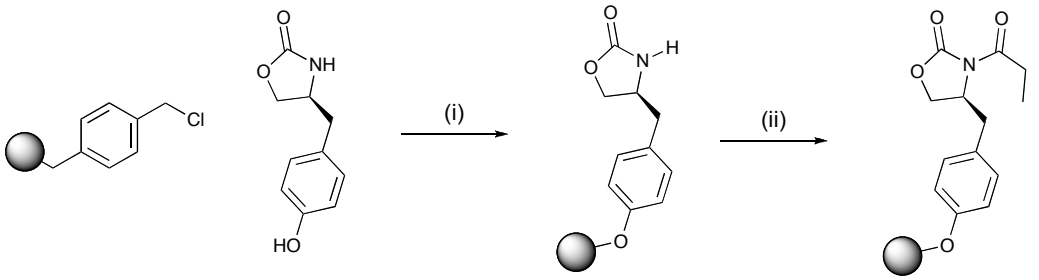
However, to confirm that polymer-supported Evans' type oxazolidin-2-one auxiliary **220** would perform correctly under our epoxidation lactonisation conditions it was decided to repeat our epoxidation/lactonisation methodology using an Evans' auxiliary in solution phase. Initially, oxazolidin-2-one **225** was acylated to afford *N*-propionyl oxazolidin-2-one which was subsequently treated under *syn*-aldol conditions (9-BBN-OTf, DIPEA, isopropyl acrolein) to yield Evans' unsaturated-*syn*-aldol **226** in 79% yield and >95% de. Treatment of *syn*-aldol **226** with vanadyl acetylacetonate and *tert*-butylhydroperoxide using our optimised epoxidation/lactonisation conditions yielded the desired lactone **163d** in a comparative 79% yield and >95% de to that obtained previously using a SuperQuat oxazolidin-2-one.



Reagents and conditions: (i) ^{n}BuLi, propionyl chloride, DCM, -78 ^{o}C to RT, 2 hours; (ii) (a) 9-BBN-OTf, DIPEA, CH_2Cl_2, 0 °C; (b) *iso*-propylacrolein **164**, -78 °C to RT; (iii) $VO(acac)_2$, ^{t}BuOOH, benzene, RT.

Scheme 3.37: Epoxidation/lactonisation protocol applied to an Evans'-type oxazolidin-2-one auxiliary.

Initially, Merrifield resin **219** was treated with 3 equivalents of L-tyrosine derived oxazolidin-2-one **220**, potassium carbonate and 18-crown-6 in dimethylformamide at 60 °C for 18 hours, with Merrifield resin being chosen for its stability under Lewis acid conditions. The resulting polymer-supported auxiliary **221** was then treated with an excess of propionic anhydride, triethylamine and lithium chloride in refluxing THF. After 3 hours the reaction was filtered and the resin dried in an oven, with gravimetric analysis indicating that the key *N*-propionyl polymer had been formed with a loading of approximately 0.79 mmol g^{-1}. IR analysis of the resin in a KBr disk indicated the presence of two carbonyl functionalities at 1705 cm^{-1} and 1783 cm^{-1} indicating that the *N*-acylation reaction had been successful.

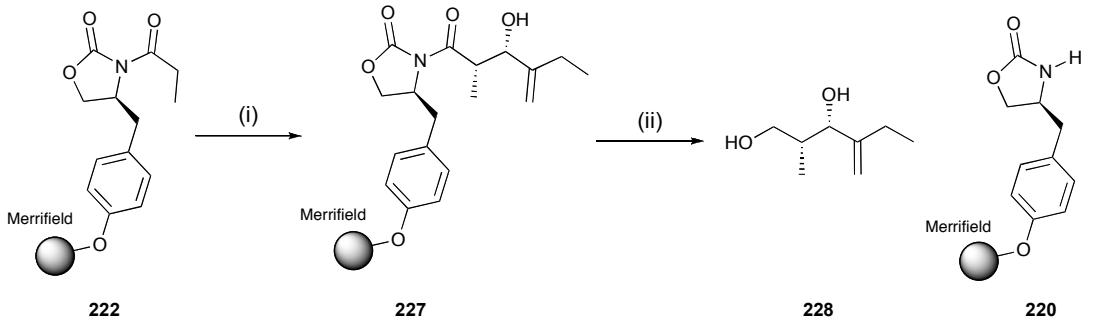


219 **220** **221** **222**

Reagents and conditions: (i) K_2CO_3 (3.0 equiv), 18-crown-6, DMF, 60°C, 18 hours; (ii) Propionic anhydride, LiCl, Et_3N, THF.

Scheme 3.38: Formation of polymer supported *N*-propionyl-Evans'-oxazolidin-2-one **222**.

N-propionyl polymer **222** was subsequently treated with 5 equivalents of 9-BBN-OTf in CH_2Cl_2 and agitated at 0 °C for 1 hour. The resulting reaction mixture was filtered under nitrogen and the polymer beads treated with 5 equivalents of *N,N*-diisopropylethylamine at 0 °C to generate a polymer-supported-(*Z*)-boron-enolate intermediate. Excess solvents and reagents were then filtered off and the polymer beads resuspended in fresh CH_2Cl_2 before being cooled to -78 °C. 2-Ethyacrolein was then added and the reactions slowly allowed to warm to 0 °C overnight. The resulting polymer-supported-*syn*-aldol **227** was isolated by filtration of the reaction mixture and a small portion characterised by subsequent reduction of the resultant resin with sodium borohydride in THF/H_2O to afford a clean sample of chiral diol **228** in >95% de whose structure was confirmed by spectroscopic analysis.

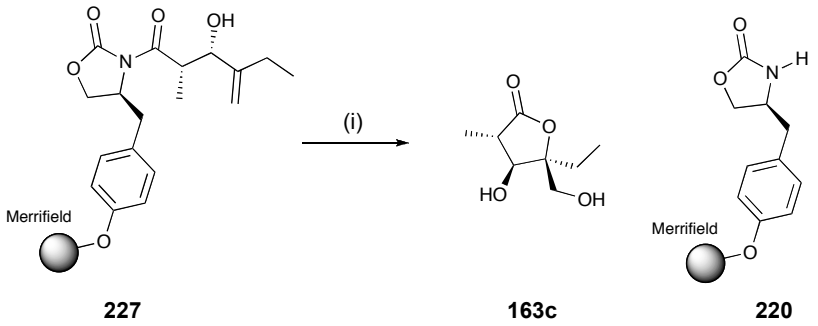


222 **227** **228** **220**

Reagents and conditions: (i) (a) 9-BBN-OTf (5.0 equiv), CH_2Cl_2, 0 °C, 1 hr; (b) DIPEA (5.0 equiv), 0 °C, 1 hour; (c) Ethyl acrolein (7 equiv), -78 °C to 0 °C, 12hr, CH_2Cl_2; (ii) $NaBH_4$, THF/H_2O.

Scheme 3.39: Directed *syn*-aldol reaction of functionalised Merrifield resin **222** and subsequent characterisation *via* reductive cleavage.

The remaining *syn*-aldol-functionalised resin **227** was then treated with 0.5 equivalents of vanadyl acetylacetonate and 5 equivalents of *tert*-butyl hydroperoxide for 24 hours before the reaction mixture was filtered to remove the polymer and the filtrate concentrated under reduced pressure to afford the desired lactone **163c** in 74% yield and >95% de.



227 **163c** **220**

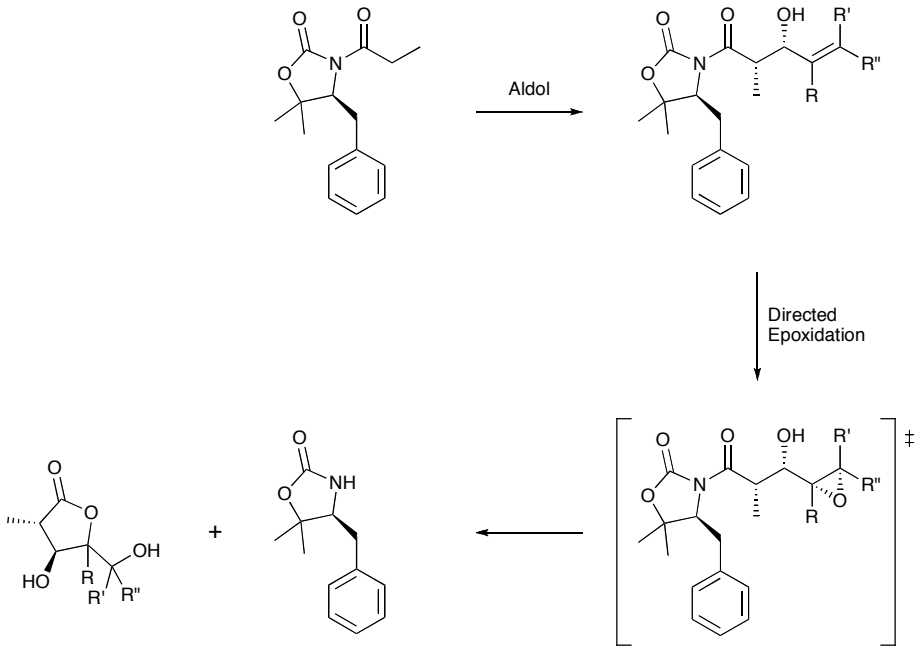
Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, Benzene, filtered.

Scheme 3.40: Solid phase lactonisation of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one **227**.

As such it can be considered that this solid supported strategy may represent a highly practical methodology for the synthesis of libraries of highly functionalised γ-lactones.

3.6 Conclusions

It has been demonstrated that chiral *N*-propionyl-oxazolidin-2-ones may be used in a highly efficient aldol/epoxidation/lactonisation protocol to afford a highly functionalised γ-lactones containing three or four contiguous stereocentres with high levels of stereocontrol (See Scheme 3.41).



Scheme 3.41: Overall transformation of α,β-unsaturated aldehydes to the highly functionalised γ-lactone moiety.

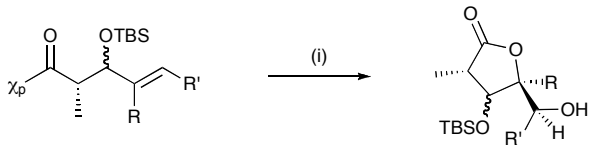
Chapter 4: An alternative dihydroxylation protocol for the asymmetric synthesis of chiral γ-butyrolactones

4.1 Epoxidation/lactonisation strategy for the asymmetric synthesis of chiral lactones

In the previous chapter we demonstrated that β-vinyl-oxazolidin-2-one derived aldol products undergo an efficient epoxidation/lactonisation reaction with catalytic vanadyl acetylacetonate and a stoichiometric equivalent of *tert*-butylhydroperoxide to afford chiral γ-lactones. Initially, a chiral epoxide is generated in high levels of diastereocontrol; concomitant nucleophilic attack of the *exo*-cyclic carbonyl (*via* neighbouring group participation) then results in opening of the epoxide intermediate with a clean inversion of stereochemistry at the C_5 position. Subsequent hydrolysis results in clean conversion to a highly functionalised hydroxy-γ-butyrolactone containing three or more contiguous stereocentres (See previous page).

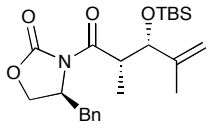
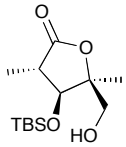
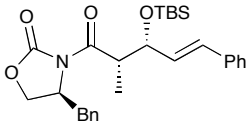
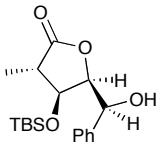
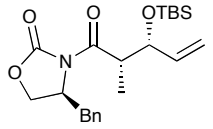
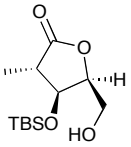
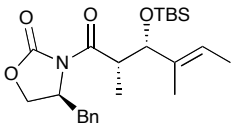
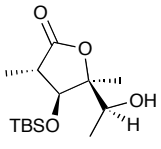
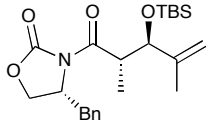
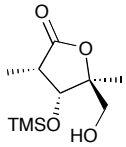
4.2 Dihydroxylation/lactonisation strategy for the asymmetric synthesis of chiral lactones

Concurrent to our investigation into this epoxidation/lactonisation strategy (*vide supra*), Dias and co-workers published a paper on the dihydroxylation of unsaturated aldol products **228a-e** as effective precursors to produce chiral trisubstituted γ-butyrolactone derivatives with good levels of diastereocontrol (See Table 4.1).[167] They reported that treatment of a series of structurally related Evans' derived β-vinyl-*O*-silyl-aldol adducts **228a-e** with a catalytic amount of osmium tetroxide and a stoichiometric amount of *N*-methylmorpholine-*N*-oxide in acetone/water (8:1) yielded the free *N*-H oxazolidin-2-one **225** and a series of γ-butyrolactones **229a-e** in reasonable yields.



228a-e **229a-e**

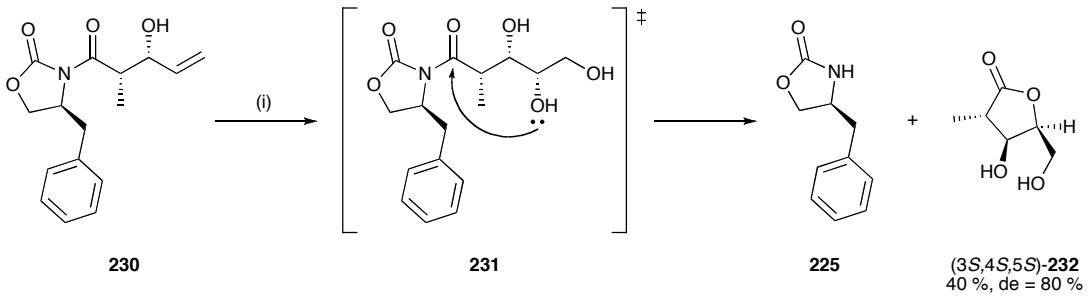
Reagents and conditions: (i) NMO, OsO_4, Acetone-H_2O (8:1), 0 °C.

Entry	*Aldol*	*Major Lactone* [a]	*Yield (%)* [b]	*dr (%)*
1	 **228a**	 **229a**	43	78:22
2	 **228b**	 **229b**	45	95:05
3	 **228c**	 **229c**	42	90:10
4	 **228d**	 **229d**	47	94:06
5	 **228e**	 **229e**	44	75:25

[a] Stereochemistry assigned from coupling constants and NOE spectroscopy; [b] Isolated yields after column chromatography.

Table 4.1: Dihydroxylation/lactonisation strategy for the asymmetric synthesis of chiral lactones.

In the same paper, Dias reported application of the same osmylation/lactonisation strategy to a non-silylated acrolein-derived aldol **230**, which yielded lactone **232** in 40 % yield and 80% de that was reported to be its (5*S*) derivative. The reported (5*S*)-configuration of **232** was identical to that described for the OTBS protective aldol derivatives **228a-e**, which were also described to afford monoprotected (5*S*)-*O*-silyl lactones **229a-e** in comparable 43-47% yields.



Reagents and conditions: (i) NMO, OsO_4, Acetone-H_2O (8:1), 0 °C

Scheme 4.1: Dias' synthesis of lactone **232**.

These reaction clearly proceed *via* a dihydroxylation/lactonisation mechanism however the results reported in this paper revealed several concerns regarding the reported stereochemical outcome of these osmylation/lactonisation reactions. These were:

(a) The relative stereochemistry of the C_4/C_5 positions of lactones **229b** and **229c** (*Entries 2 and 3*) were assigned from their ($J_{4,5}$) coupling constants, which as previously discussed is not reliable for five membered lactone systems. The conformational fluxionality of the "envelope" structure renders the elucidation of the stereochemical relationship of vicinal chiral centres from this type of coupling constant analysis precarious.[151]

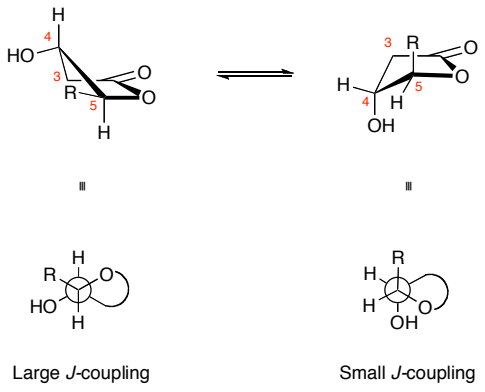


Figure 4.1: Fluxionality between conformers demonstrates that assignment of configuration from coupling constants is not reliable for five-membered lactone systems.

(b) The NOE spectrum used to assign the stereochemistry of lactone **229b** (*Entry 2*) reported NOE interactions of a conformationally mobile TBS protecting group. If we consider the two potential diastereomers, (5*S*)-**229b** and (5*R*)-**229f**, it can be seen that interactions between the TBS group with the newly formed *exo*-cyclic C5 substituents of both diastereomers can occur. As such, the NOE cross peaks observed for the TBS group do not enable unequivocal assignment of the configuration of the C_5 carbon centre.

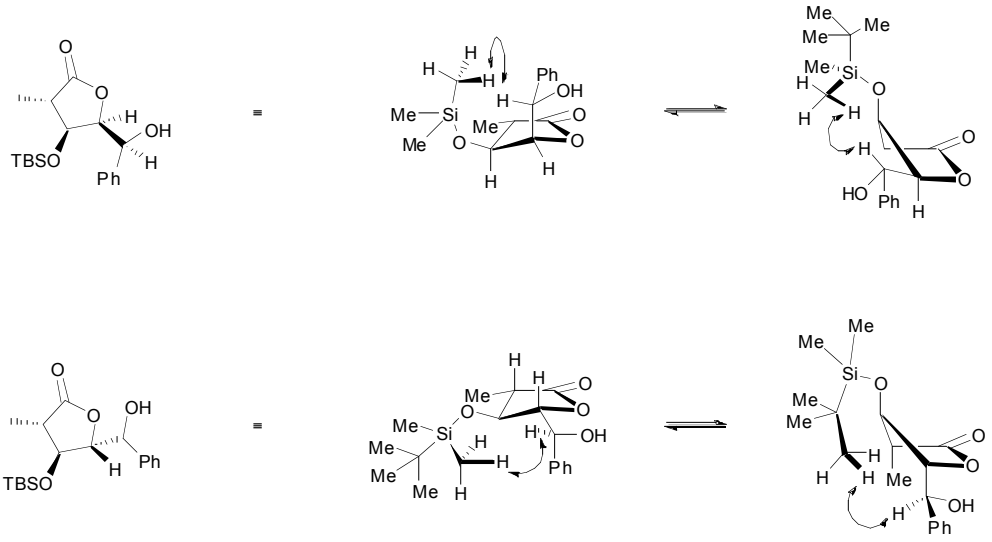


Figure 4.2: Possible NOE interactions of the OTBS group of lactones (5*S*)-**229b** and (5*R*)-**229f**.

Although, the stereochemical outcomes of the dihydroxylation reactions reported were inferred from ^{1}H NMR and NOE spectroscopy, no consideration of the literature precedent for facial selectivity of these dihydroxylation reactions were considered. Dias proposed a two-step reaction mechanism where the alkenyl system was initially dihydroxylated followed by a concomitant cyclisation-elimination reaction to give the desired γ-butyrolactone and *N*-H oxazolidin-2-one **225**. However, close examination of literature precedent (*vide infra*) revealed that the facial selectivity of a number of the proposed dihydroxylation reactions appeared to be incorrect.[168]

(c) Examination of the structures of lactones **229b** and **229d** (*Entries 2 and 4*) revealed that they could not possibly have been accessed from a conventional *syn*-dihydroxylation reaction of *trans*-alkenyl systems. Indeed, their formation would require either an *anti*-dihydroxylation of a *trans*-alkene, or a *cis*-dihydroxylation of a *cis*-alkene substituent.

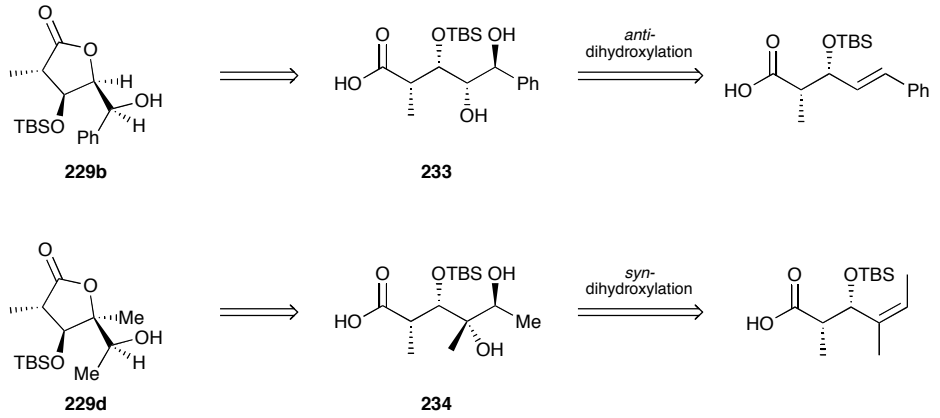


Figure 4.3: Open chain carboxylic acid equivalents of the γ-lactone products **229b** and **229d** proposed by Dias.

Given the aldol chemistry used to prepare the aldol precursors used as substrates for dihydroxylation, it is unlikely that Dias' reaction proceeded from a *cis*-alkenyl system. However, it was possible that an *anti*-dihydroxylation product could potentially have been accessed *via* a neighbouring group participation mechanism similar to that proposed for the epoxidation/lactonisation reaction discussed in Chapter 3 of this thesis.

In this case, osmium tetroxide would add across the alkenyl functionality of aldol **228b** to stereoselectively generate a (*cis*)-osmate ester **235**. Subsequent nucleophilic ring opening at C_4 of the osmate ester by intramolecular nucleophilic attack of the *exo*-cyclic carbonyl of the *N*-acyl fragment could potentially occur with resultant inversion of the C_4 stereocentre. The resultant imminium intermediate **236** would then be hydrolysed on workup to yield the parent *N-H* oxazolidin-2-one **225** and the γ-lactone with an (*anti*)-diol-configuration.

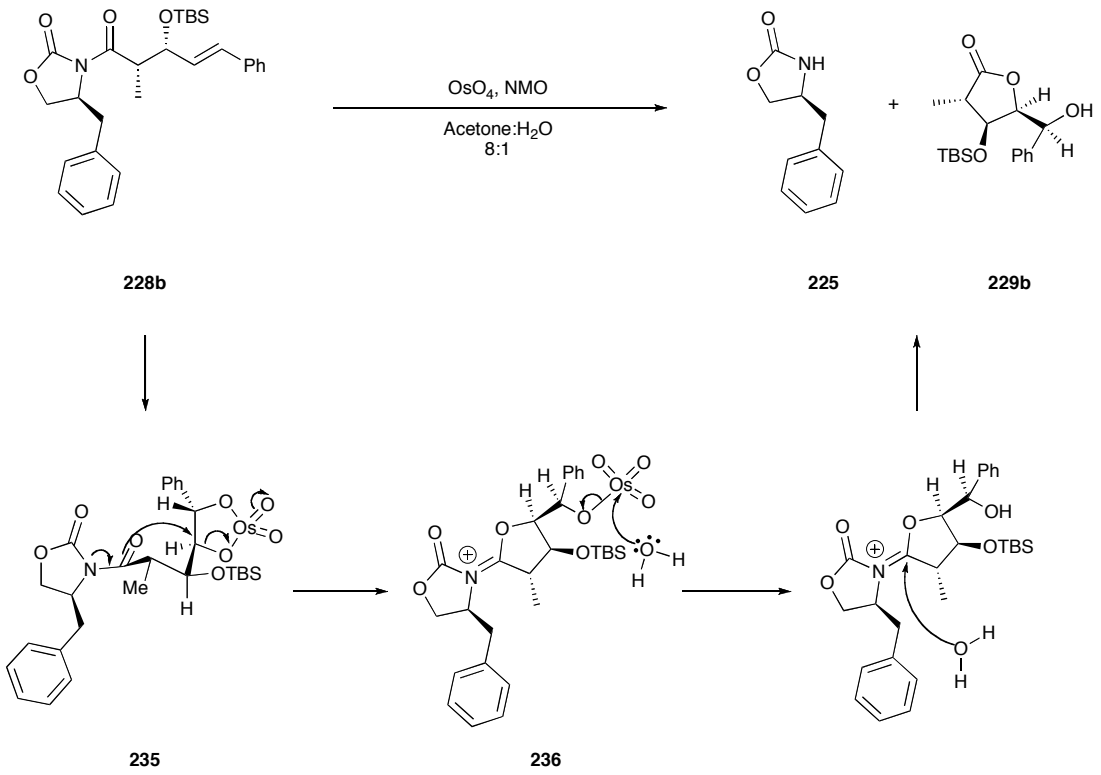


Figure 4.4: Potential mechanism for intramolecular opening of osmate ester **235** *via* neighbouring group participation.

However, a comprehensive examination of the literature revealed that there was no precedent whatsoever for this type of mechanism, with no neighbouring group participation effect having been reported to afford *anti*-diol products.

(d) Dias reported that treatment of Evans *syn*-aldol **228a** (*Entry 1*) and the non-Evans *anti*-aldol **228e** (*Entry 5*) under the osmylation/lactonisation conditions proceeded with the same facial selectivity, despite the fact that they have opposing configurations at their C_4 stereocentres. This was surprising because it would be expected that their stereogenic C_4 hydroxyl-substituents would be likely to control the facial selectivity of these dihydroxylation reactions in a similar manner, which would have afforded γ-lactone products with opposing configurations at C_5.

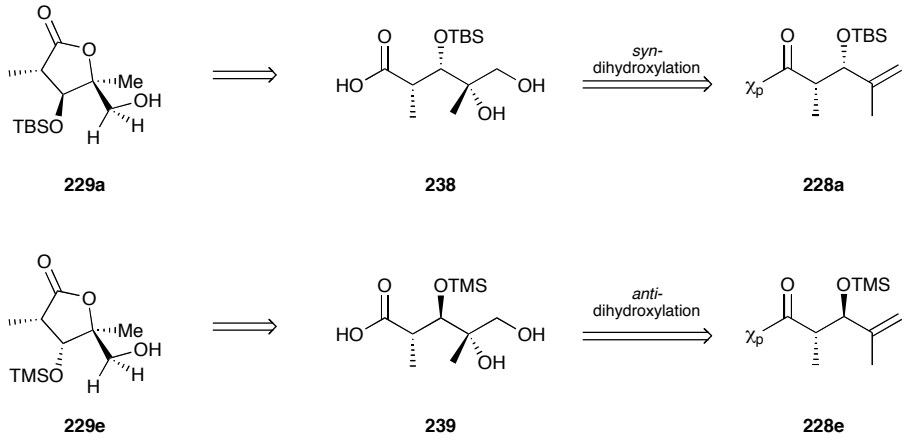


Figure 4.5: Identical facial selectivity proposed for dihydroxylation of (*syn*)-aldol **228a** and (*anti*)-aldol **228e** substrates.

(e) Finally, there were concerns over the spectroscopic data reported for *O*-TMS-lactone **229a** (*Entry 1*). Dias reported that dihydroxylation/lactonisation of 1,1-disubstituted-unsaturated-aldol proceeds with the same selectivity as that established for our epoxidation/lactonisation reaction of aldol **163b** generating (5*S*)-lactone **181b** (See Chapter 3). However, even allowing for the presence of its *O*-TBS protecting group, it was clear that our spectroscopic data for lactone **181b** was significantly different to that reported by Dias for their *O*-TBS-lactone **228a**, implying that the absolute configuration of their C_5-positions were likely to be different.

(3*S*,4*S*,5*S*)-**181b**
Product of Epoxidation/
Lactonisation

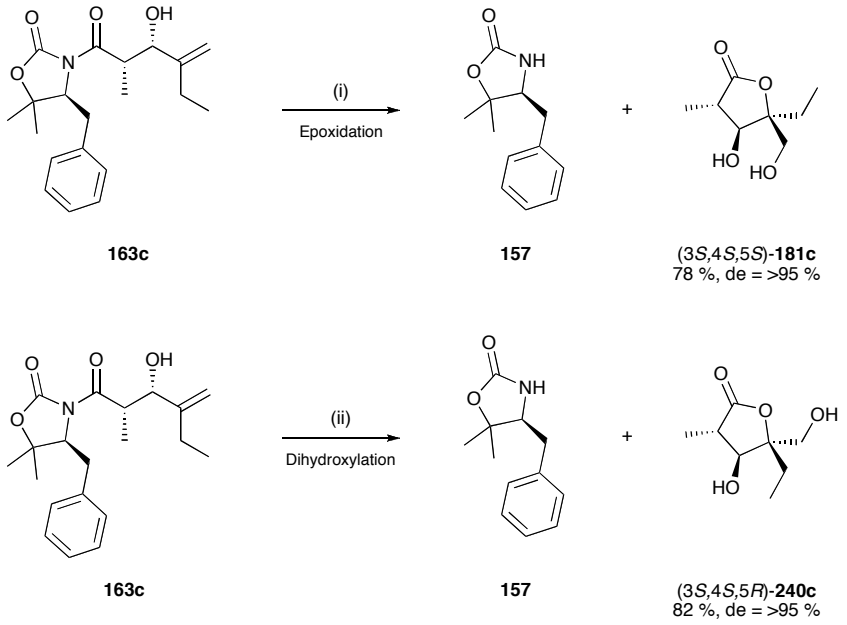
(3*S*,4*S*,5*S*)-**228a**
Dias' proposed product of
Dihydroxylation/Lactonisation

4.3 Investigation of the stereoselectivity of dihydroxylation reactions of SuperQuat derived β-vinyl-aldol products

Since we had unequivocally proven by X-ray analysis that treatment of SuperQuat derived *syn*-aldol **163c** under our epoxidation/lactonisation conditions gave lactone (5*S*)-**181c** (See Chapter 3), it was decided to dihydroxylate this *syn*-aldol **163c** to directly compare the spectroscopic data of the resultant γ-lactone.

Treatment of unsaturated aldol **163c** with osmium tetroxide (10 mol%) and *N*-methylmorpholine-*N*-oxide under Dias' conditions gave a new γ-lactone , whose spectroscopic

data was clearly different to that of the lactone (3*S*,4*S*,5*S*)-**181c** produced in our previous epoxidation reaction. Therefore it follows that its newly formed C_5 stereochemistry must in fact have an (*R*)-configuration opposite to the (5*S*)-configuration observed in our epoxidation/lactonisation reactions.



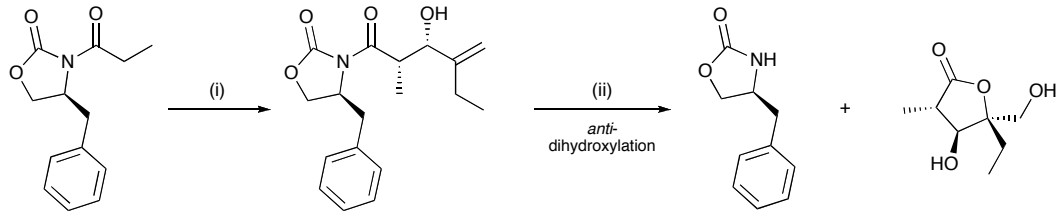
163c **157** (3*S*,4*S*,5*S*)-**181c** 78 %, de = >95 %

163c **157** (3*S*,4*S*,5*R*)-**240c** 82 %, de = >95 %

Reagents and conditions: (i) $VO(acac)_2$ (10 mol%), ^tBuOOH, Benzene, H_2O; (ii) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Scheme 4.2: Comparison of lactonisation strategies on 1,1-disubstituted-unsaturated-aldol **163c**.

In order to confirm that an Evans' derived *syn*-oxazolidin-2-one auxiliary **157** would perform in a similar manner under these osmylation/lactonisation conditions, it was decided to dihydroxylate *syn*-aldol **163c**. Towards this end, *N*-propionyl-oxazolidin-2-one **241** was treated under *syn*-aldol conditions (9-BBN-OTf, DIPEA, ethacrolein) to yield Evans' β-vinyl-*syn*-aldol **242** in 82% yield and >95 % de. Subsequent treatment of *syn*-aldol **242** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide in acetone/water (8:1) once again resulted in (3*S*,4*S*,5*R*)-lactone **240c** in a comparative 78 % yield and >95% de to that obtained previously using SuperQuat derived β-vinyl-*syn*-aldol **163c**.



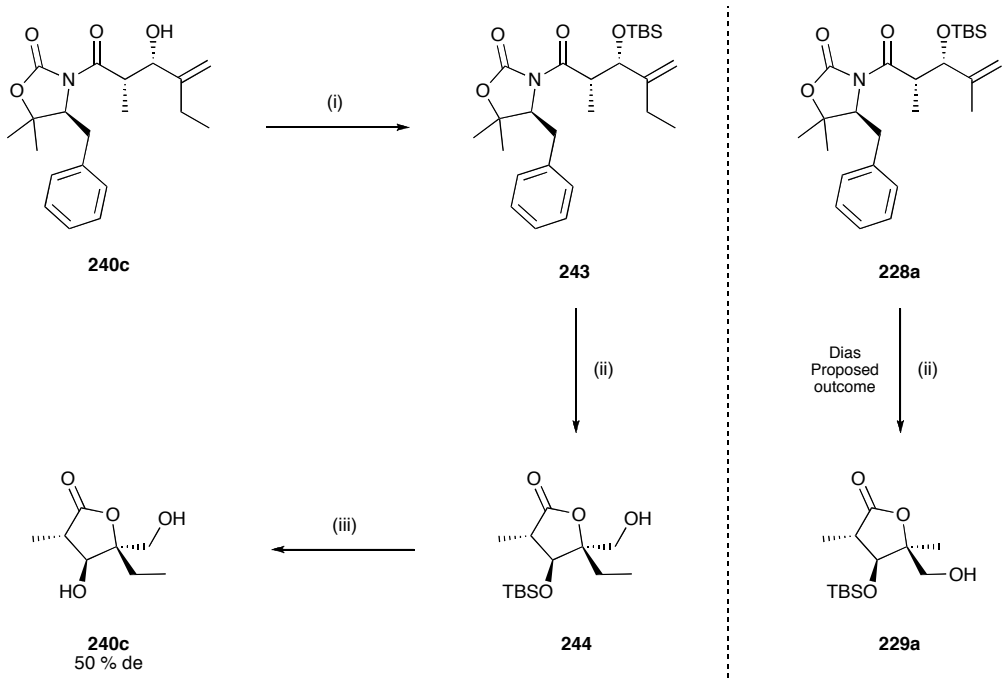
241 **242** **225** (3*S*,4*S*,5*R*)-**240c** 73 %, de = >95 %

Reagents and conditions: (i) $^{n}Bu_2BOTf$, DIPEA, CH_2Cl_2, Ethacrolein, -78 °C; (ii) NMO, OsO_4, Acetone-H_2O (8:1).

Scheme 4.3: Osmylation/lactonisation reaction of Evans derived *syn*-aldol **242**.

The dihydroxylation of simple 1,1-disubtituted-allylic alcohols with osmium tetroxide has been widely reported in the literature, with both free hydroxyl and *O*-silyl-protected systems proceeding with good levels of (*anti*)-diastereoselectivity (See Section 4.3 for further discussion).[169,170] However, application of osmium catalysed dihydroxylation reaction to oxazolidin-2-one derived aldol products had not been reported previously prior to Dias' paper. As such it was decided to investigate what effect the presence of the silyl-protecting group would have on the facial selectivity of the dihydroxylation reaction of this type of β-vinyl-aldol substrate.

Therefore, β-vinyl-*syn*-aldol **163c** was treated with TBSOTf, 2,6-lutidine in dichloromethane at 0 °C for three hours to afford *O*-TBS protected aldol **243** in 85 % yield. Subsequent treatment under UpJohn dihydroxylation conditions gave *N*-H oxazolidin-2-one (**225**) and hydroxy-butyrolactone (3*S*,4*S*,5*R*)-(**244**) in 65 % yield and a much reduced 50 % de when compared to the previous >95 % de obtained for dihydroxylation/lactonisation of unprotected *O*-H β-vinyl-*syn*-aldol **163c**.



Reagents and conditions: (i) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C; (ii) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1); (iii) TBAF, CH_2Cl_2.

Scheme 4.4: Dihydroxylation/lactonisation of silyl-protected aldol **243**.

The ratio of diastereomers obtained was similar to that published by Dias for dihydroxylation of β-vinyl-*syn*-aldol **228a**, however our results suggest that the configuration at the newly formed stereocentre was (5*R*), which is opposite to the (5*S*)-configuration that they reported. For direct comparison, the major diastereomer *O*-silyl-lactone **244** was deprotected using TBAF to access the *O*-H hydroxy-γ-butyrolactone **240c**. As expected ^{1}H NMR spectroscopic analysis indicated that the major diastereomer was identical to that obtained previously for dihydroxylation/lactonisation of the free *O*-H unsaturated aldol **163c**. Based upon these results, it appears that dihydroxylation of 1,1-disubstituted unsaturated aldols (*O*-H-aldol **163c** and *O*-silyl-aldol **243**) proceed with an overall *anti*-addition to its alkene functionality to generate a (5*R*) lactone product.

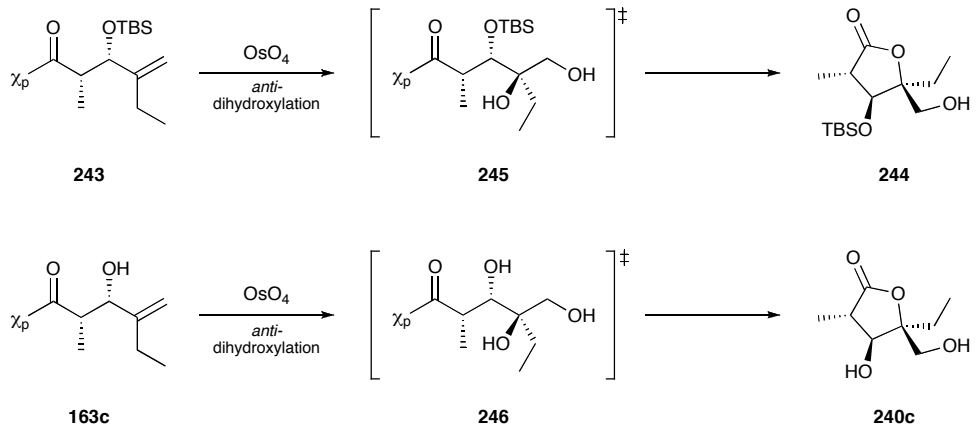


Figure 4.6: Observed stereochemical outcome from dihydroxylation of both **243** and **163c**.

Given our discovery of this incorrect stereochemical assignment, it was decided to investigate Dias' dihydroxylation results more fully in order to identify any further discrepancies in their assigned lactone structures. However, before we can rationalise the stereochemical outcome of these dihydroxylation reactions it is necessary to consider the potential transition states that operate to control the facial selectivity of dihydroxylation reactions of allylic alcohols with different alkene substitution patterns.

4.4 Hydroxyl-directed dihydroxylation reactions

The direct conversion of alkenes to *cis*-vicinal diols using catalytic amounts of osmium tetroxide is one of the most powerful and widely utilised reactions in synthesis. Despite the cost and toxicity of osmium tetroxide, its mildness, generality, chemoselectivity and low catalyst loading makes it a versatile strategy to access *cis*-vicinal diols.[168]

The mechanism of the catalytic osmium tetroxide dihydroxylation reaction has been widely investigated. Initially, osmium tetroxide adds across the alkene bond, generating an osmate ester **249** that is subsequently hydrolysed to generate a *cis*-vicinal diol (**248**) and reduced osmium oxide (Figure 4.7).[171] The catalyst is subsequently regenerated in the presence of a stoichiometric amount of an oxidant such as *N*-methylmorpholine-*N*-oxide (UpJohn), H_2O_2, or trimethylamine-*N*-oxide (Poli).[168,172]

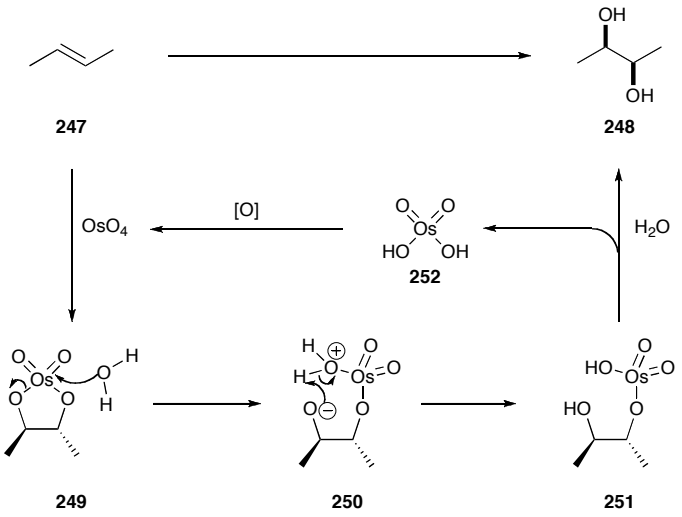


Figure 4.7: Mechanism of osmium tetroxide mediated dihydroxylation of alkene functionalities.

Until recently, the mechanism of the initial osmium addition across the alkene functionality was much debated. Originally, a concerted [3+2] cycloaddition pathway was proposed, where addition of O=Os=O across the carbon-carbon double bond generates a metallacycle intermediate (osmate ester, **249**).[173] In 1977, Sharpless challenged this concerted mechanism in favour of a step-wise process.[174,175] He proposed that Os=O adds across the alkene functionality *via* a [2+2] cycloaddition with the resulting four membered metallacycle **254** undergoing immediate rearrangement to yield the key osmate ester **253** (Scheme 4.8).

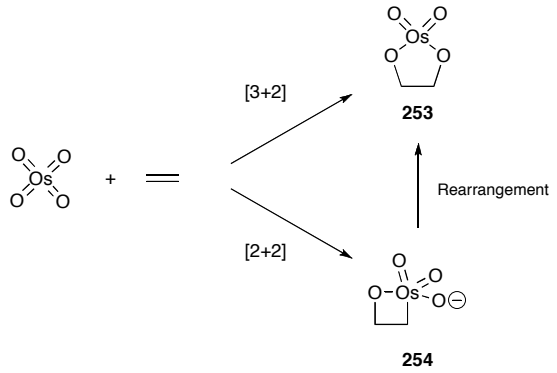


Figure 4.8: [3+2] versus [2+2] addition of osmium oxides to alkene bonds.

The debate over the mechanism of the addition pathway was subsequently solved by computational studies and detailed experimental investigation.[176-178] Comparison of activation energies indicated that the concerted [3+2] cycloaddition was the favoured reaction pathway, with a calculated activation energy of <10 kcal mol^{-1}, whereas the activation energy for the [2+2] cycloaddition was calculated as >39 kcal mol^{-1}. Houk and Sharpless corroborated the

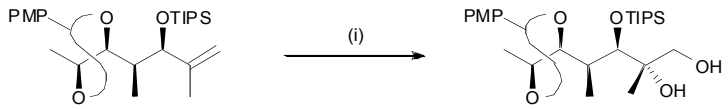
concerted [3+2] cycloaddition pathway with comparison of computed transition states, as well as by measuring kinetic isotope effects.[179]

The stereoselectivity of catalytic dihydroxylation reactions of chiral allylic alcohols systems has also been widely investigated, although it is worthy to note that, until recently, the majority of the research has focussed on *O*-protected allylic systems. Unlike the epoxidation reaction, where a chelation effect predictably and reliably controls the stereochemical outcome, dihydroxylation of allylic alcohols does not appear to proceed with such clear predictability. Therefore, it is clear that the facial selectivity of these types of dihydroxylation reactions is dependent on many factors, with the steric demand of their allylic substituents and their alkene substitution pattern playing a key role.[169]

4.4.1 *Anti*-dihydroxylation

1,1-Disubstituted, 1-substituted and (*E*)-1,2-disubstituted allylic alcohols have been shown to undergo dihydroxylation with high levels of *anti*-diastereocontrol in catalytic osmylation reactions.

For example, Chakraborty has previously reported the dihydroxylation of *O*-silyl-protected 1,1-disubstituted allylic alcohol **255** with *anti*-selectivity to generate the diol **256** in 91% yield and good de (Scheme 4.5).[180]

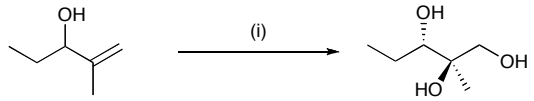


255 **256**

Reagents and conditions: (i) OsO_4 cat., NMO, Acetone-H_2O (20:1), RT, 3 days, (91 % yield).

Scheme 4.5: Dihydroxylation of 1,1-disubstituted system **255**

Similarly, Donohoe described that dihydroxylation of O-*H* allylic alcohol **257** occurs with good (*anti*)-selectivity to afford triol **258** in 80% de.[181]

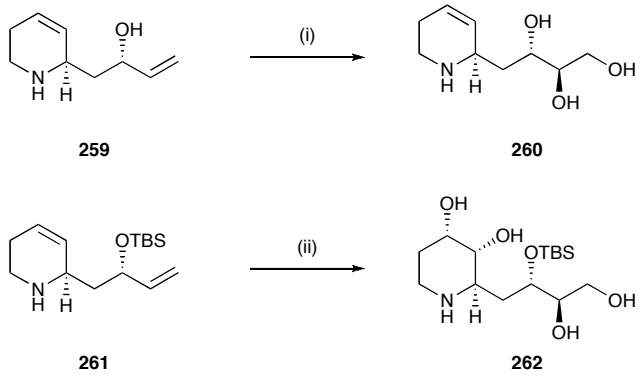


257 **258**

Reagents and conditions: (i) OsO_4 cat., NMO, Acetone-H_2O (8:1), RT, (71 % yield) 80% de.

Scheme 4.6: Dihydroxylation of allylic alcohol **257**

There are several examples in the literature of the dihydroxylation of acrolein derived allylic systems.[169,181] Blechert has demonstrated the osmium catalysed dihydroxylation reaction of the free allylic alcohol **259** was shown to proceed in 70% de in favour of the *anti*-addition product, with the silyl protected species **261** also proceeding with (*anti*)-selectivity in a reduced 50% de.[182]



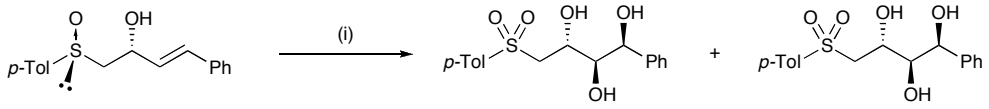
259 **260**

261 **262**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO (1.0 equiv), Acetone-H_2O (1:1), 0 °C to RT, (70 % de); (ii) OsO_4 (10 mol%), NMO (2.5 equiv), Acetone-H_2O (1:1), 0 °C to RT, (50 % de).

Scheme 4.7: Dihydroxylation of acrolein derived allylic systems **259** and **261**.

Surprisingly there are no reports in the literature on the dihydroxylation of *O*-silyl protected *trans*-allylic alcohols, however there are numerous publications focussed around the osmylation of their corresponding free allylic alcohols.[169,183,184] For example, Solladié *et al* have previously reported the dihydroxylation of a chiral allylic-β-hydroxysulphoxide **263** which gave trihydroxysulphones **264** and **265** in moderate 50 % de in favour of the (*anti*)-diol **264**.[183]



263 **264** **265**

Reagents and conditions: (i) OsO_4 (10 mol%), TMO, Acetone-H_2O

Scheme 4.8: Dihydroxylation of chiral allylic-β-hydroxysulfoxide **263**.

Several models have been proposed to rationalise the observed *anti*-diastereoselectivity for both *O*-silyl-protected and free *O*-H allylic systems, most notable being the models described by Kishi, Houk and Vedejs (Figure 4.9).

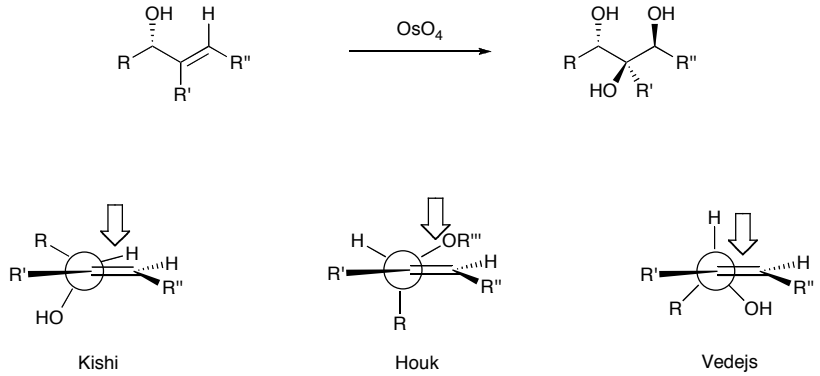


Figure 4.9: Proposed models to rationalise the *anti* stereoselectivity of the osmylation reaction.

The Kishi empirical rule is based on minimisation of 1,3-allylic strain. By positioning the hydrogen atom H_A *syn*-periplanar to the alkenyl functionality then $A^{1,3}$ strain is minimised (Figure 4.10).[185,186] It is proposed that the oxidant then approaches from the opposite face to the electron rich oxygen group (i.e. minimising the electrostatic repulsions between the oxygen functionality of the allylic alcohol and osmium reagent). As such **TS1** is the favoured transition state whose reaction proceeds with *anti*-stereocontrol.

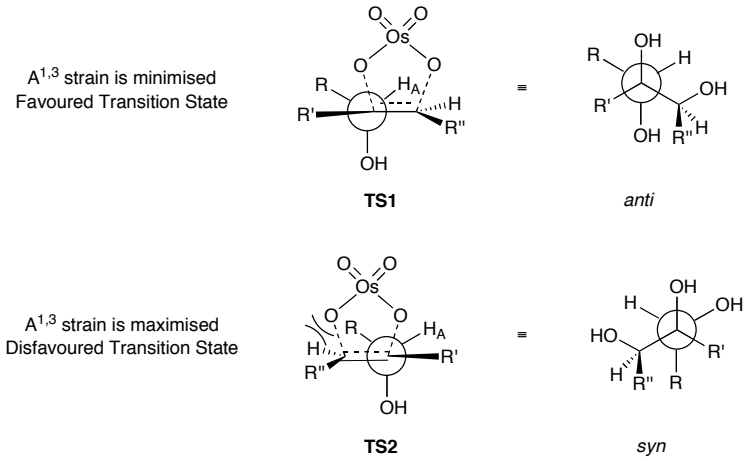


Figure 4.10: Kishi's model to rationalise the stereoselectivity for osmium catalysed dihydroxylation of allylic systems.

However, Kishi's model does not always corroborate experimental data. Evans described the dihydroxylation of several allylic systems, where increasing the size of the R-alcohol substituent resulted in an increase in stereocontrol rather than a decrease as Kishi's model would infer.[170]

Evans observed that his results better fitted the Houk and Vedej models. The Houk model is an extension of his work on the "inside alkoxy effect," which was developed to rationalise the stereochemical outcome of nitrile oxide cycloaddition reactions of related allylic alcohol systems.[187] Houk used *ab initio* calculations to show that **TS3** which positions the hydroxyl functionality in an *inside* conformation (Figure 4.11), was lower in energy than the alternative **TS4**, thus predicting *anti*-stereoselectivity in the dihydroxylation reaction.[188,189]

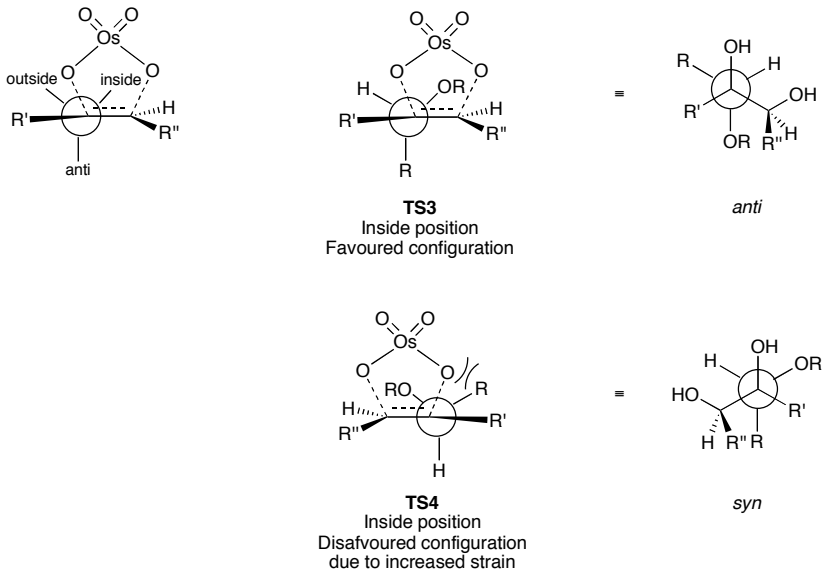


Figure 4.11: Houk model proposed for the protected and *O*-H allylic alcohol systems.

The Vedejs model rationalises the observed stereochemical outcome by considering the steric implications of the positions of the alkenyl and allylic substituents that are propagated into the osmate ester transition state. [190,191] As such, the smallest hydrogen substituent is arranged parallel to the region of greatest congestion in the transition state, i.e. the hydrogen is on the same face as the direction of attack of the osmium tetroxide, thus minimising steric hindrance with the remaining groups positioned on the opposing side. The C-O bond is directed towards the 'inside position' of the double bond as in the Houk model. Consequently, the Vedejs model also predicts an *anti* addition of osmium tetroxide across the allylic system.

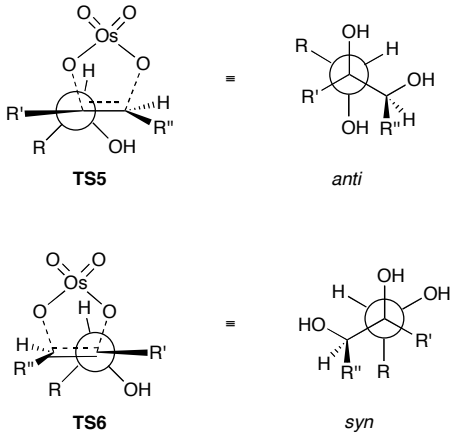
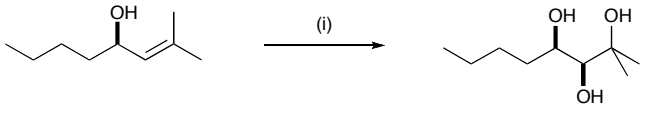


Figure 4.12: Model proposed by Vedejs to rationalise the stereoselectivity for dihydroxylation of allylic alcohols.

4.4.2 *syn*-Dihydroxylation

Both Evans and Donohoe have shown that both the Vedejs and Houk models are consistent with the observed stereochemical trends for *anti*-dihydroxylation of *O*-H 1,1-disubstituted and *trans*-1,2-allylic systems.[169,170]

However, Donohoe has shown that this is not the case for allylic alcohol systems containing *cis*-allylic substituents. For example, treatment of 2,2-disubstituted allylic system **266** under UpJohn dihydroxylation conditions gave a 2:1 mixture of diastereomers in favours of its *syn*-triol **267**.[169]



266 **267**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Scheme 4.9: Dihydroxylation 1,2,2-trisubstituted allylic alcohol **266**.

All of the previous examples in Section 4.4.3 have shown that both the Vedejs and Houk models can be used to explain the observed stereochemical trends for the dihydroxylation of *O*-H 1,1-disubstituted, monosubstituted and *trans*-1,2-allylic systems.[169,170] However, these models fail when considering *cis*-substituent. A modification of Kishi's model can be used to rationalise the observed inversion in stereoselectivity for alkenes containing *cis* substituents, although it requires that the oxidant must now add from the same face as the free hydroxyl group (Figure Figure 4.13).[169,170,189] The stereoselectivity of *cis*-systems is further enhanced when R is particularly bulky and when the alcohol is unprotected, because steric effects now dominate addition to the hydroxyl face.

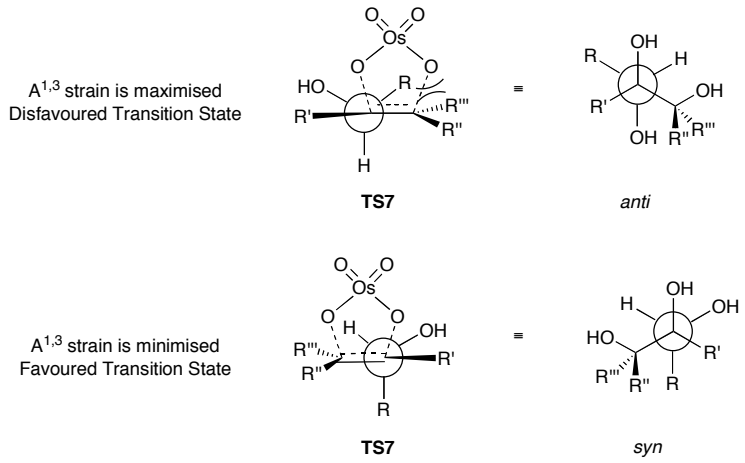
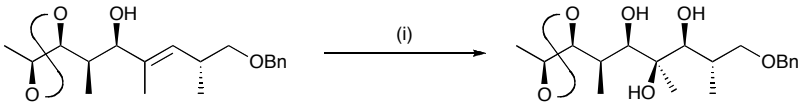


Figure 4.13: Kishi's model to predict the *syn*-selectivity for systems containing a *cis*-substituent.

4.4.3 1,1,2-Disubstituted allylic systems

The literature precedent for dihydroxylation of 1,1,2-trisubtituted allylic alcohols is limited, Chakraborty reported that dihydroxylation of allylic alcohol **268** proceeds with *syn*-selectivity to yield triol **269**.[192]

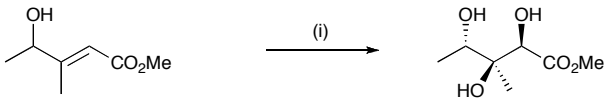


268 **269**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO (1.0 equiv), Acetone-H_2O (20:1), 12 h, 84%.

Scheme 4.10: Dihydroxylation of 1,1,2-trisubstituted allylic alcohol **268**.

However, Evans has shown that treatment of the trisubstituted allylic alcohol methyl ester **270** proceeds with *anti*-selectivity in >95% de.[170]



270 **271**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO (1.0 equiv), Acetone-H_2O (1:1)

Scheme 4.11: Dihydroxylation of 1,1,2-trisubstituted allylic alcohol **270**.

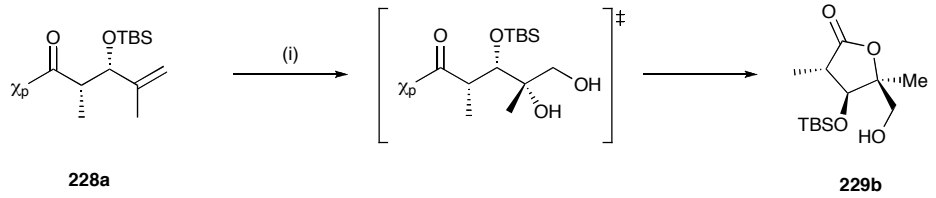
The previously discussed 1,1-disubstituted and (*E*)-1,2-disubstituted systems were shown to proceed with an overall *anti*-selectivity. From these observations (Section 4.4.1), it would be expected that (*E*)-1,1,2-trisubstituted systems would also proceed with an overall *anti*-dihydroxylation, and this would indeed fit with the previously discussed Houk model. However, the report of *syn*-selectivity by Chakraborty did leave some doubts about the stereochemical outcome of these dihydroxylation reactions.

4.5 Comparison of data

With the selectivity of each allylic system established it is now time to return to the stereochemical assignments of the lactones reported by Dias and co-workers. As we have established, it should be noted that selectivity of dihydroxylation is not significantly altered by the presence of an *O*-silyl protecting group, and that unprotected allylic alcohols generally afford higher levels of diastereocontrol. Therefore, it was decided to run all subsequent dihydroxylation reactions upon the free allylic alcohols systems, thus limiting the need to carry out unnecessary protection/deprotection steps and maximising the chances of obtaining high de's.

4.5.1 1,1-Disubstituted alkenyl systems

Dias reported that methacrolein derived *O*-silyl-*syn*-aldol **228a** undergoes catalytic dihydroxylation/lactonisation reaction to yield γ-lactone **229a** in 43% yield and 56% de. As already discussed, they implied that the dihydroxylation proceeds with *syn*-selectivity generating a (*S*)-geometry at C_5 of lactone **229a** (Scheme 4.14).

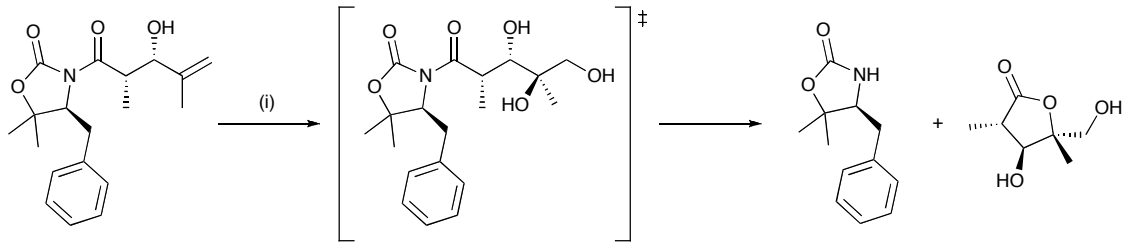


228a **229b**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Figure 4.14: Proposed dihydroxylation/lactonisation of 1,1-disubstituted alkenyl systems

We had already demonstrated that dihydroxylation of ethacrolein derived aldol **163c** afforded a (*5R*)-lactone **240c**, and as a consequence were certain that Dias' (5*S*)-stereochemical assignment of *O*-silyl-lactone **229b** was incorrect. In order to verify this, it was decided to apply the dihydroxylation reaction to the unprotected methacrolein derived *syn*-aldol **163b**. Therefore, treatment of methacrolein derived *syn*-aldol **163b** with 10 mol% osmium tetroxide and *N*-methylmorpholine-*N*-oxide yielded the γ-lactone **229b** in 75% yield and 90% de (Scheme 4.12).



163b **157** (3*S*,4*S*,5*R*)-**240b**
75 %, de = >90 %

Reagents and conditions: (i) OsO_4 cat., NMO, Acetone-H_2O (8:1), RT.

Scheme 4.12: Dihydroxylation/lactonisation of methacrolein derived aldol **163b**.

Comparison of the ^{1}H NMR spectra of the previously prepared (5*S*)-lactone **181b** (See Chapter 3) indicated that the dihydroxylation/lactonisation reaction does not yield the same lactone as generated in our epoxidation/lactonisation protocol, and consequently must have a (5*R*)-

configuration. As such the lactone generated in the dihydroxylation procedure was assigned as (3*S*,4*S*,5*R*)-**240b**, which was confirmed by examination of its NOE spectra. This showed a strong interaction between the methyl substituent of C_5 interacting with the C_3 proton, with the C_5 CH_2OH methylene resonance interacting strongly with the C_3 methyl functionality and the C_4 hydrogen. This confirms the syn relationship of these functionalities, thus providing further evidence of its (5*R*) stereochemistry.

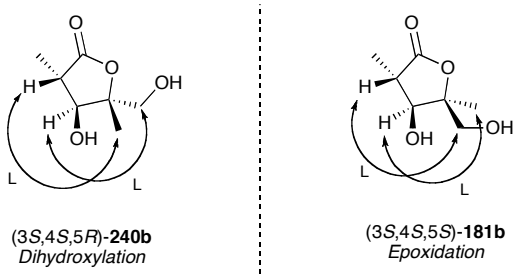
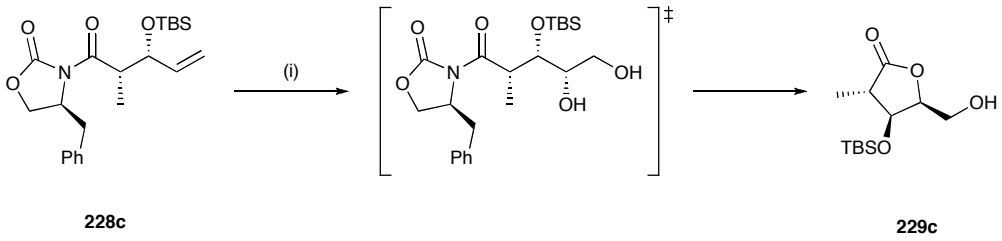


Figure 4.15: Key observed NOE interactions of both epoxidation and dihydroxylation strategies.

4.5.2 Acrolein derivative

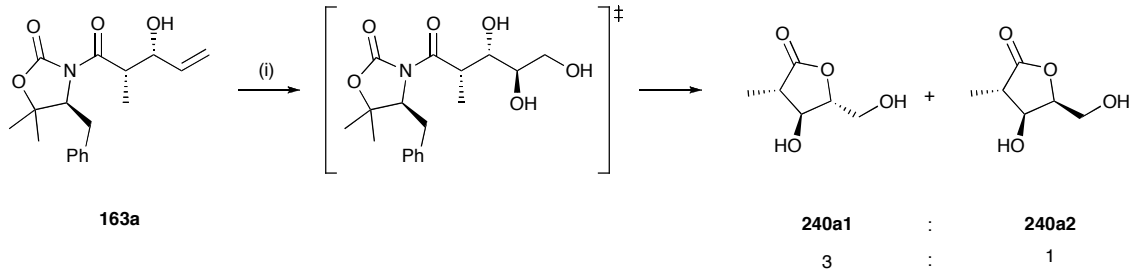
Dias reported that acrolein derived *O*-silyl-*syn*-aldol **228c** undergoes a catalytic dihydroxylation/lactonisation reaction to yield γ-lactone **229c** in 42 % yield and 80 % de (Scheme 4.14). As already discussed, Dias inferred that the dihydroxylation proceeds with a *syn*-selectivity generating an (*S*) geometry at C_5, which is opposite to the (*anti*)-stereoselectivity reported in the literature for dihydroxylation of this class of substrate.



Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Scheme 4.13: Proposed dihydroxylation/lactonisation of acrolein derived aldol **228c**.

Unsaturated aldol product **163a** was treated with osmium tetroxide (10 mol%), *N*-methylmorpholine-*N*-oxide with 8:1 mixture of acetone/H_2O, and left to stir for forty-eight hours. ^{1}H NMR spectroscopic analysis showed that the desired γ-lactone had been formed as a mixture of diastereomers **240a1** and **240a2** in a 3:1 ratio.



Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1), major diastereomer shown.

Scheme 4.14: Catalytic osmium dihydroxylation lactonisation mechanism of acrolein derived *syn*-aldol **163a**.

Attempts to purify the diastereomers proved unsuccessful; as such the structures and diastereoselectivity were assigned from the mixture of diastereomers using ^{1}H NMR, ^{13}C NMR, COSY spectroscopy and NOE spectroscopy, which allowed for complete elucidation of their stereochemistry.

The (*anti*)-diastereoselectivity reported for this class of allylic alcohol predicts that the major diastereomer should be (3*S*,4*S*,5*R*)-**240a1**, which was confirmed from our NOE analysis. Therefore, the C_3-proton of the major lactone **240a1** was shown to strongly interact with the C_5 proton, whilst its C_4 proton, was found to strongly interact with the C_5 CH_2OH methylene protons. In turn, the minor diastereomer was assigned as (3*S*,4*S*,5*S*)-**240a2** which was confirmed by the presence of a large interaction between its C_3 proton and its C_5 CH_2OH methylene protons.

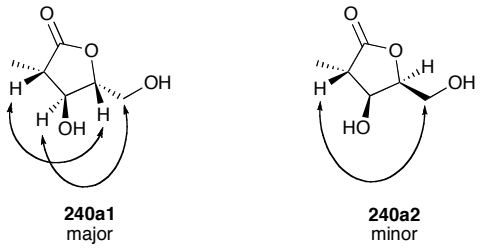
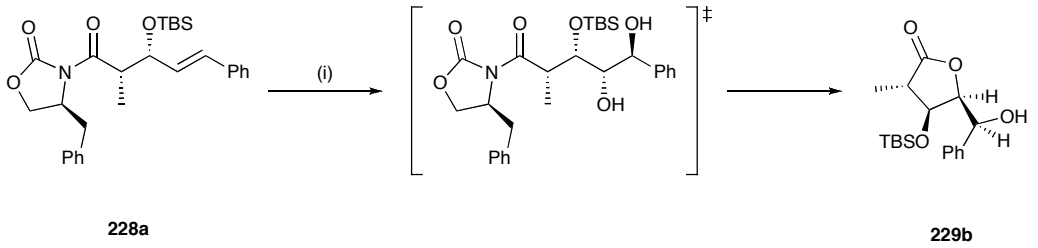


Figure 4.16: Observed stereo-defining NOE interactions

As such this confirms that although this dihydroxylation reaction proceeds with a limited stereocontrol, the predominant facial selectivity is consistent with literature precedent, showing that dihydroxylation proceeds with *anti*-selectivity and not with *syn*-selectivity as reported by Dias *et al*.

4.5.3 *trans*-Alkenyl systems

We then considered the facial selectivity of the dihydroxylation reaction of aldol **228b,** which Dias had reported proceeds to afford lactone **229b**, whose formation would have required a *trans*-dihydroxylation reaction to occur!

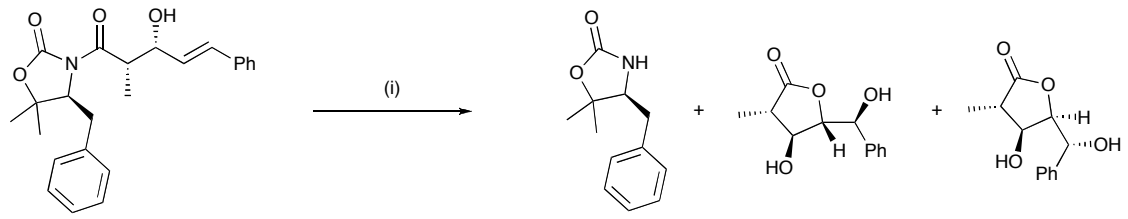


228a **229b**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Scheme 4.15: Dias' proposed dihydroxylation lactonisation of *trans*-cinnamaldehyde derived *syn*-aldol **229b**.

In order to investigate the diastereoselectivity of this substitution pattern, cinnamaldehyde derived aldol product **163g** was treated under the catalytic dihydroxylation/lactonisation conditions, after 48 hours to afford a 9:1 ratio of lactones **240g1** and **240g2** respectively.



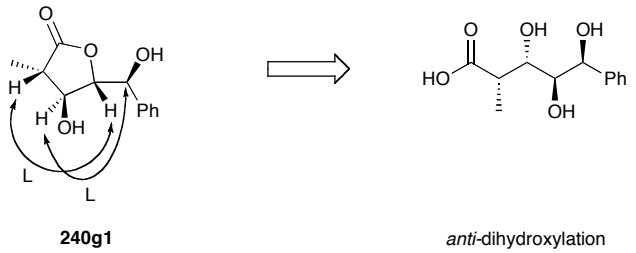
163g **157** **240g1** major **240g2** minor

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1), 80 % de.

Scheme 4.16: Dihydroxylation of cinnamaldehyde derived aldol **163g** to lactones **240g1** and **240g2**.

The major diastereomer was isolated using column chromatography and the stereochemistry was assigned from the '*anti*'-stereoselectivity predicted for this class of substrate and confirmed *via* NOE spectroscopy. Its NOE spectra indicated that the C_3-proton interacts strongly with the C_5-proton, whilst the C_4 proton interacts strongly with both the C_3 methyl group and the C_5 *H*C(OH)Ph, thus indicating a *syn* relationship between these substituents. The stereochemistry of the major diastereomeric lactone was therefore inferred as (3*S*,4*S*,5*S*)-**240g1**, which is

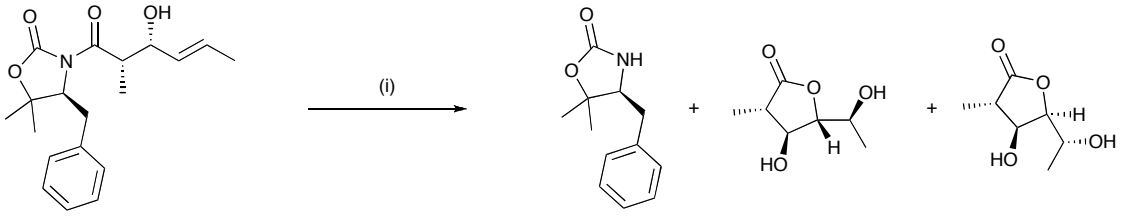
consistent with the osmylation reaction proceeding with *anti*-selectivity to the hydroxyl functionality, as previously established from literature precedent.[169,183]



240g1 *anti*-dihydroxylation

Figure 4.17: - Major lactone product **240g1**, with observed NOE interactions.

In relation to this, a *trans*-crotonaldehyde derived aldol **163f** was also treated under catalytic UpJohn dihydroxylation conditions. The resulting lactone products were inseparable from one another, however analysis of the ^{1}H NMR and COSY spectra of the resultant diastereoisomers allowed for a complete analysis and determination of their structure. Once again, NOE spectroscopic analysis indicated that *anti*-dihydroxylation had occurred to afford (3*S*,4*S*,5*S*)-lactone **240f1** as the major diastereomer.



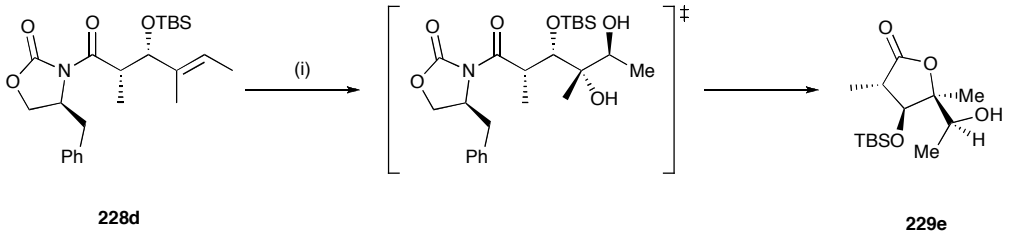
163f **157** **240f1** major **240f2** minor

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1), 67 % de.

Scheme 4.17: Dihydroxylation of crotonaldehyde derived aldol **163f** to the inseparable mixture of lactones **240f1** and **240f2**.

4.5.4 1,1,2-trisubstituted systems

We then investigated the diastereoselectivity of dihydroxylation of *O*-TBS-aldol **228d**, which Dias had once again reported as a product of '*trans*'-dihydroxylation to afford lactone **229d**.

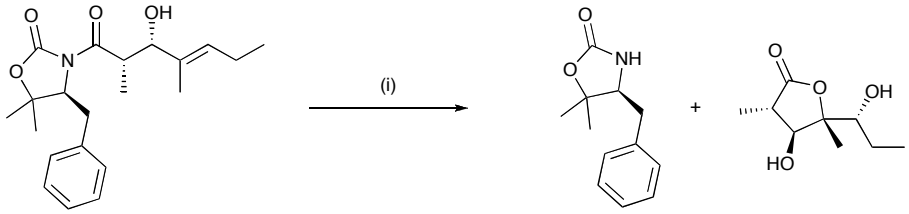


228d **229e**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1).

Figure 4.18: Proposed dihydroxylation/lactonisation of trisubstituted alkenyl system.

Unsaturated aldol **163i** was treated with osmium tetroxide, *N*-methylmorpholine-*N*-oxide in acetone/water (8:1), to give hydroxy-γ-butyrolactone **240i** in >95 % de.



163i **157** **240i**

Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1), 88% yield, >95 % de.

Scheme 4.18: - Dihydroxylation/lactonisation of trisubstituted alkene **163i** yielding γ-butyrolactone **240i**.

The observed high diastereoselectivity is consistent with that previously discussed for (*anti*)-dihydroxylation reactions of similar 1,1-disubstituted alkene systems (Figure 4.19). NOE spectroscopy indicated that the proton on C_3 strongly interacts with both the C_5 methyl group and the C_3 hydroxy functionality, whilst the C_3 methyl group was shown to interact with the C_5 C*H*-OH substituent, thus confirming the (5*R*) stereochemistry. Therefore, given the *syn*-dihydroxylation mechanisms we are able to infer that the configuration of the newly formed C_6 stereocentre is also (*R*).

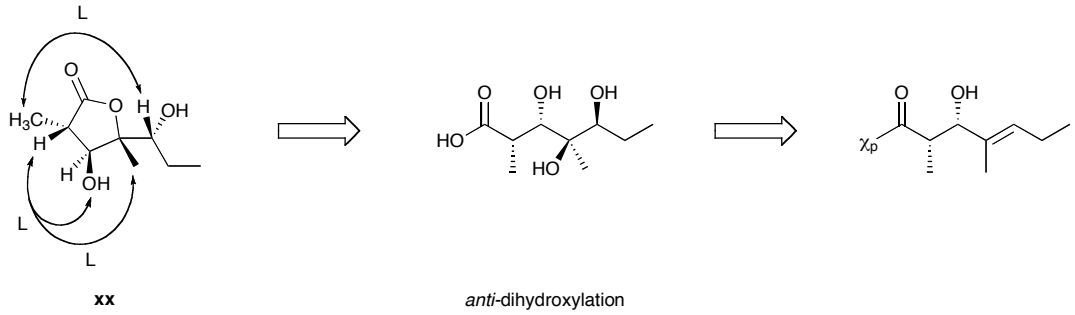
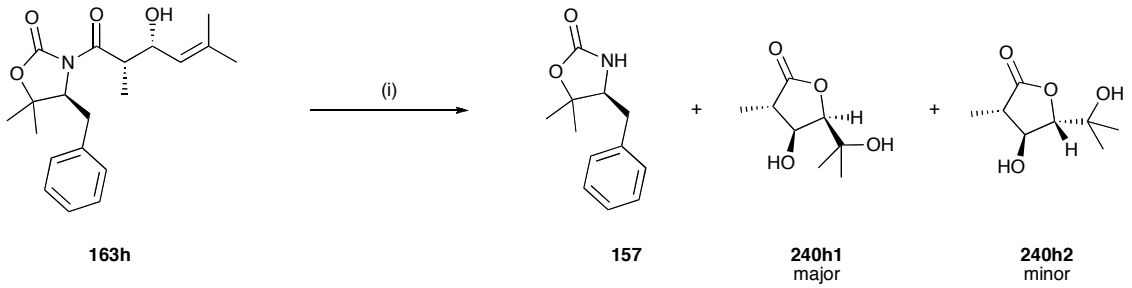


Figure 4.19: Observed key interactions.

4.5.5 *cis*-Alkenyl systems

Although Dias had not reported dihydroxylation of an aldol substrate with a *cis*-alkene substituent, it was decided to investigate dihydroxylation of 2,2-disubstituted aldol **163h**, which generated a 2:1 mixture of lactones **240h1** and **240h2** under standard dihydroxylation conditions. This observation was consistent with the poor selectivity previously observed by Donohoe for the dihydroxylation of related allylic systems.[169]



Reagents and conditions: (i) OsO_4 (10 mol%), NMO, Acetone-H_2O (8:1), 67 % de.

Scheme 4.19: Dihydroxylation of crotonaldehyde derived aldol **163h** to afford a mixture of lactones **240h1** and **240h1**.

The two diastereomers were readily separated *via* column chromatography. Analysis of the NOE spectra indicated that the major diastereomer was the product of a *syn* dihydroxylation reaction, which is consistent with Donohoe's observations on simple allylic systems (See Scheme 4.9). This was confirmed from the strong NOE between its C_3 methyl group and the C_5 hydrogen indicating the *syn* relationship of these functionalities, which implies a (5*R*) configuration. Minor diastereomer **240h2** was also isolated; with analysis of its NOE spectra indicating a large interaction between its C_3 hydrogen and C_5 hydrogen indicating a *syn* relationship, which is consistent with its expected (5*S*) geometry.

Furthermore, comparison of the ^3J coupling constants of the vicinal C_4 and C_5 protons of these lactones is consistent with their stereochemical assignments; the $^3J_{4,5}$ = 7.4 Hz observed for the major (3*S*,4*S*,5*R*)-diastereomer **240h1** is consistent with a *syn* relationship, whereas a smaller $^3J_{4,5}$ = 4.0Hz was observed for the minor product (3*S*,4*S*,5*S*)-**240h2** and indicative of an *anti* configuration.

It is worthy to note that the minor diastereomer (3*S*,4*S*,5*S*)-**240h2** is equivalent to the lactone product generated from our epoxidation/lactonisation protocol (See Chapter 3) as confirmed from comparison of their identical spectroscopic data.

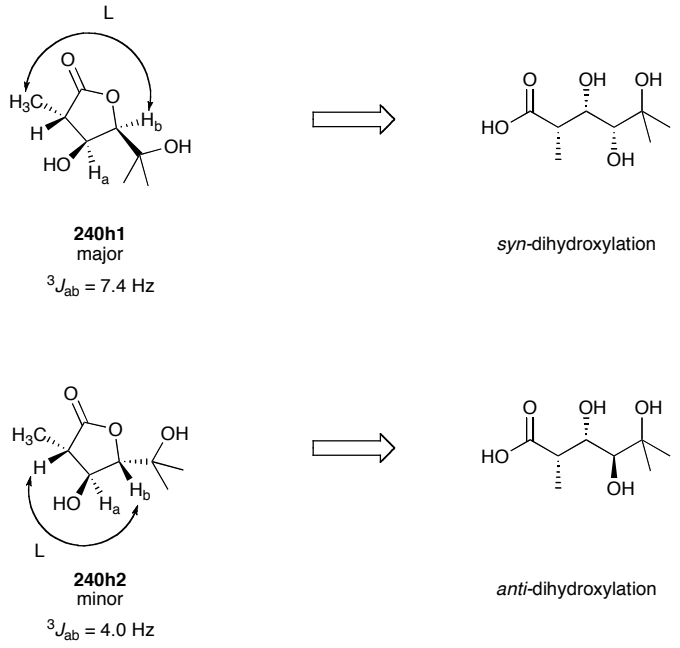
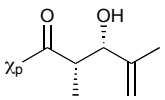
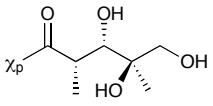
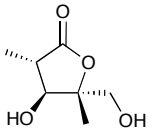
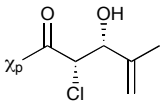
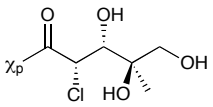
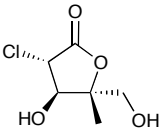
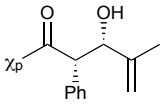
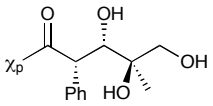
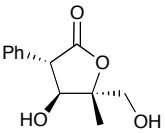
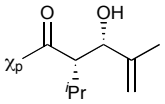
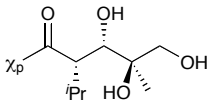
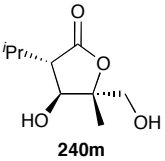
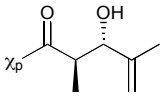
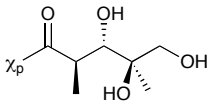
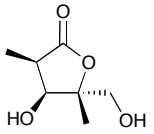


Figure 4.20: Consideration of both major and minor product of the 1,2,2-trisubstituted unsaturated aldol **163h**.

4.5.6 Effect of the α-substituent

Since it was known that the selectivity of osmylation/lactonisation reaction was not only affected by the substitution pattern of its alkene, but also affected by the steric demand of its allylic substituents, it was decided to investigate what effect varying the nature of the α-substituent might have on the dihydroxylation reaction. As such a range of methacrolein derived aldol products **163b** and **163k-n** containing different α-substituents were synthesised in >70 % yield and >95 % de using our standard boron aldol protocol (See Table 4.2).

Entry	*Aldol*	*Yield (%)* [a]	*Major Triol (Not isolated)*	*Major Lactone* [b]	*Yield (%)* [a]	*de (%)* [c]
1	 **163b**	81 [d]		 **240b**	75	90
2	 **163k**	74 [e]		 **240k**	76	82
3	 **163l**	82 [d]		 **240l**	75	80
4	 **163m**	75 [d]		 **240m**	30	8
5	 **163n**	62 [f]		 **240n**	80	85

[a] Percentage yield after column chromatography; [b] Stereochemistry of lactone structures was confirmed by NOESY analysis and used to infer the facial selectivity of the dihydroxylation reaction; [c] Determined from ^{1}H NMR spectra of crude reaction product; [d] Prepared using standard boron mediated aldol conditions (General Procedure 2); [e] Prepared using a modified boron mediated aldol (General Procedure 3); [f] Prepared using Magnesium catalysed non-Evans' *anti*-aldol conditions (General Procedure 4).

Table 4.2: Preparation and dihydroxylation of aldols **163k-n** to afford γ-butyro-lactones **240k-n**.

Each aldol substrate was then subjected to our standard osmylation/lactonisation conditions over 48 hours. It is worthy to note for the α-methyl derivative **163b** a slight decrease in reaction selectivity is observed when compared to the ethacrolein equivalent **163c**, which further demonstrates the dependence of dihydroxylation stereocontrol on the size of the alkenyl substituents.

Syn-Aldols **163b, 163k-l** and *anti*-aldol **164n** were shown to consistently generate the predicted *anti*-dihydroxylation products in reasonable diastereocontrol with only slight variations in the diastereoisomeric excesses observed. Therefore, it is interesting to note that for these cases inversion of the configuration of the α-stereocentre appears to have little effect on the diastereoselectivity of the dihydroxylation/lactonisation reaction.

However, the diastereoselectivity of the dihydroxylation/lactonisation reaction of α-isopropyl-derivative **163** was vastly inferior to that observed previously, proceeding in only 8% de. It is clear that the increased steric bulk of the α-isopropyl substituent is responsible for this reduced diastereoselectivity, which may be rationalised by consideration of the Houk model (Figure 4.21). Therefore, in this case the methyl substituent of the α-isopropyl-substituent can arrange itself in close proximity to either face of the alkene, thus equally hindering attack to the (*Re*)- and (*Si*)- faces resulting in poor de in the dihydroxylation reaction.

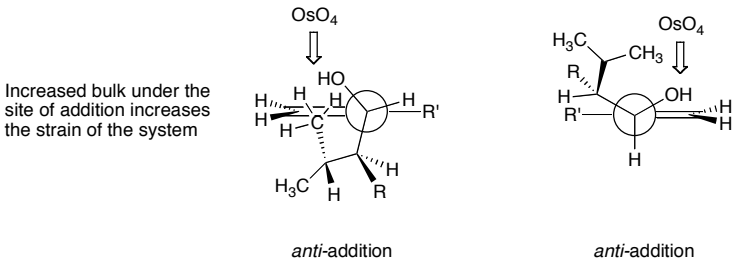
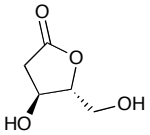


Figure 4.21: Models to rationalised the reduced selectivity in the presence of an α-isopropyl functionality.

4.6 Synthesis of 2- deoxyribonolactone

Hydroxy-γ-butyrolactones are widely observed in Nature and are often derived from the corresponding sugars. One such example is 2-deoxyribonolactone **272**, which is a by-product of oxidatively damaged DNA. DNA damage can be readily induced by a number of exogenous agents, including free radicals, UV light, and ionizing radiations and can lead to cellular death by apoptosis.[193] In the case of oxidatively damaged DNA, reactions involving reactive oxygen species are an unavoidable consequence of respiration.[194]



272

Specifically, reactive oxygen species lead to oxidative damage of the nucleobase and deoxyribose moieties of nucleotides in the DNA helix. A 2-deoxyribonolactone **272** lesion is then generated as a result of oxidation of the C1'-carbon-hydrogen bond (See Figure 4.22).

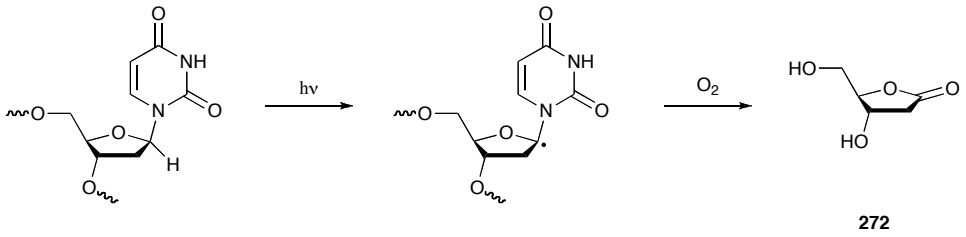
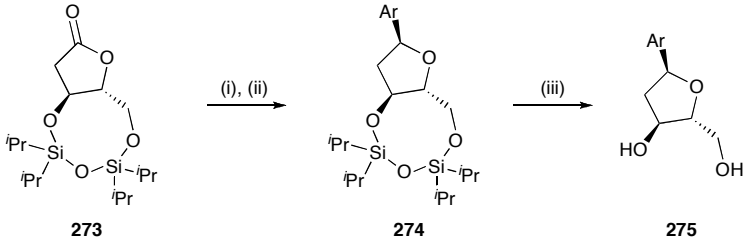


Figure 4.22: Oxidative degradation of the deoxyribose sugar backbone of the DNA helix.

2-Deoxyribonolactone **272** is also a practical synthetic precursor. Woski demonstrated that 2-deoxyribonolactone derivative **273** can be readily converted in two steps to 1,2-dideoxy-1-β-aryl-D-ribanose derivatives **275** (Scheme 4.21).[195] These nucleoside derivatives are also of structural interest because they can potentially act as universal bases and as non-hydrogen bonding isosteres of natural nucleobases in chemical biology applications.



Reagents and conditions: (i) ArLi, THF, -78 °C; (ii) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C; (iii) TBAF, THF

Scheme 4.20: Synthesis of 1,2-dideoxy-1-β-aryl-D-ribanose derivatives **275** from deoxyribonolactone derivative **273**.

The range of biological application and synthetic versatility make deoxysugar-derived lactones of particular interest as synthetic targets. Therefore, it was decided to apply our osmylation/lactonisation strategy to the synthesis of 2-deoxy-D-ribonolactone. It was proposed that deoxyribonolactone **272** could be readily accessed *via* osmylation/lactonisation of the simple acrolein derived unsaturated aldol **273** (Figure 4.23). The direct synthesis of Evans' oxazolidin-2-one derived aldol products with no α-substituent is problematic, because the diastereoselectivity of their aldol reactions are much reduced. However, compounds of this type can be readily accessed from aldol reactions of the corresponding 2-chloroacetyl derived aldol **274**. Treatment of **241b** under modified aldol conditions was predicted to afford an α-chloro-*syn*-aldol **274** with good diastereoselectivity. Subsequent dechlorination would result in

reductive elimination of the chlorine atom to yield the desired aldol **275**, which would then be subjected to out dihydroxylation/lactonisation conditions to afford γ-lactone **272**.[196]

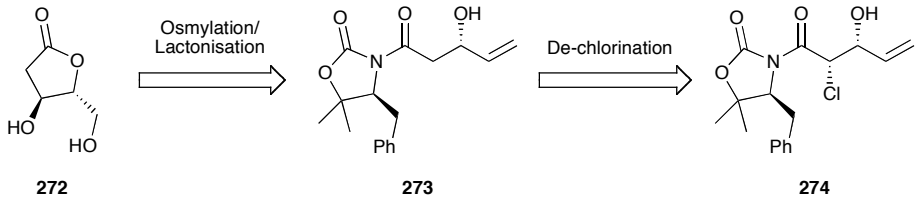
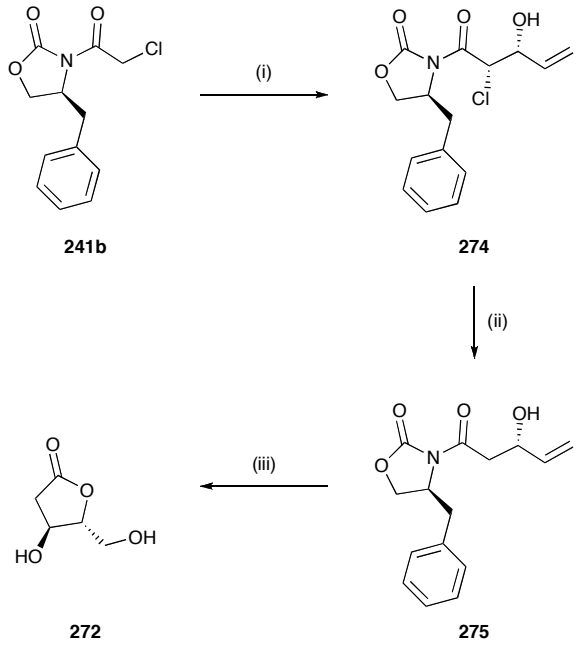


Figure 4.23: Retrosynthesis of 2-deoxyribonolactone *via* osmylation/lactonisation



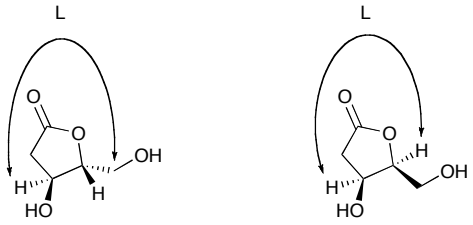
Reagents and conditions: (i) 9-BBN-OTf, DIPEA, CH_2Cl_2, -78 °C to RT, then acrolein -78 °C to RT, 24 hr, 57 % yield, > 95 % de; (ii) Zn (s), NH_4Cl, MeOH, 90 % yield; (iii) OsO_4, NMO, Acetone/H_2O (8:1), 48 hr, 82 % yield, 50 % de.

Scheme 4.21: Attempted synthesis of 2-deoxyribonolactone.

Treatment of 2-chloroacetylated oxazolidin-2-one **241b** under our modified boron mediated aldol conditions generated the *syn*-aldol **274** in 57% yield and >95% de. Subsequent treatment of the α-chloro-β-vinyl-aldol **274** with zinc dust and ammonium chloride in methanol readily eliminated the chlorine to generate the corresponding unsubstituted aldol product **275**.

Treatment of unsaturated aldol **275** under UpJohn conditions (Osmium tetroxide, *N*-methylmorpholine-*N*-oxide, acetone/water (8:1)) resulted in the expected dihydroxylation/lactonisation reaction to afford a mixture of 2-deoxy-γ-lactones **272a** and **172b**

in 50% de with no enrichment of either diastereomer in any eluted fractions. However, repeated separation of the diastereomers using column chromatography proved unsuccessful. Nevertheless, full analysis of the purified lactone mixture using ^{1}H NMR, ^{13}C NMR, COSY and NOE spectroscopy allowed for complete elucidation of the two lactone diastereomers **272a** and **272b**.



272a major

272b minor

Figure 4.24: Observed stereodefining NOE interactions of **272a** and **272b**.

This mixture of diastereomeric γ-lactones is currently being subjected to preparative HPLC chromatography to obtain a pure sample of 2-deoxyribinlactone.

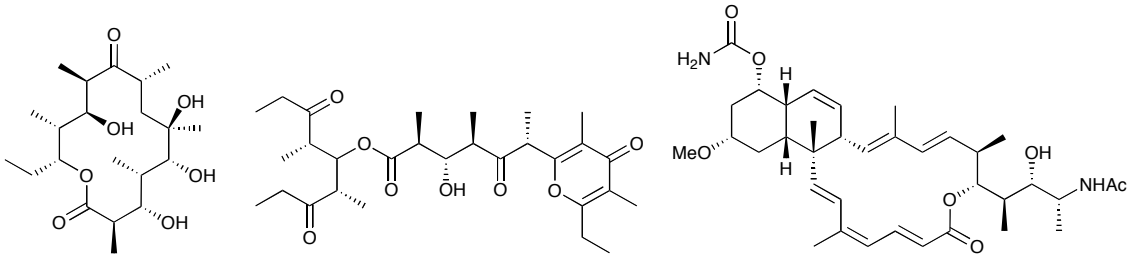
4.7 Conclusions

In conclusion, we have demonstrated the use of an osmylation/lactonisation strategy to access complimentary hydroxy-butyrolactones to those generated by epoxidation/lactonisation of unsaturated aldol products. It has been shown that, for 1,1-disubstituted, monosubstituted and 1,2-disubstituted-*trans*-alkenyl systems, that the osmylation/lactonisation reaction proceeds with *anti*-selectivity. This is consistent with the literature for simple allylic alcohol systems which have been shown to proceed with comparable levels of stereocontrol.[169,170] We have shown that Dias' literature precedent for osmylation/lactonisation of related β-vinyl-*syn*-aldol systems was flawed; however, in their defence it should be noted that assignment of stereochemistry for γ-lactone systems is notoriously problematic.[152] This dihydroxylation methodology was subsequently applied to the synthesis of 2-deoxyribonolactone **272** in moderate de.

Chapter 5: An efficient asymmetric synthesis of polypropionate precursors

5.1 Polypropionates

Polypropionate chains are structural motifs that often contain a large number of alternating vicinal stereogenic methyl and hydroxy groups that decorate an aliphatic backbone.[197] This important class of compounds form the skeleton of a wide range of important pharmaceutical compounds that can exhibit a wide range of chemotherapeutic activity. For example, erythronolide B **276** (antibacterial),[198] (-)-baconipyrone **277** (antimicrobial and cytotoxicity)[199] and (+)-superstolide A **278** (cytotoxic against several cancer cell lines) all represent potentially important medicinal agents for the treatment of disease.[200]



276
Erythronolide B

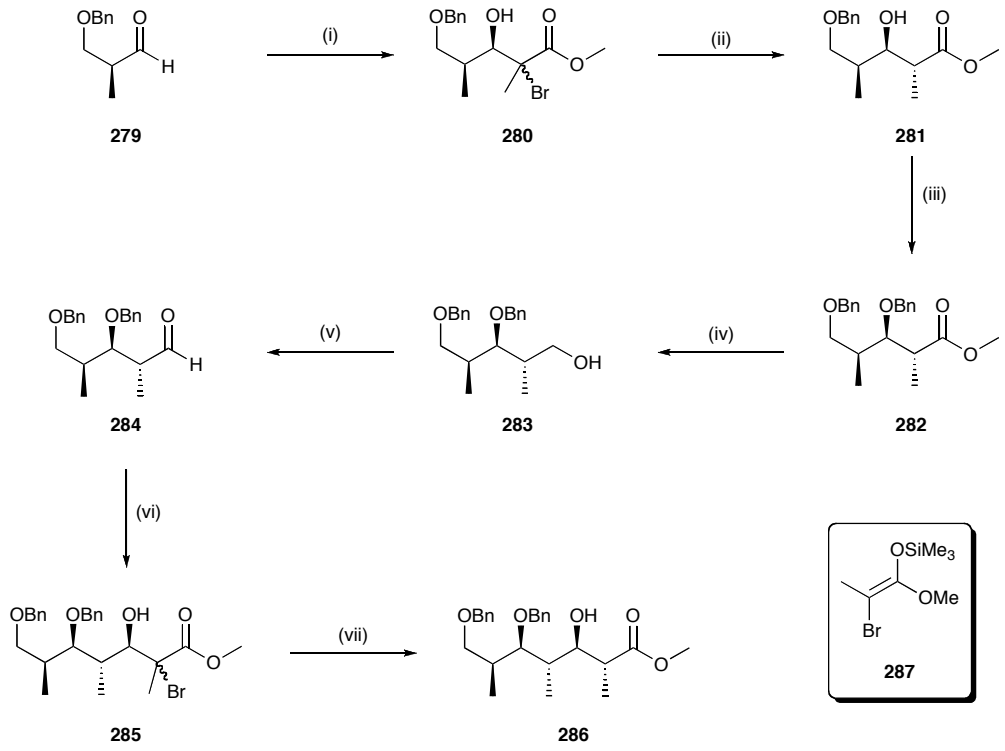
277
(-)-Baconipyrone C

278
(+)-Superstolide A

Figure 5.1: Examples of biologically active natural products containing polypropionate subunits.

Since their discovery, the development of synthetic methodology for the asymmetric synthesis of polypropionates has attracted the interests of numerous synthetic organic chemists. These stereochemically complex targets contain multiple contiguous stereocentres, often with different relative configurations, and as a consequence they represent a demanding synthetic challenge to even the most skilled synthetic practitioner. There are many strategies that have been developed to access the wide range of polypropionate motifs that exist,[197,200-202] with many approaches being based on the use of iterative aldol methodology. Whilst this approach is often successful in affording stereochemically complex polypropionates it is not particularly efficient since its success often requires a lot of redox manipulation of functional groups and the copious use of protection/deprotection strategies. A representative example of this approach is Guindon's synthesis of a polypropionate stereopentad shown in Scheme 5.1.[202-204] Initially, a Mukaiyama aldolisation reaction of aldehyde **279** and silyl-ketene acetal **287** in the presence of dibutylboron triflate generates **280**, which readily undergoes a free radical hydrogen transfer reaction in the

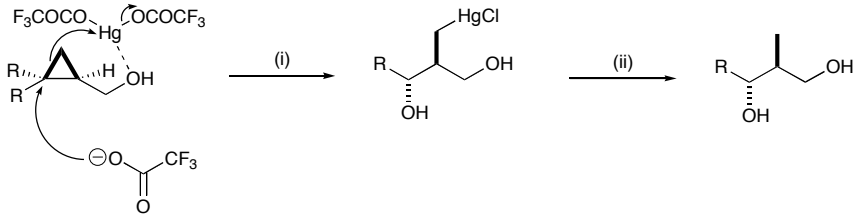
presence of the Lewis acid (triethyl borane) to generate the anti-aldol **281**. Subsequent reduction/oxidation steps generate the chiral aldehyde **284**, which undergoes a further Mukaiyama aldolisation/free radical reduction reaction to access the stereopentad **286**.



Reagents and conditions: (i) **287**, BF_3OEt_2, CH_2Cl_2; (ii) Bu_2BOTf, DIPEA, CH_2Cl_2, -78 °C followed by Bu_3SnH, Et_3B, -78 °C; (iii) $BnOC(NH)CCl_3$, TfOH, CH_2Cl_2; (iv) $LiAlH_4$, THF; (v) Oxalyl chloride, DMSO, CH_2Cl_2, -78 °C; (vi) **287**, $TiCl_3(O^iPr)$, CH_2Cl_2, -78 °C; (vii) Bu_2BOTf, DIPEA, CH_2Cl_2, -78 °C followed by Bu_3SnH, Et_3B, -78 °C.

Scheme 5.1: Guindon's synthesis of stereopentad **286.**

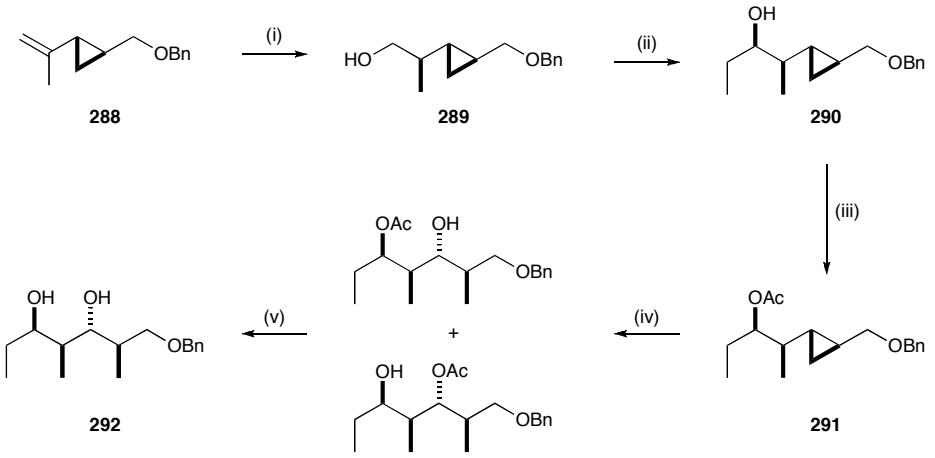
Cossy has developed an alternative strategy to access polypropionates from cyclopropanealkanols using highly regio- and stereo-selective oxymercuration ring-opening reactions of hydroxy-cyclopropanes.[205] Treatment of cyclopropanealkanols with mercuric trifluoroacetate results in coordination of a mercuric species to the hydroxyl functionality and electrophilic coordination to the cyclopropane with concomitant *anti* nucleophilic attack of a trifluroacetate counter-anion at the most electron-rich carbon centre of the cyclopropane ring to generate an organomercurial species. Subsequent hydrolysis in the presence of halide ions followed by radical mediated demercuration reaction results in the formation of a stereodefined 1,3-diol (Figure 5.2).



Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2 then NaCl; (ii) $^nBu_3SnH$, cat. AIBN, THF, RT then 60 °C

Figure 5.2: Oxymercuration/demercuration opening of cyclopropanes to generate polypropionate derivatives.

The application of Cossy's oxymercuration/demercuration strategy has been extended to more complex systems, with stereotriads, stereotetrads and stereopentads having been accessed (Scheme 5.2). For example, hydroboration of 1,1-disubstituted alkene **288** yields the primary alcohol **289** as a diastereomeric mixture, which can be readily purified *via* column chromatography. Subsequent oxidation of its oxygen functionality using TPAP generates an aldehyde, which is immediately treated with ethylmagnesium bromide to furnish a secondary alcohol **290** in 77:23 dr. Acetyl protection of the hydroxyl functionality proceeds in excellent yield with subsequent oxymercuration/demercuration/reduction to furnish the stereotetrad **292** with inversion of stereochemistry at its C_3 stereocentre.

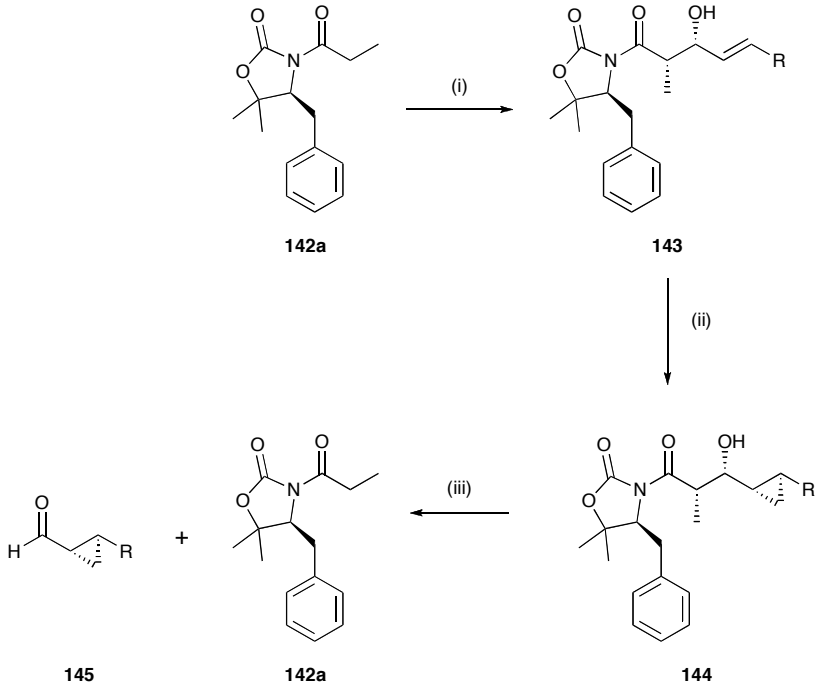


Reagents and conditions: (i) BH_3·THF, THF, -30 °C to RT then NaOH, H_2O_2, 64%, 1:1 dr, separated by column chromatography; (ii) (a) cat. TPAP, NMO, CH_2Cl_2, MeCN, 0 °C to RT; (b) EtMgBr, THF, -30 °C, 77:23 dr separated by column chromatography; (iii) Ac_2O, cat. DMAP, Et_2O, 92%; (iv) (a) $Hg(OCOCF_3)_2$, CH_2Cl_2 then NaCl; (b) $^nBu_3SnH$, cat. AIBN, THF, RT then 60 °C, 65 %; (v) $LiAlH_4$, THF, 80%.

Scheme 5.2: Cossy's multi-step route to access stereotetrad **292**.

Previous work in the Bull group has focussed on using temporary stereocentre methodology for the asymmetric synthesis of chiral cyclopropane carboxaldehydes with high levels of

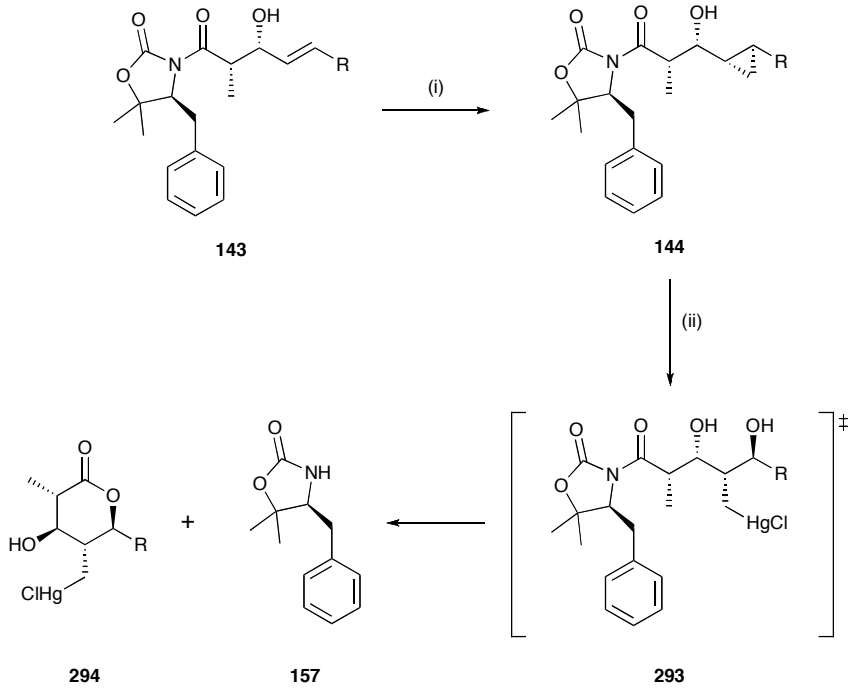
diastereocontrol. Initially, *N*-acyl-oxazolidin-2-one **142a** was treated under standard boron mediated aldol conditions to generate a *syn*-aldol product in high de. Treatment of *syn*-aldol **143** with diethyl zinc and diiodomethane in dichloromethane at –10 °C resulted in a highly diastereoselective cyclopropanation reaction to yield cyclopropyl aldol **144** in 99% yield and > 95% de. Subsequent treatment of cyclopropyl-*syn*-aldol **144** with LHMDS at 0 °C resulted in a clean *retro*-aldol reaction to yield the chiral cyclopropane carboxaldehyde **145**.



Reagents and conditions: (i) (a) 9-BBN-OTf, DIPEA, CH_2Cl_2, 0 °C; (b) α,β-Unsaturated aldehyde, -78 °C to RT; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0 °C; (iii) LHMDS, toluene, 0 °C.

Scheme 5.3: Temporary stereocentre approach for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

Since this methodology had established that a wide range of β-vinyl-*syn*-aldols **143** could be cyclopropanated cleanly with high levels of diastereocontrol,[129] it was proposed that application of Cossy's oxymercuration ring-opening methodology to these substrates could afford organomercurial lactones **294** containing three or more contiguous stereocentres with high levels of diastereocontrol. Subsequent reduction of the organomercurial species would then afford a series of highly functionalised lactones as potential precursors for natural product synthesis.

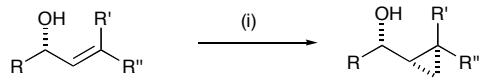


Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 °C to 0 °C; (iii) $Hg(O_2CCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq), RT

Scheme 5.4: Proposed strategy for accessing high functionalised δ-lactones.

5.2 Directed-Cyclopropanation reaction

Cyclopropanes have been widely reported in the literature as compounds that can readily undergo ring opening reactions of use in organic synthesis.[206] The cyclopropane moiety is found in numerous natural products,[207,208] a number of which display interesting properties when compared to conventional aliphatic systems with their ring strain energy having been calculated to be almost identical to that of cyclobutanes.[209] As such their synthesis has attracted a great deal of interest, with a major breakthrough coming in 1958 when Simmons and Smith discovered that treatment of alkenes with diiodomethane and an activated zinc species afforded cyclopropanes in high yield.[210,211] Since these initial studies, several modifications have been made to this cyclopropanation protocol,[212-214] with application of these conditions to allylic systems having been widely investigated.[215] For example, Charette has studied the directed cyclopropanation of numerous allylic alcohols under modified Furukawa's conditions (diethyl zinc and diiodomethane), resulting in methodology that affords cyclopropyl-alcohols with excellent levels of stereocontrol.[216-218]



Reagents and conditions: (i) Et_2Zn (5.0equiv), CH_2I_2 (5.0 equiv), CH_2Cl_2, -10 to 0 °C, 2hours

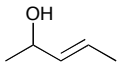
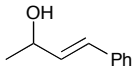
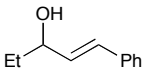
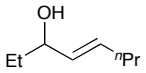
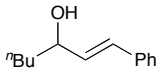
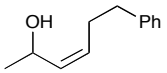
Entry	*Allylic alcohol*	*Yield (%)*	*syn:anti ratio*
1		75	6:1
2		86	7:1
3		97	130:1
4		87	110:1
5		98	150:1
6		96	>200:1

Table 5.1: Directed cyclopropanation reactions of allylic systems.

They observed that treatment of a range of 1,2-disubstituted allylic systems with excess of diethyl zinc and diiodomethane resulted in hydroxyl-directed cyclopropanations with excellent levels of diastereocontrol.[219] The mechanism of the cyclopropanation reaction has been much investigated with attention having been focused on determining the nature of the active species responsible for asymmetric induction. Upon reaction of activated zinc with diiodomethane it is postulated that a "$ZnCH_2I$" species is generated; however the actual structure of this zinc species has been much debated, with various halomethylzinc species having been isolated in the solid state.[214,217,220-222] Upon addition of these active zinc species to an alkene it is envisaged that a zinc-carbenoid equivalent is delivered to one faces of the alkene bond *via* a "butterfly-type" transition state (Figure 4.3).[223]

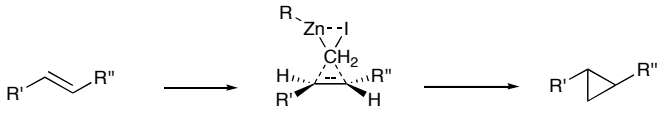
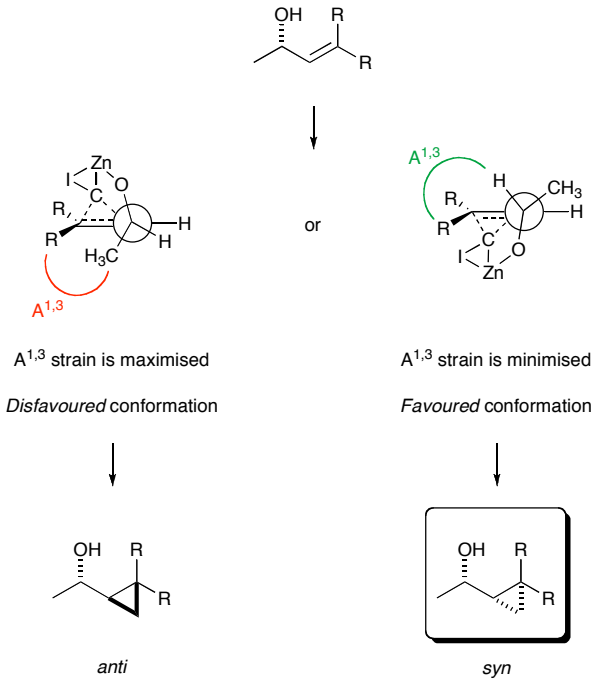


Figure 5.3: Proposed "butterfly-type" transition state for the cyclopropanation reaction.

It is proposed that treatment of allylic alcohol substrates with these halomethylzinc species, results in coordination of zinc to the hydroxyl functionality, with a methylene equivalent then being delivered selectively to one of the diastereotopic faces of the alkene bond (Scheme 4.5).[224,225] The high levels of diastereocontrol observed by Charette for substituted alkenes can then be rationalised by consideration of the allylic strain generated in the respective diastereoisomeric intermediate transition states.

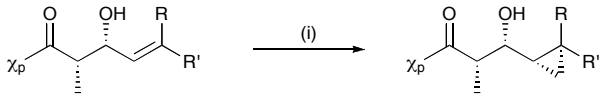
For 1,2-disubstituted alkenes and 1,2,2-trisubstituted allylic alcohols, the absence of a sterically demanding group at the α-position of the allylic system means that any contributions from $A^{1,2}$ strain can be considered to be negligible. As a consequence, minimisation of $A^{1,3}$ strain in the transition state is the dominant consideration that determines the facial selectivity of the cyclopropanation reaction. Therefore, for 1,2-disubstituted allylic alcohols, a carbenoid species is delivered to the *syn*-face of the alkene functionality due to $A^{1,3}$ strain being minimised in the transition state (**TS1**) when compared to the transition state (**TS2**) required to form an anti-cyclopropane. The presence of a *cis*-β-substituent increases the *syn*-selectivity further, as a consequence of a further increase in $A^{1,3}$ strain present in **TS2** upon approach at the *anti*-face.[225]



Scheme 5.5: Allylic strain models for rationalisation of the stereochemical outcome of the directed cyclopropanation reaction.

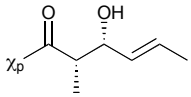
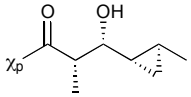
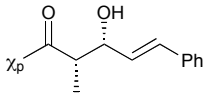
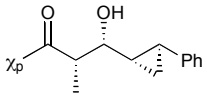
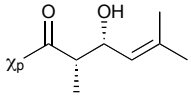
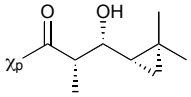
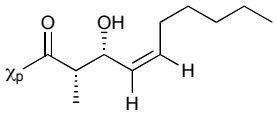
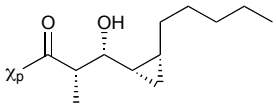
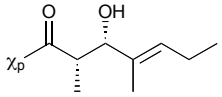
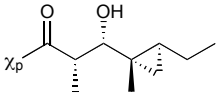
5.3 Cyclopropanation of syn-aldols

My initial target was therefore to use Furukawa's modified cyclopropanation conditions previously developed within the group to prepare a range of cyclopropane aldol adducts **295f-j** as substrates for the proposed oxymercuration/demercuration methodology. Therefore, *syn*-aldols **163f-j** were treated with diethyl zinc (5.0 equivalents) and diiodomethane (5.0 equivalents) at -10 °C to afford a series of cyclopropane-aldols **295f-j** in 95% de. Excess cyclopropanating reagents were used in order to ensure complete consumption of starting material, with the (*syn*)-configuration of the resultant cyclopropane-aldols being inferred from literature precedent for related allylic systems.



163f-j **295f-j**

Reagents and conditions: (i) Et_2Zn (5.0equiv), CH_2I_2 (5.0 equiv), CH_2Cl_2, -10 to 0 °C, 2hours

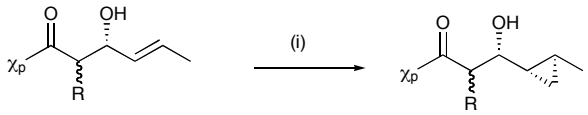
Entry	*syn-Aldol*	*Cyclopropane-aldol*[a]	*Yield (%)*[b]	*de (%)*[c]
1	 **163f**	 **295f**	96	>95
2	 **163g**	 **295g**	95	>95
3	 **163h**	 **295h**	95	>95
4	 **163j**	 **295j**	96	>95
5	 **163i**	 **295i**	96	0

[a] *Syn*-selectivity is inferred from literature precedent and confirmed previously by X-ray crystal structure of *ortho*-nitro-cinnamaldehyde derivative synthesised by Matt Cheeseman;[141,226] [b] Isolated yields after column chromatography; [c] Diastereoisomeric excess determined from analysis of their crude ^{1}H NMR spectra.

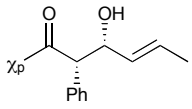
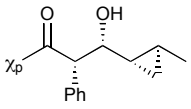
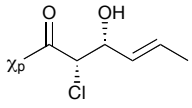
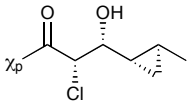
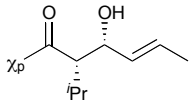
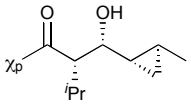
Table 5.2: Range of β-vinyl-*syn*-aldols treated under modified Furukawa conditions.

It had previously been proposed that the hydroxyl group of aldols **163f-j** were solely responsible for the high diastereocontrol in these cyclopropanation reactions and that their other stereocentres played no role in determining facial selectivity. Consequently it was decided to take this opportunity to confirm this rationale, by examining what effect changing the steric or

electronic demand of the α-substituent of these aldol substrates would have on the diastereoselectivity of their cyclopropanation reactions. As such, α-phenyl-aldol **163o**, α-chloro-aldol **163p** and α-isopropyl-aldol **163q** were prepared using our standard boron aldol conditions and cyclopropanated under Furukawa conditions to yield their corresponding cyclopropane derivatives **295o-q** in excellent yield and >95 % de in each case.



Reagents and conditions: (i) Et_2Zn (5.0equiv), CH_2I_2 (5.0 equiv), CH_2Cl_2, -10 to 0 °C, 2hours

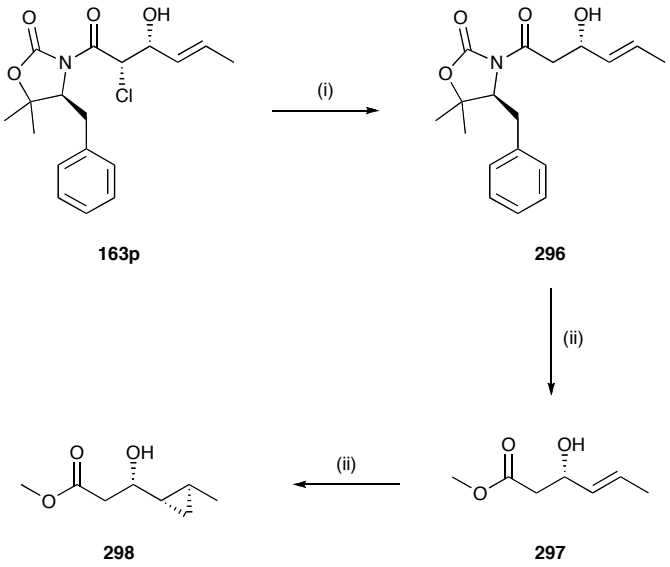
Entry	*syn-Aldol*	*Cyclopropane*	*Yield (%)*[a]	*de (%)*[b]
1	 **163o**	 **295o**	92	>95
2	 **163p**	 **295p**	93	>95
3	 **163q**	 **295q**	90	>95

[a] Isolated yields after column chromatography; [b] Diastereoisomeric excess determined from analysis of the crude ^{1}H NMR.

Table 5.3: Cyclopropanation of *syn*-aldol substrates with varying α-substituents.

We wished to further confirm that the high diastereoselectivities observed in the cyclopropanation reactions of *syn*-aldols **295f-j** and **295o-q** were solely due to the stereodirecting effect of the β-hydroxyl stereocentre and that the oxazolidin-2-one and/or α-methyl stereocentres were not contributing towards diastereocontrol. Therefore, it was decided to determine what level of diastereoselectivity would be observed for cyclopropanation of the alkene functionality of an aldol-ester **297** that contains a single β-hydroxyl stereocentre.

Consequently, ester **297** was prepared in three steps *via* reaction of the (*Z*)-boron enolate of α-chloro-propionyl-oxazolidin-2-one **241b** with crotonaldehyde to afford *syn*-aldol **163p** in 83% yield that was α-dechlorinated *via* treatment with zinc and ammonium chloride in methanol to afford *syn*-aldol **296** in 74% yield.[196] Subsequent cleavage of the oxazolidin-2-one *via* treatment with sodium methoxide gave β-vinyl-aldol-ester **297** containing a single stereocentre in 71% yield. Subsequent cyclopropanation of β-vinyl-aldol-ester **297** using our previously developed modified Furukawa conditions resulted in cyclopropyl-aldol **298** being formed in > 95% de.



Reagents and conditions: (i) Zn, NH_4Cl, MeOH; (ii) Et_2Zn (5.0equiv), CH_2I_2 (5.0 equiv), CH_2Cl_2, -10 to 0 °C, 2hours; (iii) NaOMe, CH_2Cl_2, 5 minutes.

Scheme 5.6: Investigation into the directing effects of the α-substituent and the oxazolidin-2-one upon the cyclopropanation reaction.

Therefore, since the cyclopropanation reactions of β-vinyl-*N*-acyl-oxazolidin-2-one **296** and β-vinyl-aldol-ester **297** both proceed with essentially identical diastereoselectivity, we can conclude that the oxazolidin-2-one and α-stereocentres of β-vinyl-*N*-acyl-oxazolidin-2-one **163** do not play an important role in diastereocontrol. Furthermore, these results provide compelling evidence that the concept of using aldol/*retro*-aldol reactions to reversibly generate 'temporary' β-hydroxyl stereocentres for the stereoselective functionalisation of remote allylic alkene functionality has been fully validated.

5.4 Oxymercuration of cyclopropanes

The reactivity of the cyclopropane functionality is often attributed to the strain of the ring system with three sp^3 carbon centres being confined in a ring system with C-C-C bond angles of 60°, which is much reduced from the optimal bond angle of 109.5° normally observed for tetrahedral carbon centres.[206] This results in cyclopropane ring systems undergoing reactions that are normally associated with double bond systems, meaning that they are much more reactive than other cyclic counterparts.

Walsh's model of the bonding that occurs in cyclopropanes envisages a ring system constructed of three sp^2 hybridised carbon centres, that are directed towards the centre of the ring system, as shown in ψ_1 (Figure 5.4).[227] This can be used to rationalise the concept of σ-aromaticity, which arises from occupation of the ψ_1 orbital generating a three-centre-two-electron bond, that fits Huckel's (4n+2) rule for aromaticity.[206,209]

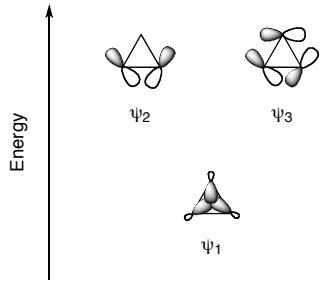
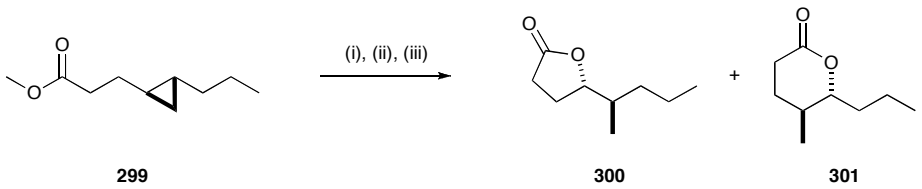


Figure 5.4: The Walsh Model

The presence of σ-aromaticity within its ring system accounts for the reactivity of cyclopropanes toward electrophiles and the upshield shift of the cyclopropane protons in their ^{1}H NMR spectra.[206,209] Cyclopropanes employ their σ-aromatic component to coordinate to an adventitious electrophiles, which are then ring opened to afford stable carbocation intermediates, or trigger ring opening *via* reaction with an incipient nucleophile.[228]

Synthetic strategies that incorporate mercury mediated intramolecular ring-opening reactions of cyclopropanes have been reported to generate γ-lactone products.[205] Collum and co-workers previously reported that treatment of cyclopropane methyl ester **299** with mercury(II) trifluoroacetate generates both a γ-lactone **300** and δ-lactone **301**. These lactonisation reactions

proceeds with inversion of stereochemistry to generate a mixture of 5- and 6-membered *anti*-lactones **300** and **301** in a ratio of 1:12 ratio respectively.[229,230]



299 **300** **301**

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, (ii) KBr (aq), (iii) $^nBu_3SnH$

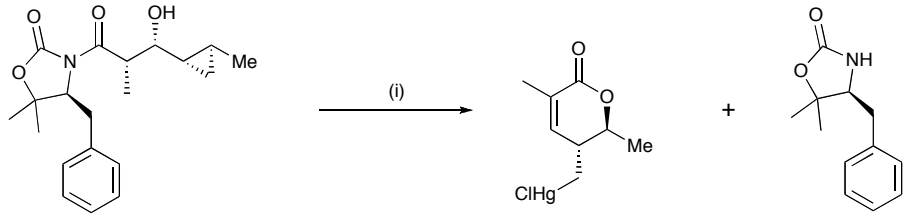
Scheme 5.7: Mercury mediated oxymercuration-lactonisation.

With this literature precedent in mind, it was decided to apply these conditions to *syn*-cyclopropane aldol **295f** in order to determine whether its *N*-acyl-oxazolidin-2-one fragment was sufficiently nucleophilic to trigger mercury catalysed ring-opening of its cyclopropane ring system.

5.4.1 Application to SuperQuat derived aldol systems ♣

SuperQuat aldol **295f** was treated with mercury(II) trifluoroacetate and stirred for 24 hours, after which time the reaction was quenched with saturated sodium chloride solution. Analysis of the crude ^1H NMR spectrum of the crude reaction product indicated that cleavage had occurred to afford the parent *N*-H oxazolidin-2-one **157** and a new product which was tentatively assigned as α,β-unsaturated-δ-lactone **302**. This was proposed from the indicative resonance of its vinyl proton at δ 6.34 ppm, an infra-red carbonyl absorption at 1684 cm^{-1}, and a molecular ion with a multiple isotope pattern for $C_8H_{11}ClHgO_2$ in its mass spectrum.

♣ A preliminary report of a single example of this cyclopropane ring-opening transformation appears in a thesis from the Bull group submitted by Matthew Cheeseman in 2005.

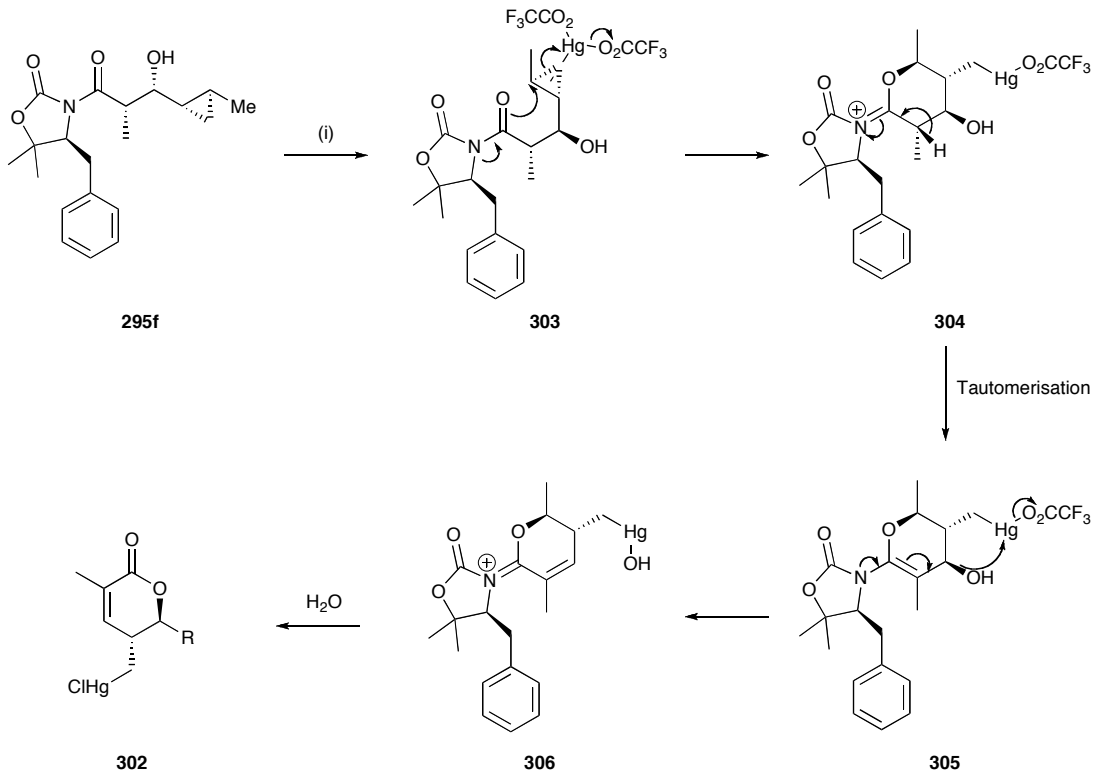


295f **302** **157**

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2. RT, the NaCl (aq)

Scheme 5.8: Observed oxymercuration reaction.

The mechanism of formation of lactone **302** may be rationalised *via* a mechanism, whereby initial coordination of the mercury species to its cyclopropane ring system activates it to ring opening at its δ-centre using the exocyclic carbonyl of its *N*-acyl-oxazolidin-2-one fragment as an intramolecular nucleophile. This pathway would result in an unstable cyclic imminium intermediate **302**, whose β-hydroxyl group can potentially coordinate to the mercury atom to trigger an elimination reaction that generates the alkene functionality of imminium species **306**. Subsequent hydrolysis of imminium species **306** then generates the *N*-H oxazolidin-2-one **157** and α,β-unsaturated-δ-lactone **302**.

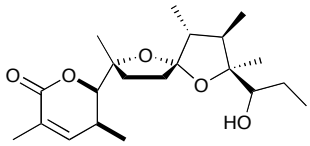


295f **303** **304** **305** **306** **302**

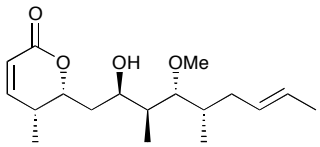
Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq)

Figure 5.5: Proposed reaction mechanism for the synthesis of organomercurial α,β-unsaturated lactone **302**.

Although δ-lactones that contain α,β-unsaturated functionality of this type are interesting synthetic targets that also appear widely in the side-chains of polyketide natural products (Figure 5.6), it is clear that the resultant destruction of two stereocentres that occurs in this reaction was far from desirable. As previously discussed, Collum reported the efficient generation of functionalised δ-lactones **300** *via* treatment of cyclopropane methyl ester **299** with mercury(II) trifluoroacetate (Scheme 5.7), with no report of any elimination products having been formed.[229] Consequently, it was decided to convert our SuperQuat-cyclopropyl aldols **295** into their corresponding esters **309**, which would then be subjected to the oxymercuration conditions.



xx
Erythronolide I

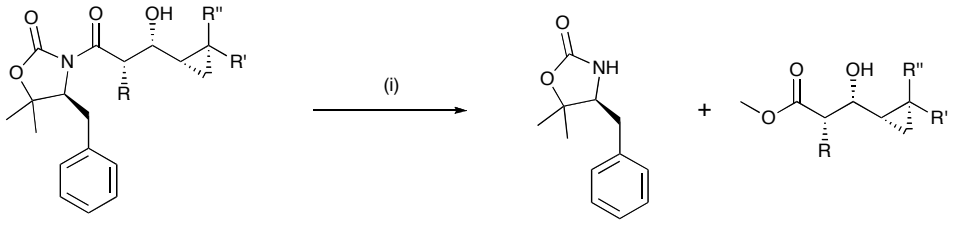


xx
Pironetin

Figure 5.6: Natural products containing the α,β-unsaturated lactones.

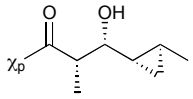
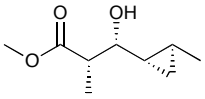
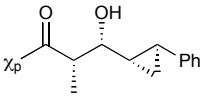
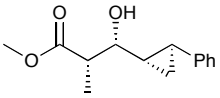
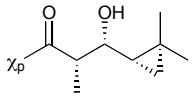
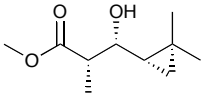
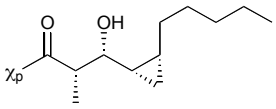
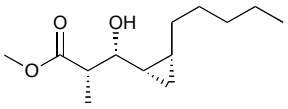
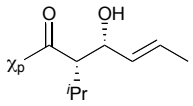
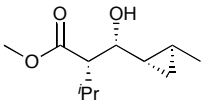
5.4.2 Transesterification

Therefore, cyclopropyl-aldols **295f-h** and **295i** were treated with sodium methoxide in CH_2Cl_2 for 5 minutes which resulted in clean conversion to their parent oxazolidin-2-one and corresponding methyl esters **309f-g** and **309i** in 71-89 % yield.[231]



295 **157** **309**

Reagents and conditions: (i) NaOMe (1.1 equiv), CH_2Cl_2 (c. 0.5 M), 5 mins.

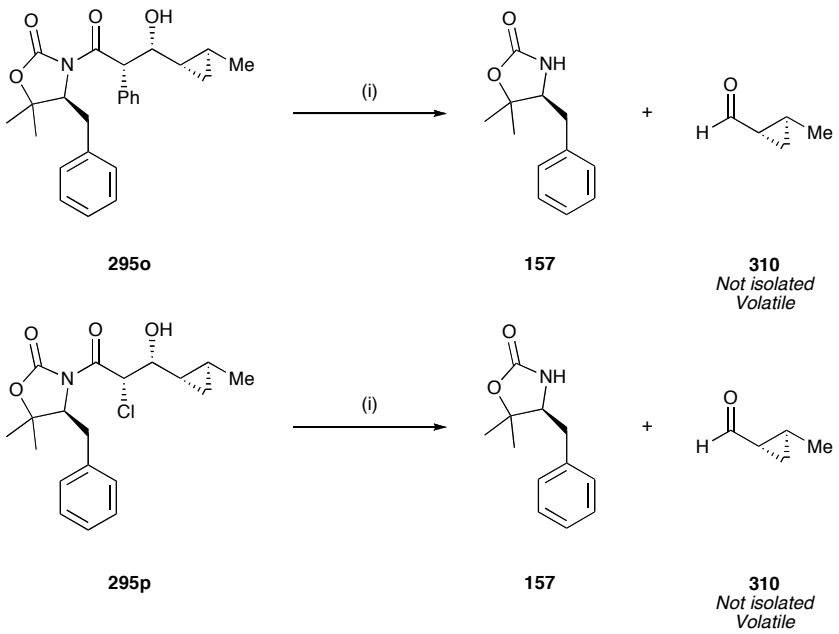
Entry	*Cyclopropane Aldol*	*Methyl ester*	*Yield (%)*	*de (%)*
1	 **295f**	 **309f**	80	>95
2	 **295g**	 **309g**	89	>95
3	 **295h**	 **309h**	71	>95
4	 **295j**	 **309j**	81	>95
5	 **163q**	 **309q**	75	>95

[a] Isolated yields reported after column chromatography; [b] de determined from crude ^{1}H NMR spectroscopy, the high de indicates that no racemisation of the α-stereocentre occurs.

Table 5.4: Transesterification reaction.

For the majority of aldol substrates (Entries1-5), treatment with 1.1 equivalents of sodium methoxide cleanly generated a 1:1 mixture of N-*H* oxazolidin-2-one **157** and the desired methyl-ester **309** in good yields with no evidence of any racemisation at their α-stereocentres. However, examination of the ^{1}H NMR spectra of the methanolysis products of aldols **295o** and **295p** revealed that these substrates had instead undergone a clean sodium methoxide catalysed

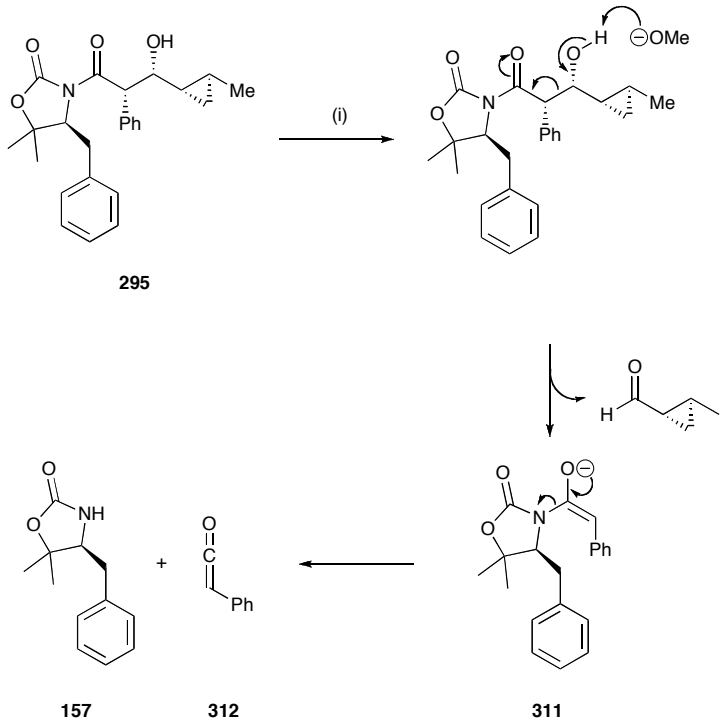
retro-aldol reaction to afford its parent oxazolidin-2-one and cyclopropyl aldehyde **310** (not observed due to its volatility), with none of the desired methyl esters having been formed.



Reagents and conditions: (i) NaOMe (1.1 equiv), CH_2Cl_2 (c. 0.5 M), 5 mins.

Scheme 5.9: Attempted transesterification of cyclopropane aldols **295o** and **295p**.

Therefore, it is clear that the competing *retro*-aldol pathway available to these aldol products is not accelerated by the presence of sterically demanding substituents at their α-position, since methanolysis of α-isopropyl aldol **295q** resulted in clean conversion to its parent oxazolidin-2-one **157** and methyl ester **309q**. However, the presence of an electron withdrawing α-chloro and α-phenyl functionalities of aldol products **295p** and **295o** clearly favour retro-aldol reaction, presumably *via* stabilisation of the resultant sodium enolate intermediate **311** that is generated in these cleavage reactions.



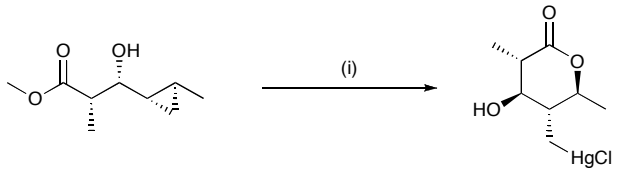
Reagents and conditions: (i) NaOMe (1.1 equiv), CH_2Cl_2 (c. 0.5 M), 5 mins.

Figure 5.7: Mechanism of *retro*-aldol cleavage.

With a range of cyclopropane methyl esters in hand, we then carried out mercury mediated ring opening of their cyclopropane ring systems in order to determine whether their oxymercuration/demercuration reactions could be used to generate chiral δ-lactones retaining four contiguous stereocentres.

5.4.3 Oxymercuration

To this end, cyclopropane methyl ester **295f** was treated with mercury trifluoroacetate (2.5 equivalents) in dichloromethane at ambient temperature for 24 hours before quenching with saturated sodium chloride solution. To our delight, ^{1}H NMR spectroscopic analysis revealed that it had been cleanly converted into its corresponding tetrasubstituted-δ-mercuro-lactone **313f**, with no evidence of any α,β-unsaturated lactone having been formed from the competing elimination pathway.



295f **313f**

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq)

Scheme 5.10: Oxymercuration of cyclopropane methyl ester **295f**.

The structure of δ-lactone **313f** was confirmed from analysis of its spectroscopic data. Therefore, infrared analysis revealed strong absorptions at 3335 cm^{-1} and 1681 cm^{-1} corresponding to the hydroxyl and carbonyl functionalities of its six-membered lactone ring respectively. The ^1H NMR spectra indicated a dq at 2.43 ppm, which was indicative of a CH proton α- to the carbonyl group and a dq at 4.06 ppm assigned to a proton adjacent to the oxygen atom. The ^{13}C NMR indicated a single carbonyl resonance at 173.2 ppm and two carbon centres attached to oxygen heteroatoms at 80.1 ppm and 74.8 ppm. The ^{199}Hg NMR spectra indicated the presence of a species containing a single mercury atom, with a singlet present at -933.92 ppm that is consistent for the proposed sp^3 organomercurial lactone **133f**. The structure of lactone **313f** was further confirmed by HRMS, which revealed a molecular ion $[M+H]^+$ at 395.0338 with a multiple isotope pattern consistent for a compound with a molecular formula of $C_8H_{13}O_3ClHg$.

All of the protons of lactone **313f** were then assigned from examination of its ^1H and COSY NMR spectrum, which allowed us to use NOE spectroscopy to confirm the absolute configuration of stereocentres of lactone **313f**. Therefore, this NOE experiment revealed that the C_3 hydrogen atom strongly interacts with the C_5 hydrogen (Figure 5.8) indicating a *syn* relationship between these substituents. Further to this, the C_4 hydrogen atom strongly interacts with the C_6 hydrogen atom indicating that these functionalities are on the same face of the six-membered ring. Given the known (2*S*,3*S*)- configuration of the *syn*-aldol **295f** that was initially cyclopropanated, these NOE's are indicative of an (*R*)- configuration at the newly formed C_5 and an (*S*)-configuration at the C_6 stereocentres of lactone **313f**. Further to this, coupling constants confirmed the relative stereochemistry with the $^3J_{5,6}$ = 9.9 Hz indicating a *trans* relationship, and the $^3J_{4,5}$ = 10.1 Hz also indicating a *trans* relationship.

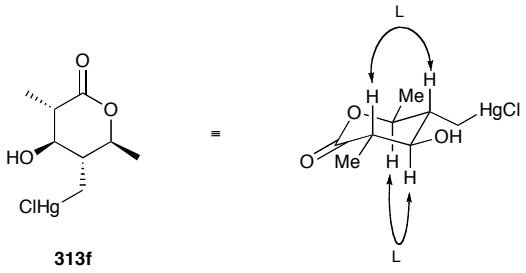


Figure 5.8: Indicative NOE interactions observed for δ-lactone **313f**.

We considered that there were two potential mechanisms operating that would result in the observed inversion of stereochemistry at the δ cyclopropyl centre of *syn*-cyclopropyl-aldol. Firstly, an external nucleophile mechanism could be envisaged whereby the mercury ion undergoes electrophilic coordination to the cyclopropane ring in methyl ester **295f** followed by concomitant *anti* nucleophilic attack of a trifluroacetate counter-anion at the most electron-rich carbon centre of the cyclopropane ring to generate organomercurial species **315**. Subsequent treatment with saturated sodium chloride solution would hydrolyse the resultant trifluoroacetate to give a δ-hydroxy-ester that then cyclises to afford the observed δ-lactone **313f** (Scheme 5.9).[205,230,232]

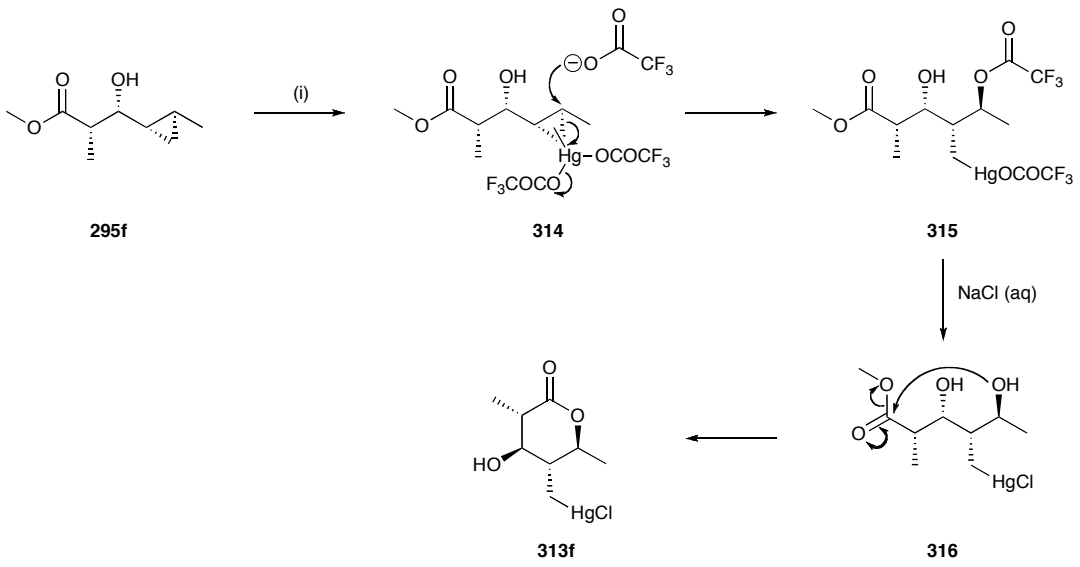
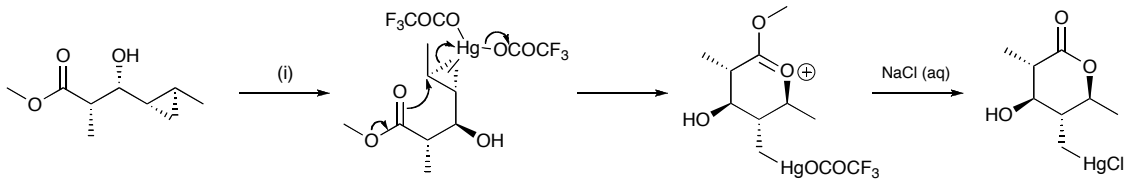


Figure 5.9: Proposed mechanism for lactonisation.

An alternative explanation could invoke the neighbouring group participation mechanism described previously for the epoxidation/lactonisation reactions of β-vinyl-*N*-acyl-oxazolidin-2-ones (see Chapter 3). Therefore, initial electrophilic coordination of mercury to the

cyclopropane ring of methyl ester **295f** would facilitate intramolecular nucleophilic attack of the endocyclic carbonyl of its *N*-acyl-oxazolidin-2-one fragment to generate an oxonium intermediate **318**, which is subsequently hydrolysed to afford the observed lactone **313f**.

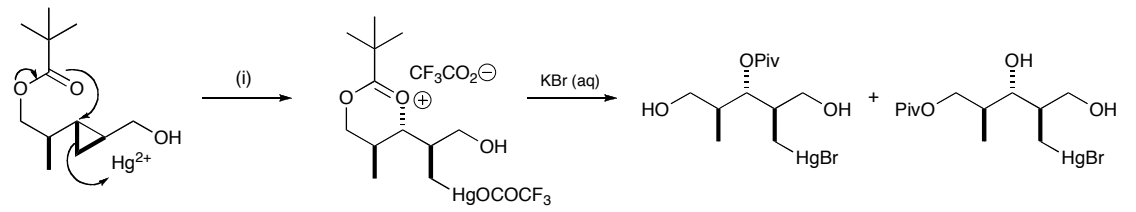


295f **317** **318** **313f**

Reagents and conditions: (i) (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq)

Figure 5.10: Potential neighbouring group participation mechanism

Compelling evidence that this latter neighbouring group participation mechanism was likely to be operating in our system comes from work from Cossy and co-workers who have previously reported the role of remote ester functionalities in the oxymercuration ring-opening reactions of cyclopropanemethanols **319**.[205] They rationalised their results by proposing that attack of the oxygen lone pair of the remote carbonyl functionality of ester **319** at the mercury-coordinated cyclopropane ring proceeds with inversion of stereochemistry to generate an oxonium intermediate **320,** which on hydrolysis generates a mixture of the regioisomeric organomercuric mono *O*-pivaloyl triols **321** and **321**.[205]



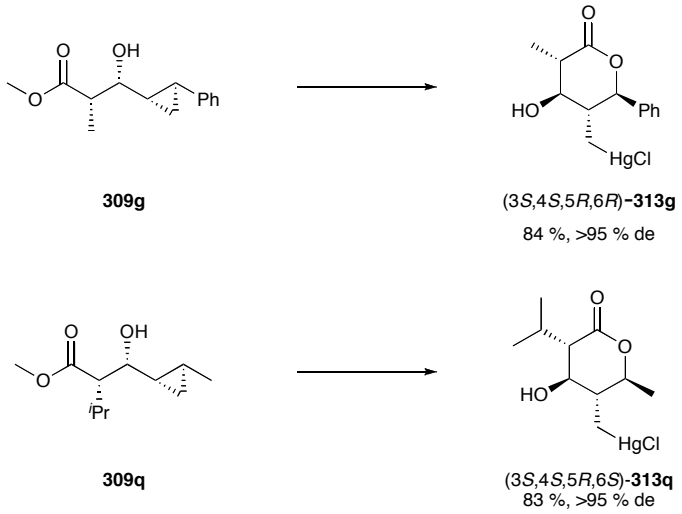
319 **320** **321** **322**

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then KBr (aq)

Figure 5.11: Oxymercuration of cyclopropane methanol **319**.

These oxymercuration conditions were then applied to ring-open a range of cyclopropane methyl esters **309** in good yield. Treatment of the *trans*-alkene derived cyclopropanes **309g** and **309q** with mercury(II) trifluoroacetate yielded the desired tetra-substituted-δ-lactones **313g** and **313q** respectively in 83-84% yields and with high levels of diastereocontrol. These reactions gave only six membered lactones **313g** and **313q** with no γ-lactone species being observed in

the crude ^{1}H NMR spectra. ^{1}H NMR and NOE analysis once again indicated that the oxymercuration reaction had proceeded with inversion of the δ-stereocentre to generate (3*S*,4*S*,5*R*,6*R*)-**313g** and (3*S*,4*S*,5*R*,6*S*)-**313q**.



Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq)

Scheme 5.11: Generation of tetrasubstituted-δ-mercurolactones **313g** and **313q**.

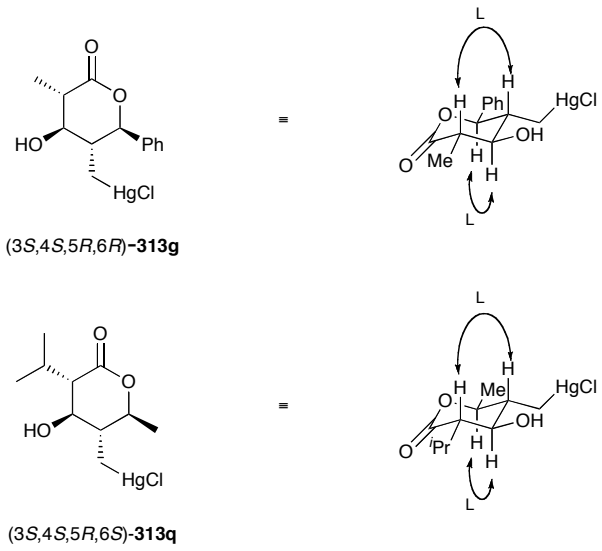
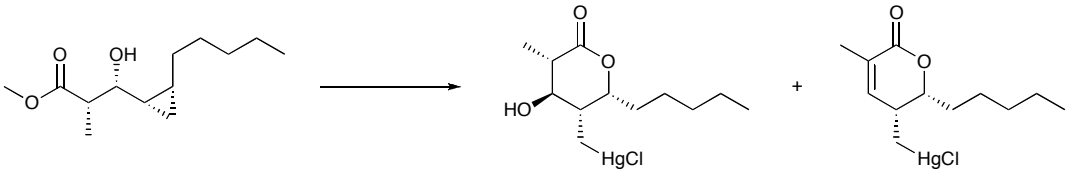


Figure 5.12: Stereo-defining NOE interactions observed for lactones **313g** and **313q**.

Oxymercuration of the *cis*-alkene derived cyclopropane ester **309j** with mercury(II) trifluoroacetate under these reactions did not proceed as cleanly, with the crude ^{1}H NMR spectra indicating formation of a mixture of (3*S*,4*S*,5*R*,6*R*)-lactone **313j** and α,β-unsaturated-δ-lactone (5*R*,6*R*)-**323** had been formed in a 3:1 ratio. Chromatographic purification of this mixture allowed access to both the purified tetrasubstituted lactone (3*S*,4*S*,5*R*,6*R*)-**313j** in 55 % yield

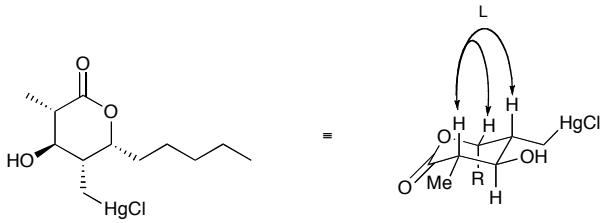
and >95% de and the α,β-unsaturated derivative (5*R*,6*R*)-**323** in 30 % yield and >95 % de, whose structures were assigned *via* ^{1}H NMR and NOE spectroscopic analysis as described previously.



309j (3*S*,4*S*,5*R*,6*R*)-**313j** 55 %, >95 % de (5*R*,6*R*)-**323** 30 %, >95 % de

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then $NaCl_{(aq)}$

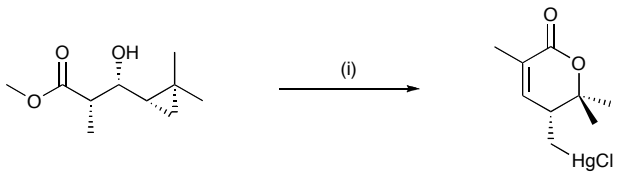
Scheme 5.12: Oxymercuration of *cis*-alkene derived cyclopropane **309j**.



(3*S*,4*S*,5*R*,6*R*)-**313j**

Figure 5.13: Observed NOE interactions for the elucidation of stereochemistry of **313j**.

Further to this, treatment of *gem*-dimethyl aldol derivative **309h** under oxymercuration conditions gave clean conversion to the α,β-unsaturated-δ-lactone substrate **324** with no tetrasubstituted-δ-lactone having been formed after 24 hours. The stereochemistry of this α,β-unsaturated lactone was inferred as (5*R*) from consideration of the mechanism previously determined for these lactonisation reactions.



309h **324** 83 %

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, then NaCl (aq)

Scheme 5.13: Oxymercuration reaction of 1,2,2-trisubstituted alkene derived cyclopropane **309h**.

In order to rationalise these results it was proposed that the elimination reaction of trans-substituted cyclopropyl-aldols **309f,g,q** are slower than for cyclopropyl-aldols **309j** and **309h** containing a *cis*-substituent. This is because the organomercurial species derived from *trans*-substituted cyclopropyl-aldols **309f,g,q** can adopt a chair-like conformation whose ring-substituents all occupy stable equatorial conformations, whilst *cis*-substituted cyclopropyl-aldols **309j** and **309h** contain an axial C_5-substituent which is less stable and more prone to elimination (Figure 4.14).

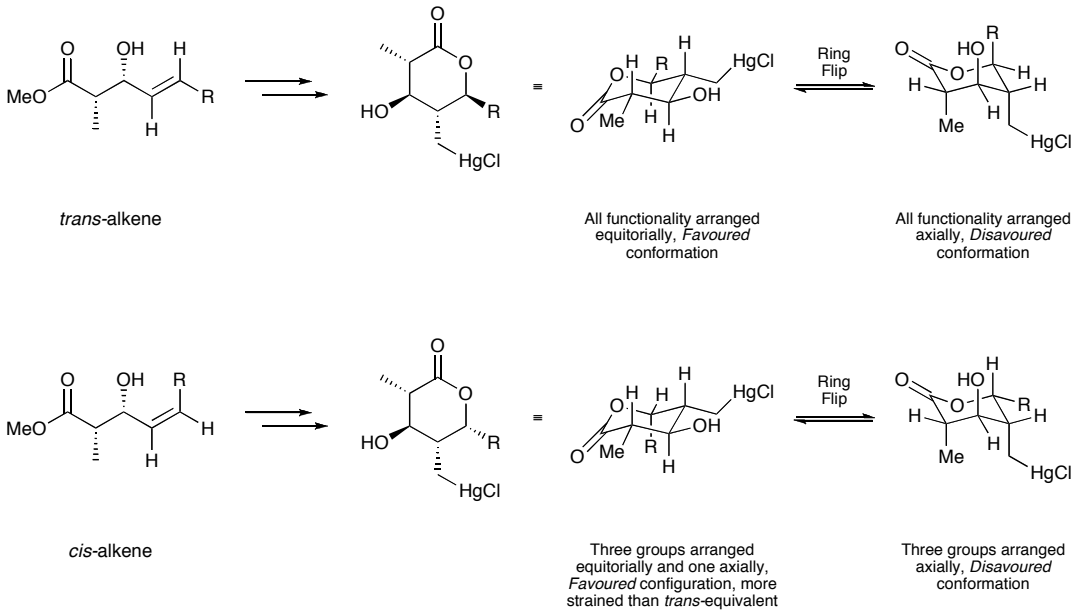
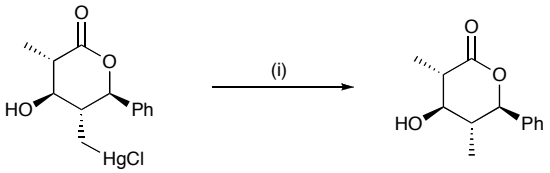


Figure 5.14: Conformers of lactones derived from both *cis* and *trans* allylic systems.

5.5 Demercuration

With a range of mercuro-δ-lactones accessed, it was now necessary to develop a demercuration strategy to access the desired highly functionalised chiral-δ-lactones. Initially it was decided to investigate the tin mediated radical demercuration methodology developed by Cossy and co-workers.[205] As such, mercuro-δ-lactone **313g** was treated with tributyltin hydride (1.2 equiv) and a catalytic amount of AIBN in dry tetrahydrofuran at ambient temperature and stirred for 30 minutes. After this time, the reaction was hydrolysed with saturated sodium fluoride and worked up to afford the crude lactone product **325**.



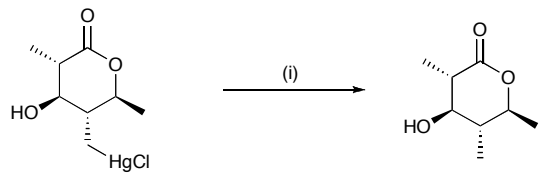
313g 325

Reagents and conditions (i) Bu_3SnH (1.2 equiv), AIBN, THF, RT, 30 min then NaF (aq.)

Scheme 5.14: Radical demercuration of mercuro-δ-lactone **313g**.

Although crude ^1H NMR spectra indicated that the majority of the starting material had been consumed, many of the diagnostic resonances of the target lactone were swamped by the presence of excess tributyltin species, although its presence was confirmed from its molecular ion of $[M+H]^+ = 159.1$ in its mass spectrum. All Attempts to purify the δ-lactone **325** from this reaction to homogeneity *via* chromatography/distillation proved unsuccessful, because of residual contamination from unseparable tributyltin residues.

A survey of the literature revealeded that mercuro lactones of this type could be readily demercurated utilising sodium borohydride.[233] Therefore, mercuro-δ-lactone **313f** was dissolved in methanol and sodium hydroxide solution (2.0 M) and the resulting solution treated with sodium borohydride (3 equiv, 0.5 M in 2.0 M sodium hydroxide) for one minute at 0 ºC. After this time the reaction mixture was immediately quenched with 1.0 M hydrochloric acid solution and worked up to afford the desired tetrasubstituted lactone **326** containing 4 stereocentres in 77 % yield**.**



313f 326

Reagents and conditions: (i) $NaBH_4$ (3.0equiv), NaOH (aq.), MeOH

Scheme 5.15: Sodium borohydride mediated reductive demercuration to generate the lactone **313f**.

The structure of lactone **326** was confirmed from analysis of spectroscopic data. Therefore, infrared analysis revealed strong absorptions at 3423.7 cm^{-1} and 1711.8 cm^{-1} corresponding to the hydroxyl functionality and the carbonyl of a six-membered lactone respectively. The ^1H NMR spectra indicated; a dq at 2.43 ppm, which was indicative of a CH α- to the lactone

carbonyl, a dq at 4.06 ppm assigned to the C_6 proton which is adjacent to an electron withdrawing lactone oxygen. The ^{13}C NMR spectra indicated a single carbonyl resonance at 173.5 ppm and two carbon centres adjacent to oxygen centres at 79.0 ppm and 75.6 ppm. The structure of lactone **326** was further confirmed by HRMS, which revealed a molecular ion $[M+H]^+$ at 159.1026 with an isotope pattern consistent for a molecular formula of $C_8H_{14}O_3$.

All of the protons of lactone **326** were assigned from examination of its ^1H and COSY NMR spectrum, which allowed us to use NOE spectroscopy to confirm the absolute configuration of stereocentres of lactone **326**. Therefore, this NOE experiment revealed that the C_3 hydrogen atom strongly interacts with the C_5 hydrogen (Figure 5.5) indicating a *syn* relationship between these substituents. Further to this, the C_4 hydrogen atom strongly interacts with the C_6 hydrogen atom indicating that these functionalities are on the same face of the six-membered ring. Given the known (2*S*,3*S*)-configuration of the *syn*-aldol **163f** that was initially cyclopropanated, these NOE's indicated the generated δ-lactone as (3*S*,4*R*,5*R*,6*S*)-**326** which is consistent with the stereochemistry assigned for the mercuro-δ-lactone **326** starting material.

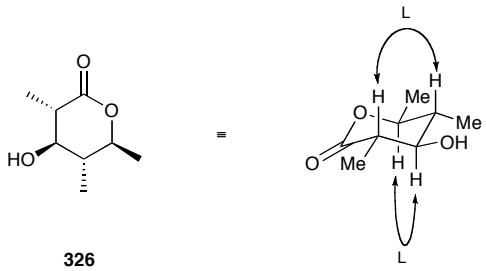
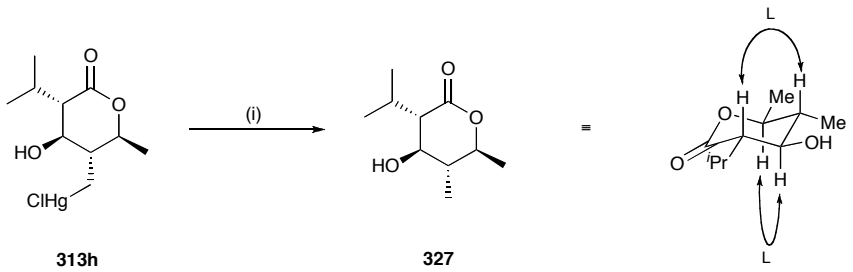


Figure 5.15: Observed stereodefining NOE interactions of δ-lactone **326**

Further to this, mercuro-δ-lactone **313h** was also shown to cleanly undergo reductive demercuration to generate tetrasubstituted δ-lactone in a comparable 73 % yield. Analysis of the NOE spectra indicated the reaction had proceeded with complete retention of stereochemistry generating (3*S*,4*R*,5*R*,6*S*)-**327**.



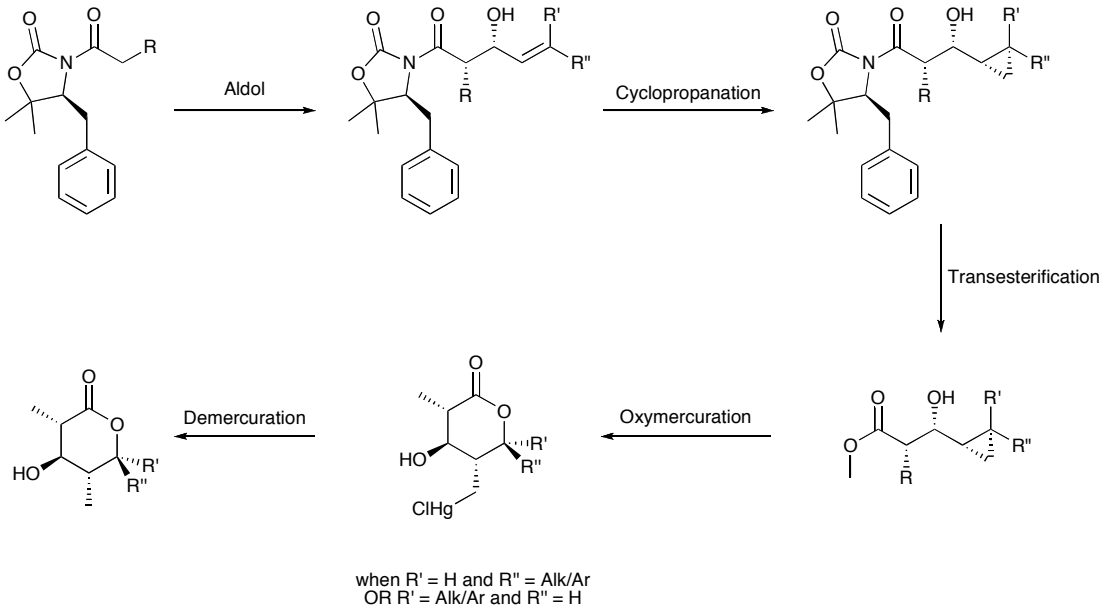
Reagents and conditions: (i) $NaBH_4$ (3.0equiv), NaOH (aq.), MeOH

Scheme 5.16: Reductive demercuration and stereodefining NOE interactions.

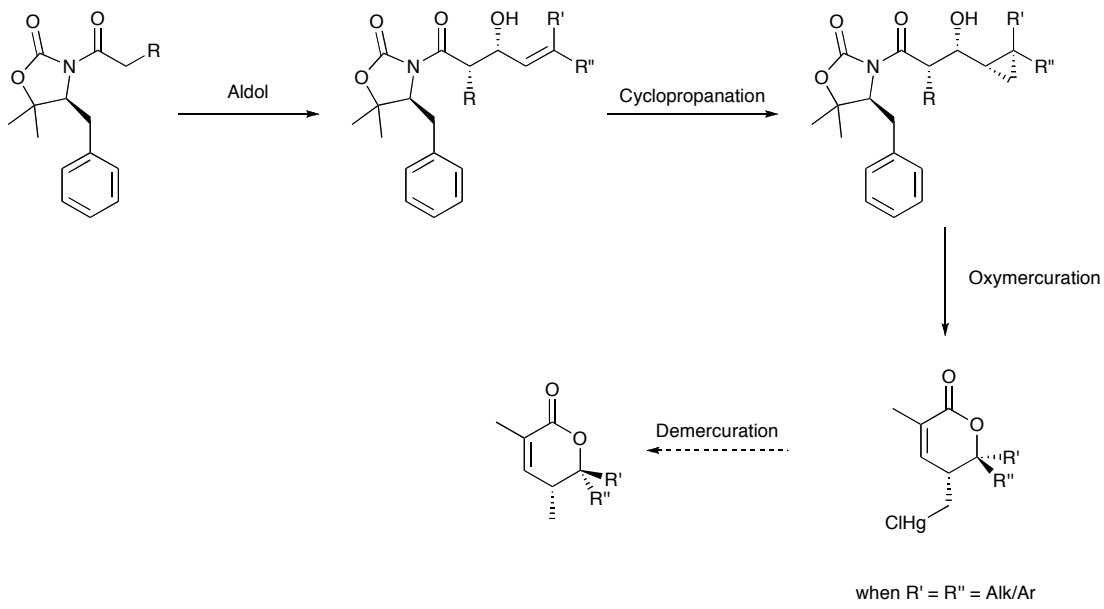
However, attempts to demercurate the α,β-unsaturated-δ-lactone proved problematic. Treatment with sodium borohydride did not result in clean conversion to the desired demercurated product, with a complex mixture of products being observed, which according to examination of the crude TLC were inseparable. Further investigations into this methodology are currently underway in the SDB group, directed towards applying this strategy to new substrates containing different ring- substitution patterns.

5.6 Conclusions

We have demonstrated that β-vinyl-*syn*-aldols can be used as efficient precursors to access both tetrasubstituted δ-lactones and α,β-unsaturated-δ-lactones in high levels of stereocontrol (See Scheme 5.17). It has been shown that cyclopropanes accessed from *trans*-alkenyl systems are readily ring-opened to afford tetrasubstituted-δ-lactones with high levels of diastereocontrol. Those cyclopropanes derived from *cis*-alkenyl systems proceed with less selectivity generating both saturated and unsaturated lactones.



Scheme 5.17: General five-step strategy to access highly substituted δ-lactones



Scheme 5.18: General five-step strategy to access α,β-unsaturated-δ-lactone.

Chapter 6: Experimental

General Experimental

All reactions were performed under a nitrogen or argon atmosphere in oven-dried apparatus, unless otherwise stated. Anhydrous acetonitrile, diethyl ether, dichloromethane, hexane, toluene and tetrahydrofuran were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. All other commercially available compounds were used as obtained from the chemical suppliers. Analytical thin layer chromatography was carried out using commercially available aluminium backed plates coated with Merck G/UV254 silica gel. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid followed by heating. Flash chromatography was carried out using chromatography grade silica (60Å particle size, 35-70 microns) from Fisher Scientific. Samples were pre-absorbed onto silica or loaded as saturated solutions in an appropriate solvent. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C.

Proton NMR spectra were recorded at 300 MHz on a Brüker Avance 300 spectrometer or at 500 MHz on a Brüker Avance 500 spectrometer. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; dtd, doublet of triplets of doublets; dq, doublet of quartets; dqd, doublet of quartets of doublets; tt, triplet of triplets; qd, quartet of doublets; m, multiplet; app., apparent and br, broad. Chemical shifts δ are quoted in parts per million and are referenced to the residual solvent peak. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. $^{13}C\{^{1}H\}$ NMR spectra were recorded at 75 MHz on a Brüker Avance 300 spectrometer. Chemical shifts δ are quoted in parts per million and are referenced to the residual solvent peak.

Mass spectra were either recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea or were obtained on a Brüker Daltonics micrOTOF spectrometer using either positive or negative electrospray ionisation (ESI) as stated. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with only selected absorbances quoted as ν in cm^{-1}. All capillary melting points were measured using a Büchi 535 melting point apparatus and are reported uncorrected.

X-ray data were collected at 150 K on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ = 0.71073 Å), and all structures were solved by direct methods and refined on all *F2* data using SHELXL-97 suite of programs, with hydrogen atoms included in idealized positions and refined using the riding model.

6.1 General Procedures

General Procedure 1: *N*-Acylation of oxazolidin-2-ones.

A solution of butyllithium (1.1 equiv) was added dropwise to a stirring solution of oxazolidin-2-one (1.0 equiv) in dry tetrahydrofuran at -78 °C under nitrogen. The reaction was stirred for 30 minutes, after which the appropriate acid chloride (1.1 equiv) was added dropwise and the reaction was allowed to warm to 0 °C over 2 hours. After this period the reaction was quenched with saturated ammonium chloride solution and diluted with ethyl acetate, the resulting organics were washed with saturated sodium hydrogencarbonate solution (enough to dissolve the white precipitate) and brine and dried over magnesium sulphate. The solvent was removed under reduced pressure and the resulting crude product was purified either by recrystallisation from an appropriate solvent or over a column of silica gel.

General Procedure 2: *syn*-Selective aldol *via* a boron enolate.

A solution of 9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (1.1 equiv, 0.5M solution in hexanes) was added in one portion to a stirring solution of the required *N*-acylated auxiliary (1.0 equiv) in dry dichloromethane at 0 °C under nitrogen. After 30 minutes *N,N*-diisopropylethylamine (1.3 equiv) was added in one portion and stirred for a further 30 minutes at 0 °C. After this period the reaction mixture was cooled to -78 °C and stirred for 30 minutes, upon which the appropriate aldehyde (1.3 equiv) was added in one portion. The resulting mixture was allowed to warm to room temperature overnight and was subsequently quenched with Na_2PO_4/NaH_2PO_4 (pH7 buffer solution, 10 cm^3) and was stirred for 10 minutes, followed by the addition of hydrogen peroxide/methanol solution (1:2 mixture, 10 cm^3) and stirred for up to 24 hours. The mixture was concentrated under reduced pressure and dissolved in dichloromethane, the resulting organics were washed with saturated sodium hydrogencarbonate solution, brine and dried over magnesium sulphate. The solvent was removed under reduced pressure and the resulting crude was purified either by recrystallisation from an appropriate solvent or over a column of silica gel.

General Procedure 3: *syn*-Selective aldol with a α-chloro-substituent *via* a boron enolate.

A stirring solution of *S*-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one (**142d**, 1.0 equiv) under nitrogen was cooled to -78 °C. A solution of dibutylboron trifluoromethanesulphonate (1.1 equiv, 1.0M in dichloromethane) was added dropwise over 20 minutes and was immediately followed by the addition of *N,N*-diisopropylethylamine (1.25 equiv) in one portion and was stirred for 30 minutes. After which the reaction mixture was allowed to warm to room temperature and stirred for 90 minutes, and was subsequently recooled to -78 °C and stirred for 20 minutes. After this period the appropriate aldehyde (1.25 equiv) was added dropwise, the temperature was maintained for 5 hours. The resulting mixture was allowed to warm to room temperature overnight and was subsequently cooled to 0 °C, quenched with Na_2PO_4/NaH_2PO_4 (pH7 buffer solution, 10 cm^3), methanol (10 mL) and was stirred for 30 minutes. After which hydrogen peroxide (20 cm^3) was added dropwise and stirred for 1 hour. The mixture was concentrated under reduced pressure and dissolved in dichloromethane, the resulting organics were washed with saturated sodium hydrogencarbonate solution, brine and dried over magnesium sulphate. The solvent was removed under reduced pressure and the resulting crude was purified over a column of silica gel.

General Procedure 4: *non*-Evans'-selective *anti*-aldol *via* a magnesium enolate.

Magnesium chloride (0.1 equiv) was added in one portion to a stirring mixture of *N*-acylated-oxazolidin-2-one (1.0 equiv), triethylamine (2.0 equiv), trimethylsilyl chloride (1.5 equiv), sodium hexafluoroantimonate (0.3 equiv), the appropriate aldehyde (1.5 equiv) and dry ethylacetate (0.5 M) under nitrogen and was stirred at room temperature for 24 hours. The resulting reaction mixture was concentrated under reduced pressure; the concentrate was dissolved in methanol (30 ml) and trifluoroacetic acid (1 mL) and stirred for 30 minutes. After which the reaction mixture was concentrated under vacuum and partitioned between saturated sodium hydrogencarbonate and DCM, the resulting organics were washed with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure and the resulting crude was purified over a column of silica gel.

General Procedure 5: Synthesis of α-methylene aldehydes.

A mixture of the aldehyde (1.0 equiv), dimethylamine hydrochloride (1.2 equiv) and 37 % aqueous formaldehyde (1.2 equiv) was stirred at 70 °C for 24 hours. After this time an excess of saturated aqueous sodium hydrogencarbonate was added; the aqueous phase was separated and extracted with hexane (3 x 10mL). The organics were combined, washed with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to afford the α-methylene aldehyde.

General Procedure 6: Epoxidation/lactonisation

Vanadyl acetylacetonate (0.1 equiv) was added in one portion to a stirring solution of the appropriate aldol product (1.0 equiv) in benzene under nitrogen. After 5 minutes, *tert*-butyl hydroperoxide (5 to 6M solution in decane, 1.1 equiv) was added in one portion and stirred. After one hour, 1 mL of water was added to the reaction mixture and was allowed to stir overnight. The resulting reaction mixture was concentrated under reduced pressure and immediately purified over a column of silica gel.

General Procedure 7: Dihydroxylation/lactonisation

Osmium tetroxide (0.1 equiv) was added in one portion to a stirring solution of the appropriate aldol product (1.0 equiv) in acetone/water (8:1 ratio) under nitrogen. After 5 minutes, 4-methylmorpholine *N*-oxide (50 wt. % solution in water, 1.1 equiv) was added in one portion and stirred for 48 hours. The resulting reaction mixture was concentrated under reduced pressure and immediately purified over a column of silica gel.

General Procedure 8: α-chloro elimination reaction.

Zinc dust (4 equiv.) and ammonium chloride were added to a solution of the appropriate α-chloro-*syn*-aldol (1.0 equiv.) in methanol (14 mL/g) and sonicated for 5 minutes at ambient temperature. The resulting reaction mixture was stirred for 3 hours under nitrogen for 3 hours. After this time, the reaction mixture was diluted with an excess of diethyl ether and filtered through a pad of Celite ® and concentrated under reduced pressure and the filtration process repeated. The resulting crude was purified over a column of silica gel.

General Procedure 9: Cyclopropanation

The appropriate *syn*-aldol product (1 equiv.) was dissolved in dichloromethane and stirred at -10 °C under nitrogen. Diethyl zinc (5 equiv.) was added in one portion followed by diiodomethane (5 equiv.). The reaction was stirred for 2 hours in the absence of light and allowed to warm to 0 °C. The reaction was quenched with saturated sodium sulphite (5 mL) and stirred for 10 minutes before sufficient 1.0 M HCl was added to dissolve the white precipitate. The aqueous layer was separated and extracted with dichloromethane and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the crude *syn*-aldol cyclopropane product, which was purified by recrystallisation from an appropriate solvent or over a column of silica gel.

General Procedure 10: Transesterification

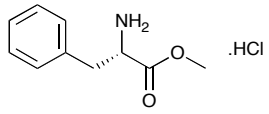
The appropriate *syn*-aldol cyclopropane product (1 equiv.) was dissolved in dichloromethane under nitrogen. A solution of sodium methoxide (1 equiv.) was added and the reaction was stirred for 5 minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude methyl ester cyclopropane product, which was purified over a column of silica gel.

General Procedure 11: Oxymercuration

Mercury trifluoroacetate (2.5 equiv) was added in one portion to a stirred solution of the appropriate cyclopropane methyl ester (1.0 equiv) in dichloromethane (10 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford crude product, which was purified over a column of silica gel.

6.2 Compounds for Chapter 3

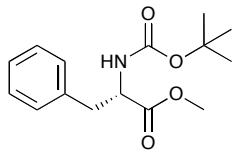
6.2.1 (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride, 154



The preparation of the title compound was adapted from the previously published procedure.[156] Thionyl chloride (33.1 mL, 0.45 mol, 1.1 equiv) was added dropwise to a stirring solution of L-phenyl alanine (50 g, 0.30 mol, 1.0 equiv) in methanol (500 mL), and was allowed to react under nitrogen overnight. The resulting reaction mixture was concentrated under reduced pressure, **(*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride, 154** was subsequently precipitated from the concentrate by addition of diethyl ether (100 mL). The precipitate was filtered and washed with a further 30 mL portion of diethyl ether and the resulting product was carried forward without any further purification.

$[\alpha]_D^{23}$ = -38 (c = 1.0 in MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.43 – 7.20 (5H, m, Ph), 4.32 (1H, dd, C*H*N, *J* = 8.1 and 5.0 Hz), 3.78 (3H, s, CH_3O), 3.20 (1H, dd, CH_AH$_B$Ph, *J* = 14.0 and 5.0 Hz), 3.25 (1H, dd, CH$_A$$H_B$Ph, *J* = 14.0 and 5.0 Hz); ^{13}C (75 MHz, MeOD) δ 170.9, 135.7, 130.9, 130.6, 129.4, 55.6, 54.0, 37.8; IR (ATR) ν (cm^{-1}): 1740.7 (C=O); HRMS (ES+): *m/z* calculated for $C_{10}H_{13}NO_2$ requires 180.1024 for $[M+H]^+$, found 180.1016; requires 202.0843 for $[M+Na]^+$, found 202.0834.

6.2.2 (*S*)-methyl 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate, 155

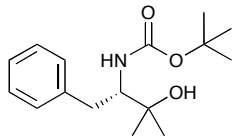


The preparation of the title compound was adapted from the previously published procedure. Boc_2O (72.5 g, 0.332 mol, 1.1 equiv) was added in one portion to a solution of (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride **154** (65.1 g, 0.302 mol, 1.0 equiv) in absolute ethanol (sufficient to dissolve the compound) at 0 °C. Solid sodium hydrogencarbonate (76.11 g, 0.906

mol, 3 equiv) was added in one portion and the reaction was stirred for 48 hours. The solvent was then removed under reduced pressure and the crude mixture dissolved in ether (50 cm^3). The mixture was filtered through a pad of Celite® with diethyl ether as eluent (3 x 20 cm^3). The solvent was removed under reduced pressure to give the crude product **(*S*)-methyl 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate 155**, which matched the previously published data for this compound.[234] The crude product was carried on to the next step without further purification.

$[\alpha]_D^{23}$ = -42 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.10 (5H, m, Ph,), 4.97 (1H, broad d, *J* = 6.0 Hz, N*H*), 4.61 (1H, dd, *J* = 14.0 Hz and 6.0 Hz NC*H*), 3.73 (3H, s, OCH_3), 3.10 (2H, m, CH_2Ph), 1.40 (9H, s, Boc); ^{13}C (75 MHz, $CDCl_3$) δ 172.5, 156.0, 137.3, 129.3, 128.6, 127.4, 80.2, 54.2, 52.3, 38.2, 28.5; IR (ATR) ν (cm^{-1}): 1735.7 (C=O), 1701.6 (C=O); HRMS (ES+): *m/z* calculated for $C_{15}H_{21}NO_4$ requires 280.1549 for $[M+H]^+$, found 280.1554; requires 302.1368 for $[M+Na]^+$, found 302.1377.

6.2.3 (*S*)-*tert*-butyl 3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, 156

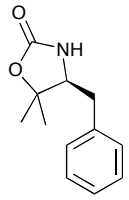


The preparation of the title compound was adapted from the previously published procedure.[133] A small volume of methyl iodide (12.97 g, 208.3 mmol, 4.0 equiv) was added to a stirring suspension of magnesium turnings (5.07 g, 208.3 mmol, 4.0 equiv) in dry diethyl ether (100 mL), and gently heated to initiate the formation of Grigniard reagent, sufficient is added to maintain a gentle reflux. The remainder of methyl iodide was diluted with diethyl ether (50 mL) and added dropwise to the reaction mixture over a period of 30 minutes. The solution was allowed to cool to room temperature, after this period (*S*)-methyl 2-(*tert*-butoxycarbonyl)-3-phenylpropanoate, **155** (15.27 g, 52.1 mmol, 1.0 equiv) in 50 mL of diethyl ether was added drop-wise to the reaction mixture over a period of 15 minutes. The reaction was stirred for 48 hours after which the reaction mixture was quenched with Rochelle's salt, filtered through Celite® and washed with ethyl acetate (3 x 20 cm^3). The organics were washed with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to give the crude product **(*S*)-*tert*-butyl 3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, 156,** which was carried on to the next step without purification.

mp 100 – 103 °C; $[\alpha]_D^{24}$ = -45.1 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 – 7.29 (5H, m, Ph), 4.52 (1H, d, N*H*, *J* = 8.9 Hz), 3.60 (1H, m, C*H*N), 3.02 (1H, dd, CH_AH$_B$Ph, *J* =

13.5 and 3.5 Hz), 2.53 (1H, m, CH_AH_BPh), 1.23 (6H, s, $(CH_3)_2$), 1.20 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 139.3, 129.2, 128.7, 126.4, 79.7, 73.4, 60.7, 36.4, 28.5, 27.5, 26.6; IR (ATR) ν (cm^{-1}): 3500 (broad OH), 3334 (NH), 1670 (C=O); HRMS (ES+): *m/z* calculated for $C_{16}H_{25}NO_3$: requires 280.1907 for $[M+H]^+$; found: 280.1909.

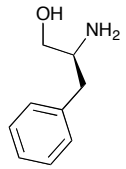
6.2.4 (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, 157



The preparation of the title compound was adapted from the previously published procedure. [156] Potassium *tert*-butoxide (4.5 g, 40.3 mmol, 1.1 equiv) was added in one portion to a stirring solution of (*S*)-*tert*-butyl 3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, **156** (7.5 g, 26.0 mmol, 1.0 equiv) in dry tetrahydrofuran (40 cm^3) under nitrogen and stirred for two hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride (10 cm^3), extracted with diethyl ether (3 x 20 cm^3) washed with saturated sodium hydrogencarbonate solution (10 cm^3), brine (10 cm^3) and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield the crude product. Purification by recrystallisation (diethyl ether and hexane) gave **(*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, 157** (4.0 g, 19.5 mmol, 77 %) as a white solid, which matched the previously published data for this compound.[133]

mp = 60 – 61 °C, $[\alpha]_D^{23}$ = -103.0 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.08 (5H, m Ph), 5.09 (1H, broad s, N*H*), 3.63 (1H, dd, *J* = 10.5 Hz and 4.0 Hz, C*H*N), 2.77 (1H, dd, *J* = 13.5 Hz and 4.0 Hz, CH_AH_BPh), 2.62 (1H, dd, *J* = 13.5 Hz and 10.0 Hz, CH_AH_BPh), 1.39 (3H, s, $(CH_3)C(CH_3)$), 1.38 (3H, s, $(CH_3)C(CH_3)$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 137.3, 129.5, 129.3, 127.6, 83.6, 63.5, 37.5, 27.9, 22.4.; IR (ATR) ν (cm^{-1}): 3254.4 (N-H), 1717.2 (C=O); HRMS (ES+): *m/z* calculated for $C_{12}H_{15}NO_2$ requires 206.1181 for $[M+H]^+$, found 206.1168; requires 228.1000 for $[M+Na]^+$, found 228.0985.

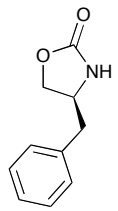
6.2.5 (*S*)-2-amino-3-phenylpropan-1-ol, 327



Boron trifluoride diethyl etherate (7.60 mL, 60.6 mmol) was added dropwise over 15 minutes to a suspension of L-Phenylalanine (10 g, 60.5 mmol) in 70 mL of dry tetrahydrofuran. The resulting mixture was stirred at ambient temperature for 15 minutes and subsequently heated to reflux and stirred for 2 hours. Borane dimethyl sulphide complex (7.2 mL, 75.6 mmol) was subsequently added over 90 minutes and the solution refluxed for 16 hours before cooling to room temperature. After this time tetrahydrofuran/methanol (1:1, 10 mL) and sodium hydroxide solution (5.0 M, 50 mL) were added dropwise and the resulting mixture heated to reflux for six hours. The resulting precipitate was filtered and the resulting filtrate concentrated under reduced pressure. The resulting mixture was extracted into dichloromethane (30 mL x 3), and the resulting organics were washed with brine and dried over magnesium sulphate. Purification of the resulting pale yellow solid by recrystallisation (diethyl ether and hexane) gave **(*S*)-2-amino-3-phenylpropan-1-ol, 327** (7.9 g, 52.1 mmol) as a white solid in 85% yield.

mp = 83 – 84 °C; $[\alpha]_D^{24}$ = -21.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.35 (5H, m, Ph), 3.65 (1H, dd, *J* = 10.5 Hz and 3.4 Hz, CH_AH$_B$OH), 3.40 (1H, dd, *J* = 10.5 Hz and 7.4 Hz, CH$_A$$H_B$OH), 3.10 (1H, m, C*H*N), 2.80 (1H, dd, *J* = 13.5 Hz and 5.5 Hz, CH_AH$_B$Ph), 2.55 (1H, dd, *J* = 13.5 Hz and 8.7 Hz, CH$_A$H$_B$Ph), 1.68 (3H, br. s, O*H*, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 129.6, 129.1, 126.8, 66.3, 54.6, 41.1; IR (ATR) ν (cm^{-1}): 3330 (broad N-H), 3298 (broad O-H).

6.2.6 (*S*)-4-benzyloxazolidin-2-one, 225

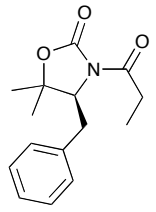


(*S*)-2-Amino-3-phenylpropan-1-ol **327** (10 g, 66.3 mmol, 1.0 equiv), anhydrous potassium carbonate (0.92 g, 6.63 mmol, 0.1 equiv.) and diethyl carbonate (16.07 ml, 132.6 mmol, 2.0 equiv) were placed in round bottom flask fitted with Vigreux column and distillation head and

receiving flask. The mixture was heated to 135 °C and stirred for 4 hours, after which time the resulting pale yellow solution was cooled to room temperature, diluted with dichloromethane and washed with water and brine. The resulting organics were dried over magnesium sulphate and concentrated under reduced pressure to yield the crude product. Recrystallisation from hot ethyl acetate and hexane yielded **(*S*)-4-benzyloxazolidin-2-one, 225** (8.57 g, 48.4 mmol, 73 %) as white solid.

mp = 83 – 85 °C; $[\alpha]_D^{24}$ = 5.5 (c = 0.66 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.38 (3H, m, Ph), 7.20 (2H, app. d, *J* = 7.0 Hz, Ph), 5.05 (1H, br. s, N*H*), 4.50 (1H, app. t, *J* =8.5 Hz CH_AH$_B$OH), 4.20 (1H, m, CH$_A$$H_B$OH), 4.10 (1H, m, C*H*N), 2.90 (1H, m, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 136.3, 129.5, 129.3, 127.5, 70.1, 54.2, 41.8; IR (ATR) ν (cm^{-1}): 3278.7 (N-H), 1746.9 (C=O); HRMS (ES+): *m/z* calculated for $C_{10}H_{11}NO_2$: requires 178.0863 for $[M+H]^+$; found: 178.0860.

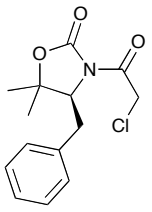
6.2.7 (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 142a



The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, **157** (2.0 g, 9.75 mmol), butyllithium (2.5 M in hexanes, 4.29 mL, 10.76 mmol) and propionyl chloride (1.02 mL, 9.75 mmol). Purification by recrystallisation (diethyl ether and hexane) gave (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **142a** as a white solid (2.40 g, 9.16 mmol, 94%).

$[\alpha]_D^{24}$ = -46.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (5H, m, Ph), 4.50 (1H, dd, *J* = 9.5, 4.0 Hz, NC*H*), 3.15 (1H, dd, *J* = 14.5, 4.0 Hz, CH_AH$_B$Ph), 2.96-2.84 (3H, m, CH$_A$$H_BPh, CH_2CH_3$), 1.37 (3H, s, CC$H_3$), 1.36 (3H, s, CC$H_3$), 1.14 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 137.0, 129.1, 128.6, 126.8, 82.2, 63.5, 35.4, 30.9, 29.3, 28.6, 22.3, 8.3; IR (KBr)/ cm^{-1} ν = 1774 (C=O), 1708 (C=O); HRMS (ESI): *m/z* for $C_{15}H_{20}NO_3$ requires $[M+H]^+$ requires 262.1438; found 261.1442;

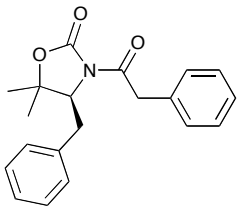
6.2.8 (*S*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one, 142d



The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, **157** (3.048 g, 14.80 mmol), butyllithium (2.5 M in hexanes, 6.6 mL, 16.30 mmol) and chloroacetyl chloride (1.42 mL, 17.80 mmol). Purification by recrystallisation (diethyl ether and hexane) gave **(*S*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one, 142d** as a pale yellow solid (2.87 g, 10.21 mmol, 69 %).

R_f (CH_2Cl_2) = 0.74; $[\alpha]_D^{25}$ = +40 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.34-7.19 (5H, m, Ph), 4.56 (1H, d, *J* = 12.5 Hz, C*H*$_A$H$_B$Br), 4.49 (1H, dd, *J* = 10.0 Hz and 4.0 Hz, CHN), 4.42 (1H, d, *J* = 12.5 Hz, CH$_A$*H*$_B$Br), 3.18, (1H, dd, *J* = 14.5 Hz and 4.0 Hz, PhC*H*$_A$H$_B$), 2.89 (1H, dd, *J* = 14.5 Hz and 10.0 Hz, PhCH$_A$*H*$_B$), 1.38 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.37 (3H, s, (CH$_3$)C(C*H*$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 152.3, 137.1, 129.4, 129.2, 127.4, 84.0, 63.4, 35.3, 29.0, 28.7, 22.7; IR (ATR) ν (cm^{-1}): 1787.4 (C=O), 1711.4 (C=O$_{ox}$); HRMS (ES+): *m/z* calculated for $C_{14}H_{16}ClNO_3$ requires 304.0716 for $[M+Na]^+$, found 304.0711.

6.2.9 (*S*)-4-benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one, 142c

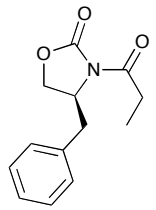


The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, **157** (991.0 mg, 4.83 mmol), butyllithium (2.5 M in hexanes, 2.12 mL, 5.31 mmol) and phenylacetyl chloride (0.83 mL, 6.28 mmol). Purification by recrystallisation (diethyl ether and hexane) gave **(*S*)-4-benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one, 142c** as a white solid (1.11 g, 3.43 mmol, 71 %).

R_f (CH_2Cl_2) = 0.45; $[\alpha]_D^{25}$ = -17.0 (c = 0.73 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.19 (10H, m, Ph), 4.50 (1H, dd, *J* = 10.0 Hz and 4.0 Hz, CHN), 4.30 (2H, app. s, COC*H*$_2$), 3.18

(1H, dd, J = 14.5 Hz and 10.0 Hz, CH_AH$_B$Ph), 2.85 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH$_A$$H_B$Ph), 1.37 (3H, s, (C$H_3$)C(CH$_3$), 1.32 (3H, s, (CH$_3$)C(C$H_3$)); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.9, 153.0, 137.2, 134.1, 130.1, 129.5, 129.1, 129.0, 127.6, 127.2, 82.8, 64.2, 42.2, 35.6, 29.0, 22.7; IR (ATR) ν (cm^{-1}): 1766.4 (C=O); 1712.7 (C=O$_{ox}$); HRMS (ES+): *m/z* calculated for $C_{20}H_{21}NO_3$ requires 324.1600 for $[M+H]^+$, found 324.1607; requires 346.1419 for $[M+Na]^+$, found 346.1424.

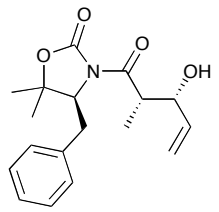
6.2.10 (*S*)-4-benzyl-3-propionyloxazolidin-2-one, 241



The title compound was prepared according to General Procedure 1 (*S*)-4-benzyl-oxazolidin-2-one, **225** (6.18 g, 34.90 mmol) butyllithium (2.5 M in hexanes, 15.36 mL, 38.39 mmol) and propionyl chloride (3.65 mL, 41.8 mmol). Purification by recrystallisation (diethyl ether and hexane) gave **(*S*)-4-benzyl-3-propionyloxazolidin-2-one, 241** as a white solid (5.61 g, 24.08 mmol, 69 %).

mp = 41-42 °C, $[\alpha]_D^{26}$ = + 90.4 (*c* = 0.95 in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25-7.19 (5H, m, Ph), 4.65 (1H, m, NC*H*), 4.10 (2H, m, CH$_2$O), 3.25 (1H, dd, J = 13.5, 3.5 Hz, CH_AH$_B$Ph), 2.88 (2H, m, CH$_2$CH$_3$), 2.72 (1H, dd, J = 13.5, 9.5 Hz CH$_A$$H_B$Ph), 1.14 (3H, t, J = 7.3 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.6, 154.1, 135.6, 129.7, 129.3, 127.9, 66.5, 55.4, 38.3, 29.1, 8.8; IR (ATR) ν (cm^{-1}): 1782.0 (C=O), 1699.3 (C=O$_{ox}$); HRMS (ESI): *m/z* calculated for $C_{13}H_{16}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1134; requires 256.0950 for $[M+Na]^+$; found: 256.0948.

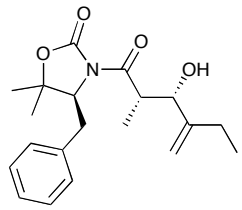
6.2.11 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163a



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (3.78 mL, 1.89 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (0.400 g, 1.71 mmol) in dichloromethane (90 mL) followed by addition of *N,N*-diisopropylethylamine (0.43 ml, 2.45 mmol) and acrolein (0.16 mL, 2.45 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163a** (0.26 g, 0.90 mmol, 53 %) as a colourless oil.

R_f (CH_2Cl_2) = 0.13; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.12 (5H, m, Ph), 5.83-5.70 (1H, ddd, *J* = 10.5 Hz, 5.5 Hz and 5.275 Hz, C*H*=CH_2), 5.25 (1H, dt, *J* = 1.5 Hz, C$H_{cis}H_{trans}$=C), 5.13 (1H, dt, *J* = 10.5 Hz and 1.5 Hz, C$H_{cis}H_{trans}$=C), 4.49 (1H, dd, *J* = 9.0 Hz and 4.5 Hz, CHN), 4.38 (1H, m, C*H*OH), 3.85 (1H, dq, *J* = 7.0 Hz and 4.0 Hz, C*H*CH_3), 3.0 (1H, dd, *J* = 14.5 Hz and 4.5 Hz, CH_AH_BPh), 2.85 (1H, dd, *J* =14.5 Hz and 9.0 Hz, CH_AH_BPh), 2.65 (1H, broad s, OH), 1.33 (3H, s, (CH_3)C(CH_3)), 1.31 (3H, s, (CH_3)C(CH_3)), 1.10 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 152.8, 137.7, 137.0, 129.5, 129.1, 127.3, 116.8, 82.8, 73.2, 63.8, 42.85, 35.9, 28.8, 22.6, 11.7; IR (ATR) ν (cm^{-1}): 3501.1 (broad OH), 1754.2 (C=O), 1702.2 (C=O_{ox}); HRMS (ESI); *m/z* calculated for $C_{16}H_{19}NO_4$: requires 290.1392 for $[M+H]^+$; found: 290.1385; requires 312.1212 for $[M+Na]^+$; found: 312.1206.

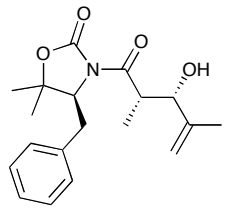
6.2.12 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one, 163c



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (9.46 mL, 4.7 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (1.080 g, 4.3 mmol) in dichloromethane (90 mL) followed by addition of *N,N*-diisopropylethylamine (0.94 ml, 5.37 mmol) and ethacrolein (0.450 g, 5.37 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one, 163c** (1.187 g, 3.44 mmol, 80 %) as a colourless oil.

$[\alpha]_D^{21}$ = -36 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (5H, m, Ph), 5.16 (1H, app. t, *J* = 1.0 Hz, CH_{cis}H$_{trans}$=C), 4.98 (1H, app. t, *J* = 1.0 Hz, CH$_{cis}$$H_{trans}$=C), 4.53 (1H, dd, *J* = 9.0 Hz and 4.0 Hz, C*H*N), 4.40 (1H, d, *J* = 3.5 Hz, C*H*OH), 3.96 (1H, qd, *J* = 7.0 Hz and 3.5 Hz, C*H*CO), 3.08 (1H, dd, *J* = 14.0 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.91 (1H, dd, *J* =14.0 Hz and 9.5 Hz, CH$_A$$H_B$Ph), 2.91 (1H, br. s, OH), 2.02 (2H, m, CH_2CH$_3$) 1.40 (3H, s, (CH_3)C(CH$_3$)), 1.38 (3H, s, (CH$_3$)C(CH_3)), 1.11 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.07 (3H, t, *J* = 7.0, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 152.6, 150.3, 137.0, 129.5, 129.1, 127.3, 109.9, 82.7, 74.1, 63.8, 41.1, 35.8, 28.8, 25.7, 22.6, 12.5, 11.1; IR (thin film / cm^{-1}) 3497 (broad O-H), 1773 (C=O$_{ox}$), 1700 (C=O); HRMS (ES+): *m/z* calculated for $C_{20}H_{27}NO_4$: requires 346.2013for $[M+H]^+$; found: 346.2014.

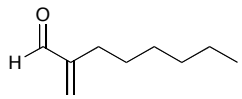
6.2.13 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,4-dimethylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163b



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (9.7 mL, 4.85 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (1.0551 g, 4.04 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.46 ml, 4.85 mmol) and methacrolein (0.46 mL, 4.85 mmol) according to General Procedure 2 to afford the crude product as a coloured oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,4-dimethylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163b** (1.084 g, 3.27 mmol, 81%) as a colourless oil.

$[\alpha]_D^{20}$ = -34 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (5H, m, Ph), 5.12 (1H, app. t, *J* = 1.1 Hz, C*H*$_{cis}$H$_{trans}$=C), 4.96 (1H, app. t, *J* = 1.1 Hz, CH$_{cis}$*H*$_{trans}$=C), 4.53 (1H, dd, *J* = 9.0 Hz and 4.5 Hz, C*H*N), 4.43 (1H, m, C*H*OH), 3.98 (1H, qd, *J* = 7.0 Hz and 4.0 Hz, C*H*CO), 3.08 (1H, dd, *J* = 14.5 Hz and 4.5 Hz, C*H*$_A$H$_B$Ph), 2.91 (1H, dd, *J* =14.5 Hz and 9.0 Hz, CH$_A$*H*$_B$Ph), 2.84 (1H, broad s, OH), 2.40 (3H, s, C*H*$_3$C=C), 1.42 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.39 (3H, s (CH$_3$)C(C*H*$_3$)), 1.29 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.4, 152.7, 144.3, 137.0, 129.5, 129.0, 127.3, 112.3, 82.8, 74.6, 63.8, 40.8, 35.8, 28.8, 22.6, 19.7; 11.0; IR (KBr / cm^{-1}) 3501 (broad O-H), 1770 (C=O$_{ox}$), 1685 (C=O); HRMS (ES+): *m/z* calculated for $C_{19}H_{25}NO_4$: requires 354.1681 for $[M+Na]^+$; found: 354.1687.

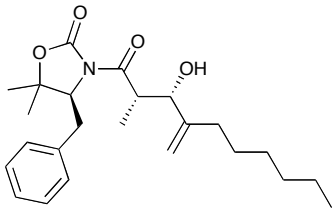
6.2.14 2-methyleneoctanal, 165



Octanal (10 mL, 64.0 mmol), formaldehyde (6.3 mL, 84.4 mmol, 37% in water) and dimethylamine hydrochloride (6.89 g, 84.4 mmol) were treated according to General Procedure 5. Concentration of the combined organics yielded **2-methyleneoctanal, 165** (6.91 g, 49.28 mmol, 77 %) as a clear oil without the need for further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, s, C*H*O), 6.18 (1H, s, C=CH_AH_B), 5.93 (1H, s, C=CH_AH_B), 2.20 (1H, t, *J* = 7.5 Hz, CH_2C=CH_2), 1.17-1.27 (8H, br. m, (CH_2)$_4$), 0.87 (3H, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 150.7, 134.2, 30.5, 20.3, 27.4, 26.7, 23.1, 14.7; IR (thin film / cm^{-1}) 1725.4 (C=O).

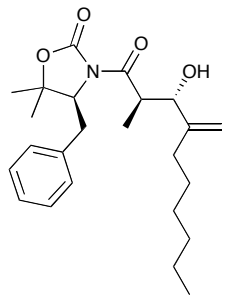
6.2.15 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylenedecanoyl)-5,5-dimethyloxazolidin-2-one, 163e



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (8.58 mL, 4.29 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (1.020 g, 3.90 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.88 mL, 5.07 mmol) and 2-methyleneoctanal (0.711 mg, 5.03 mmol) according to General Procedure 2 to afford the crude product as a yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylenedecanoyl)-5,5-dimethyloxazolidin-2-one, 163e** (1.174 g, 2.92 mmol, 75 %) as a colourless oil.

$[\alpha]_D^{25}$ = -27.8 (*c* = 1.15 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (5H, m, Ph), 5.15 (1H, app. s, CH_{cis}H$_{trans}$=C), 4.96 (1H, m, CH$_{cis}$$H_{trans}$=C), 4.53 (1H, dd, *J* = 9.0 Hz and 4.5 Hz, C*H*N), 4.38 (1H, d, *J* = 3.4 Hz, C*H*OH), 3.95 (1H, qd, *J* = 7.2 Hz and 3.4 Hz, C*H*CO), 3.08 (1H, dd, *J* = 14.5 Hz and 4.5 Hz, CH_AH$_B$Ph), 2.90 (1H, dd, *J* =14.5 Hz and 9.0 Hz, CH$_A$$H_B$Ph), 2.76 (1H, br. s, OH), 1.98 (2H, m, CH_2C=C) 1.45 (2H, m, CH_2CH$_3$) 1.39 (3H, s, (CH_3)C(CH$_3$)), 1.37 (3H, s, (CH$_3$)C(CH_3)), 1.28 (6H, m, (CH_2)$_3$), 1.11 (3H, d, *J* = 7.2 Hz, CH_3CH), 0.87 (3H, t, *J* = 7.0, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 152.6, 148.8, 137.0, 129.5, 129.1, 127.3, 110.8, 82.7, 73.8, 63.8, 41.0, 35.8, 33.1, 32.1, 29.5, 28.8, 28.27, 23.0, 22.6, 14.5, 11.0 ; IR (thin film / cm^{-1}) 3499 (broad O-H), 1780 (C=O$_{ox}$), 1700 (C=O); HRMS (ES): *m/z* calculated for $C_{24}H_{35}NO_4$: requires 402.2639 for $[M+H]^+$; found: 402.2637.

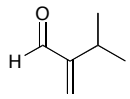
6.2.16 (*S*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyl-4-methylenedecanoyl)-5,5-dimethyloxazolidin-2-one, 146



According to General Procedure 4, to a stirring mixture of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one (100 mg, 0.38 mmol) in dry ethyl acetate (2 mL) was added magnesium chloride (7.3 mg, 0.076 mmol), sodium hexafluoroantimonate (29.5mg, 0.114 mmol), triethylamine (0.11 mL, 0.76 mmol), trimethylsilyl chloride (0.07 mL, 0.57 mmol) and the 2-methyleneoctanal (64 mg, 0.46 mmol) under nitrogen and was stirred at room temperature for 48 hours. The resulting reaction mixture was filtered through a pad of Celite® and washed with diethyl ether and concentrated under reduced pressure. The concentrate was dissolved in methanol (30 ml) and trifluoroacetic acid (1 mL) and stirred for 30 minutes. The resulting crude was purified *via* column chromatography to yield **(*S*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyl-4-methylenedecanoyl)-5,5-dimethyloxazolidin-2-one, 146** (101.9 mg, 0.253 mmol, 67 %) as a colourless oil.

$[\alpha]_D^{24}$ = -42.1 (*c* = 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.31 (5H, m, Ph), 5.03 (1H, app. s, CH_{cis}H$_{trans}$=C), 4.91 (1H, m, CH$_{cis}$$H_{trans}$=C), 4.47 (1H, dd, *J* = 9.8 and 3.4 Hz, C*H*N), 4.14 (2H, m, C*H*OH and C*H*CO), 3.15 (1H, dd, *J* =14.7 and 3.4 Hz CH_AH$_B$Ph), 2.83 (1H, dd, *J* = 14.7 and 9.8 Hz, CH$_A$$H_B$Ph), 2.77 (1H, br. s, OH), 2.10 (1H, m, CH_AH$_B$C=C), 2.0 (1H, m, CH_AH$_B$C=C), 1.46 (2H, m, CH_2CH$_3$), 1.33 (3H, s, (CH_3)C(CH$_3$)), 1.31 (3H, s, (CH$_3$)C(CH_3)), 1.28 (6H, m, (CH_2)$_3$), 1.13 (3H, d, *J* = 6.4 Hz, CH_3CH), 0.87 (3H, t, *J* = 6.7 Hz, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 153.2, 149.7, 137.5, 129.4, 129.1, 127.2, 112.4, 82.7, 79.1, 64.5, 41.3, 35.6, 32.2, 31.4, 29.6, 28.9, 28.3, 23.0, 22.7, 15.4, 14.5; IR (ATR) ν (cm^{-1}): 3499 (broad O-H), 1780 (C=O), 1700 (C=O); HRMS (ES): *m/z* calculated for $C_{24}H_{35}NO_4$: requires 402.2639 for $[M+H]^+$; found: 402.2638.

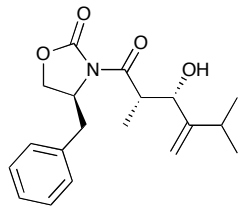
6.2.17 3-methyl-2-methylenebutanal, 164



Isovaleraldehyde (10 mL, 0.08 mol), formaldehyde (9 mL, 37% in water) and dimethylamine hydrochloride (9.12 g, 0.23 mol) were treated according to General Procedure 5. Concentration of the combined organics yielded **3-methyl-2-methylenebutanal, 164** (8.53 g, 88%) as a clear oil without the need for further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (1H, s, C*H*O), 6.18 (1H, s, C=CH_AH_B), 5.90 (1H, s, C=CH_AH_B), 2.69 (1H, d.sept, *J* = 7.0 Hz and 1.1 Hz, C*H*$(CH_3)_2$), 1.17-1.27 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 1.18 (3H, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 156.0, 132.1 , 25.3, 19.8; IR (thin film / cm^{-1}) 1696.5 (C=O).

6.2.18 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,5-dimethyl-4-methylenehexanoyl)oxazolidin-2-one, 163d

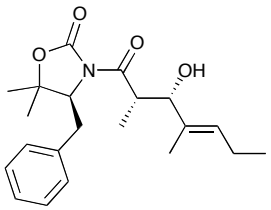


9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (13.2 mL, 6.61 mmol) was added to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one, **142a** (1.4023 g, 6.01 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (1.50 ml, 8.59 mmol) and 3-methyl-2-methylenebutanal, **164** (0.46 mL, 4.85 mmol) according to General Procedure 2 to afford the crude product as a coloured oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,5-dimethyl-4-methylenehexanoyl)oxazolidin-2-one, 163d** (1.708 g, 4.82 mmol, 71%) as a colourless oil which was recrystallised from Et_2O and petroleum ether.

mp = 97-99 °C; $[\alpha]_D^{27}$ = +38.9 (*c* = 0.88 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.07 (5H, m, Ph), 5.13 (1H, t, *J* = 1.1 Hz, C$H_{cis}H_{trans}$=C), 4.98 (1H, t, *J* = 1.1 Hz, CH$_{cis}$*H*$_{trans}$=C), 4.65 (1H, C*H*N), 4.43 (1H, br. d, *J* = 2.1 Hz, C*H*OH), 4.22 - 4.07 (2H, m, CH_2O), 3.89 (1H, dq, *J* = 7.2 and 3.2 Hz, C*H*CO), 3.20 (1H, dd, *J* = 13.45 and 3.25 Hz, CH_AH_BPh), 2.82 (1H, br. s, O*H*),

2.73 (1H, dd, J = 13.6 and 9.5 Hz, CH_AH_BPh), 2.13 (1H, p, J = 6.9 Hz), 1.13 (3H, d, J = 6.9 Hz, CH_3), 1.02 (3H, d, J = 6.8 Hz, CH_3), 0.99 (3H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 155.2, 153.37, 135.4, 129.8, 129.4, 127.9, 108.8, 72.8, 66.6, 55.6, 40.8, 38.1, 30.8, 23.8, 22.3, 10.6; IR (thin film / cm^{-1}) 3684.3 (broad O-H), 1781.2 ($C=O_{ox}$), 1681.1 (C=O); HRMS (ESI): *m/z* calculated for $C_{19}H_{25}NO_4$: requires 354.1681 for $[M+Na]^+$; found: 354.1676.

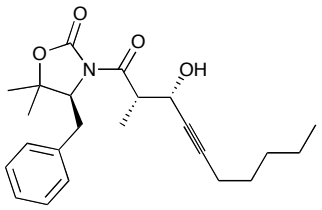
6.2.19 (*S*)-4-benzyl-3-((2*S*,3*S*,*E*)-3-hydroxy-2,4-dimethylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163i



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (7.08 mL, 3.539 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (841 mg, 3.217 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.73 mL, 4.182 mmol) and 2-methyl-pent-2-enal (0.477 mL, 4.182 mmol) according to General Procedure 2 to afford the crude product as a dark yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*,*E*)-3-hydroxy-2,4-dimethylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163i** (948.2 mg, 2.64 mmol, 82%) as a colourless oil.

$[\alpha]_D^{25}$ = -5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.12 (5H, m, Ph), 6.51 (1H, tt, J = 7.0 Hz and 1.5 Hz, C=C*H*), 4.45 (1H, dd, J = 9.0 Hz and 4.5 Hz), 4.23 (1H, br. s), 3.91 (1H, dq, J = 7.0 and 4.0 Hz), 3.10 (1H, dd J = 14.5 and 4.5 Hz), 2.84 (1H, dd, J = 14.5 and 9.0 Hz), 2.84 (1H, broad d), 2.1 – 1.9 (2H, m), 1.53 (3H, s), 1.32 (3H, s), 1.29 (3H, s), 1.00 (3H, d, J = 7.0 Hz) 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 152.7, 137.1, 133.4, 129.5, 129.0, 128.8, 127.2, 82.67, 76.1, 63.8, 41.1, 35.8, 28.7, 22.5, 21.3, 14.4, 13.5, 11.5; IR (ATR) ν (cm^{-1}): 3493 (broad O-H), 1777 (C=O), 1680 (C=O); HRMS (ES): *m/z* calculated for $C_{21}H_{29}NO_4$ requires 382.1994 for $[M+Na]^+$, found 382.1977.

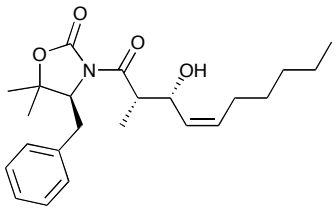
6.2.20 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyldec-4-ynoyl)-5,5-dimethyloxazolidin-2-one, 170



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (6.31 mL, 3.157 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (750 mg, 2.87 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.65 ml, 3.73 mmol) and 2-octynal (0.53 mL, 3.73 mmol) according to General Procedure 2 to afford the crude product as a yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyldec-4-ynoyl)-5,5-dimethyloxazolidin-2-one, 170** (929.4 mg, 2.4108 mmol, 84 %) as a colourless oil.

$[\alpha]_D^{23}$ = -7.5 (*c* = 0.75 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.15 (5H, m), 4.63 (1H, m), 4.50 (1H, dd, *J* = 9.0 Hz and 4.5 Hz), 3.84 (1H, qd, *J* = 7.0 and 4.5 Hz), 3.00 (1H, dd *J* = 14.0 Hz and 4.5 Hz), 2.85 (1H, dd, *J* = 14.0 Hz and 9.0 Hz), 2.66 (1H, d, *J* = 4.0 Hz, OH), 2.12 (2H, app. td, *J* = 7.0 Hz and 2.5 Hz), 1.48-1.19 (6H, m), 1.33 (3H, s), 1.31 (3H, s), 1.25 (3H, d, *J* = 7.0 Hz), 0.82 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 176.0, 152.6, 137.1, 129.6, 129.0, 127.3, 87.0, 83.0, 78.9, 64.0, 63.8, 44.6, 36.0, 31.4, 26.8, 26.5, 22.6, 19.1, 14.3, 12.8; IR (film / cm^{-1}): 3494 (broad OH), 1778 ($C=O_{ox}$), 1698 (C=O); HRMS (ES): *m/z* calculated for $C_{23}H_{31}NO_4$ requires 386.2326 for $[M+H]^+$, found 386.2330.

6.2.21 (*S*)-4-benzyl-3-((2*S*,3*R*,*Z*)-3-hydroxy-2-methyldec-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163j

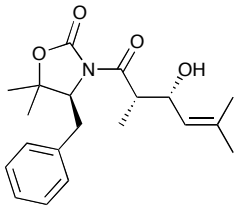


Lindlar's catalyst (10 mol%) was added to a solution of alkyne-aldol **170** (230 mg, 0.60 mmol) in dry methanol (10 mL), and the reaction mixture stirred under one atmosphere of hydrogen for one hour before the crude reaction mixture was filtered through Celite® using dichloromethane

(3 x 10 mL) as an eluent. The combined solvent was removed under reduced pressure to give a crude product, that was purified by chromatography to afford the title compound **(*S*)-4-benzyl-3-((2*S*,3*R*,*Z*)-3-hydroxy-2-methyldec-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163j** (220 mg, 0.56 mmol) as a yellow oil in 95% yield.

$[\alpha]_D^{23}$ = -28 (*c* = 0.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27- 7.12 (5H, m), 5.48 (1H, dtd, *J* = 11.0, 7.0, 1.0 Hz), 5.36 (1H, ddt, 11.0, 8.5, 1.5 Hz), 4.62 (1H, dd, *J* = 8.5, 5.0 Hz), 4.45 (1H, dd, *J* = 9.0, 4.5 Hz), 3.89 (1H, qd, *J* = 7.0, 5.0 Hz), 3.00 (1H, dd, *J* = 14.5, 4.5 Hz), 2.83 (1H, dd, *J* = 14.5, 9.0 Hz), 2.28 (1H, broad s, O*H*), 2.01 (2H, m), 1.33-1.17 (6H), 1.32 (3H, s),1.31 (3H, s), 1.12 (3H, d, *J* = 7.0 Hz), 0.82 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 176.5, 152.9, 137.1, 134.4, 129.5, 129.0, 128.9, 127.2, 82.6, 69.0, 63.8, 43.5, 35.9, 31.8, 29.6, 28.8, 28.2, 22.9, 22.6, 14.4, 12.7; IR (film / cm^{-1}): 3497 (broad OH), 1778 ($C{=}O_{ox}$), 1698 (C=O); HRMS (ES): *m/z* calculated for $C_{23}H_{33}NO_4$ requires 405.27483 for $[M+H]^+$, found 405.2749.

6.2.22 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163h

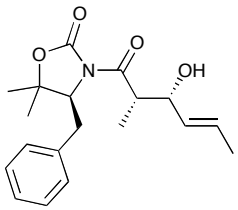


9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (8.05 mL, 4.023 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (956.1 mg, 3.658 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.828 ml, 4.755 mmol) and 3-methyl-2-butenal (0.46 mL, 4.76 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163h** (1.278 g, 3.70 mmol, 92%) as a white solid.

$[\alpha]_D^{21}$ = -27 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17 (5H, m), 5.23 (1H, d, *J* = 9.0 Hz), 4.60 (1H, m), 4.52 (1H, dd, *J* = 9.0 Hz and 4.5 Hz), 3.93 (1H, qd, *J* = 7.0 and 5.0 Hz), 3.05 (1H, dd *J* = 14.5 Hz and 4.5 Hz), 2.90 (1H, dd, *J* = 14.5 Hz and 9.0 Hz), 2.35 (1H, broad s), 1.72 (3H, s), 1.68 (3H, s), 1.39 (3H, s), 1.37 (3H, s), 1.18 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 176.7, 153.0, 137.2, 137.1, 129.5, 129.1, 127.3, 124.5, 82.6, 69.9,

63.8, 43.4, 35.9, 28.6, 26.4, 22.5, 18.8, 12.6; IR (ATR) ν (cm^{-1}): 3479 (broad O-H), 1769 (C=O), 1681 (C=O); HRMS (ES+) calculated for $C_{20}H_{27}NO_4$ requires 346.2013 for$[M+H]^+$; found 346.2011.

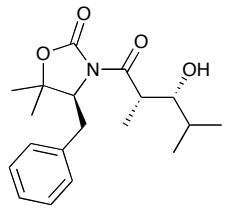
6.2.23 (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163f



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (5.56 mL, 2.78 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (605.8 mg, 2.32 mmol) in dichloromethane (50 mL) followed by addition of *N,N*-diisopropylethylamine (0.53 ml, 3.02 mmol) and (*E*)-crotonaldehyde (0.25 mL, 3.02 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163f** (701.2 mg, 2.11 mmol, 91%) as a clear oil.

$[\alpha]_D^{21}$ = -14 (*c* = 0.84 in $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.17 (5H, m), 5.74 (1H, dqd, *J* = 15.5 Hz, 6.5 Hz and 1.0 Hz), 5.48 (1H, ddd, *J* = 15.5 Hz, 6.5 Hz and 1.0 Hz), 4.60 (1H, dd, *J* = 9.0 Hz and 4.5 Hz), 4.53 (1H, m), 3.91 (1H, qd, *J* = 7.0 and 4.5 Hz), 3.05 (1H, dd. *J* = 14.5 and 4.5 Hz), 2.90 (1H, dd. *J* = 14.5 and 9.0 Hz), 2.60 (1H, d, *J* = 2.5 Hz), 1.70 (3H, d, *J* = 7.0 Hz), 1.39 (3H, s), 1.38 (3H, s), 1.15 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.9, 137.1, 130.5, 129.5, 129.1, 128.9, 127.3, 82.7, 73.6, 63.8, 43.2, 35.9, 28.7, 22.5, 18.2, 12.1; IR (KBr / cm^{-1}): 3508 (broad OH), 1775 ($C=O_{ox}$), 1696 (C=O); HRMS (ES): *m/z* calculated for $C_{19}H_{25}NO_4$: requires 332.1856 for $[M+H]^+$; found: 332.1855.

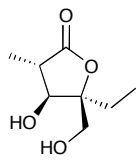
6.2.24 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethylpentanoyl)-5,5-dimethyloxazolidin-2-one, 198



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (8.42 mL, 4.209 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **142a** (1000.0 mg, 3.83 mmol) in dichloromethane (50 mL) followed by addition of *N,N*-diisopropylethylamine (0.80 ml, 4.59 mmol) and *iso*-butyraldehyde (0.41 mL, 4.59 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethylpentanoyl)-5,5-dimethyloxazolidin-2-one, 198** (1033.5 mg, 3.10 mmol, 81%) as a clear oil.

Rf (CH_2Cl_2) = 0.24; $[\alpha]_D^{24}$= -35 (*c* = 0.91 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (5H, m, Ph), 4.53 (1H, dd, *J* = 8.4 Hz and 4.5 Hz, C*H*N), 3.92 (1H, qd, *J* = 7.3 Hz and 3.2 Hz, COC*H*), 3.53 (1H, app. dt, *J* = 8.5 Hz and 3.2 Hz, C*H*OH), 3.06 (1H, dd, *J* = 14.5 Hz and 4.5 Hz, CH_AH$_B$Ph), 2.90 (1H, dd, *J* = 14.5 Hz and 8.4) Hz, CH$_A$*H*$_B$Ph), 1.70 (1H, m, C*H*$(CH_3)_2$), 1.42 (3H, s, (C*H*$^A{}_3$)C(CH$^B{}_3$), 1.40 (3H, s, (CH$^A{}_3$)C(C*H*$^B{}_3$), 1.18 (3H, d, *J* = 7.3 Hz, C*H*CH$_3$), 1.01 (3H, d, *J* = 7.0 Hz, (C*H*$^A{}_3$)CH(CH$^B{}_3$)), 0.92 (3H, d, *J* = 7.0 Hz, (CH$^A{}_3$)CH(C*H*$^B{}_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 152.5, 137.0, 129.5, 129.1, 127.3, 82.7, 77.3, 63.2, 40.2, 35.9, 31.1, 28.9, 22.6, 19.5, 19.2, 10.7; IR (ATR) ν (cm^{-1}): 3530 (O-H), 1780 (C=O$_{ox}$), 1694 (C=O); HRMS (ES): *m/z* calculated for $C_{19}H_{27}NO_4$: requires 334.2018 for $[M+H]^+$; found: 334.2012: requires 356.1838 for $[M+N]^+$; found: 3356.1833.

6.2.25 (3*S*,4*S*,5*S*)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181c

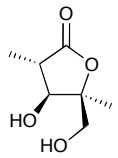


Vanadyl acetyl acetonate (9.75 mg, 0.037 mmol) was added to a solution of aldol **163c** (169.2 mg, 0.368 mmol) in benzene (3 mL) followed by addition of *tert*-butyl hydroperoxide (0.088 mL, 0.442 mmol) according to General Procedure 5 to afford the crude product as a green oil.

Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181c** (49.9 mg, 0.287 mmol, 78%) as a white solid, recrystallisation of the pure material was achieved using petroleum ether and diethyl ether.

Rf (7:3 DCM/EtOAc) = 0.32; $[\alpha]_D^{25}$ = -44.4 (*c* = 0.14 in $CHCl_3$); mp = 76-77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (1H, d, *J* = 12.3 Hz, C*H*OH), 3.88 (1H, d, *J* = 8.4 Hz, CH_AH$_B$OH), 3.79 (1H, d, *J* = 12.3 Hz, CH$_A$$H_B$OH), 2.79 (1H, dq, *J* = 8.7 and 7.2 Hz, CH_ACH$_B$CH$_3$), 1.76-1.53 (2H, m, CH$_A$CH_BCH$_3$, C*H*CH$_3$), 1.26 (3H, d, *J* = 7.2, CHCH_3), 0.90 (3H, t, *J* = 7.6, CH_2CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 88.0, 80.9, 65.3, 44.9, 28.8, 14.4, 7.7; IR (ATR) ν (cm^{-1}): 3286.5 (O-H), 1740.4 (C=O); HRMS (ES): *m/z* calculated for $C_8H_{14}O_4$ requires 192.1230 for $[M+NH_4]^+$, found 192.1233.

6.2.26 (3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 181b

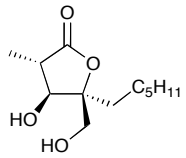


Vanadyl acetyl acetonate (27.8 mg, 0.105 mmol) was added to a solution of aldol **163b** (348.7 mg, 1.052 mmol) in benzene (5 mL) followed by addition of *tert*-butyl hydroperoxide (0.22 mL, 1.157mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 181b** (128.1 mg, 0.800 mmol, 76%) as a white solid.

Lit for (*ent*)-**181b** $[\alpha]_D^{25}$ = +26.8 (*c* = 0.91 in $CHCl_3$)[157]

Rf (7:3 DCM/EtOAc) = 0.26; $[\alpha]_D^{25}$ = -35.8 (*c* = 0.34 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (1H, d, *J* = 10.5 Hz, C*H*OH), 3.77 (1H, d, *J* = 12.1 Hz, CH_ACH$_B$OH), 3.62 (1H, d, *J* = 12.1 Hz, CH$_A$CH_BOH), 2.83 (1H, dq, *J* = 9.3, and 7.1 Hz, C*H*CO), 1.29 (3H, s, CH_3), 1.22 (3H, d, *J* = 7.3 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 86.2, 82.1, 65.5, 44.0, 22.4, 14.1; IR (ATR) ν (cm^{-1}): 3340.8 (O-H), 1735.5 (C=O); HRMS (ES): *m/z* calculated for $C_7H_{12}O_4$ requires 178.1074 for $[M+NH_4]^+$, found 178.1074.

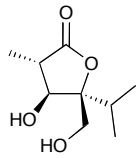
6.2.27 (3*S*,4*S*,5*S*)-5-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181e



Vanadyl acetyl acetonate (6.89 mg, 0.026 mmol) was added to a solution of aldol **163e** (102.9 mg, 0.256 mmol) in benzene (2.5 mL) followed by addition of *tert*-butyl hydroperoxide (0.056 mL, 0.282 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-5-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181e** (48.8 mg, 0.212 mmol, 83%) as a clear oil.

Rf (7:3 DCM/EtOAc) = 0.62; $[\alpha]_D^{25}$ = -31.2 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, d, *J* = 11.9 Hz, C*H*$_A$CH$_B$OH), 3.87 (1H, d, *J* = 8.3 Hz, C*H*OH), 3.87 (1H, d, *J* = 11.9 Hz, CH$_A$C*H*$_B$OH), 2.86 (1H, dq, *J* = 8.6, and 6.9 Hz, C*H*CH$_3$), 1.77-1.54 (2H, m, CC*H*$_2$), 1.44-1.18 (8H, m, C$_4$*H*$_8$), 0.89 (3H, t, *J* = 6.7 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 88.2, 81.4, 65.4, 44.9, 36.3, 31.9, 29.9, 23.3, 22.9, 14.5, 14.4; IR (ATR) ν (cm^{-1}): 3325.6 (O-H), 1751.8 (C=O); HRMS (ESI): *m/z* calculated for $C_{12}H_{22}O_4$ requires 231.1596 for $[M+H]^+$, found 231.1598; requires 253.1416 for $[M+Na]^+$, found 253.1424.

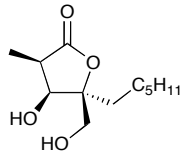
6.2.28 (3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-5-isopropyl-3-methyl-dihydrofuran-2(3*H*)-one, 181d



Vanadyl acetyl acetonate (17.9 mg, 0.068 mmol) was added to a solution of aldol **163d** (233.3 mg, 0.674 mmol) in benzene (6 mL) followed by addition of *tert*-butyl hydroperoxide (0.15 mL, 0.741 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-5-isopropyl-3-methyl-dihydrofuran-2(3*H*)-one, 181d** (93.7 mg, 0.498 mmol, 74%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.41; $[\alpha]_D^{25}$ = -30.6 (*c* = 0.43 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (1H, d, *J* = 12.2 Hz, C*H*$_A$CH$_B$OH), 3.92 (1H, app. t, *J* = 8.7 Hz, C*H*OH), 3.83 (1H, d, *J* = 12.2 Hz, CH$_A$C*H*$_B$OH), 2.85-2.69 (2H, m, C*H*CH$_3$, O*H*), 2.35 (1H, br. s, O*H*), 1.86 (1H, septet, *J* = 6.5 Hz, C*H*(CH$_3$)$_2$), 1.27 (3H, d, *J* = 7.4 Hz, CHC*H*$_3$), 0.94 (3H, d, *J* = 3.5 Hz, CCHC*H*$_3$), 0.92 (3H, d, *J* = 3.3 Hz, CCHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 90.6, 79.8, 63.9, 45.9, 45.6, 34.4, 17.5, 16.9, 14.6; IR (ATR) ν (cm^{-1}): 3313.0 (O-H), 1736.6 (C=O); HRMS (ESI): *m/z* calculated for $C_9H_{16}O_4$ requires 211.0946 for $[M+Na]^+$, found 211.0931.

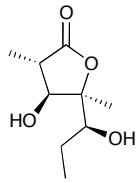
6.2.29 (3*R*,4*S*,5*S*)-5-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 205



Vanadyl acetyl acetonate (9.02 mg, 0.034 mmol) was added to a solution of aldol **146** (138.0 mg, 0.34 mmol) in benzene (3 mL) followed by addition of *tert*-butyl hydroperoxide (0.075 mL, 0.378 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*R*,4*S*,5*S*)-5-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 205** (58.3 mg, 0.253 mmol, 74%) as a clear oil.

Rf (7:3 DCM/EtOAc) = 0.53; $[\alpha]_D^{25}$ = +4.65 (*c* = 0.43 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (1H, d, *J* = 7.0 Hz, C*H*OH), 3.91 (1H, d, *J* = 12.0 Hz, C*H*$_A$CH$_B$OH), 3.85 (1H, d, *J* = 12.0 Hz, CH$_A$C*H*$_B$OH), 2.86 (1H, m, C*H*CH$_3$), 1.65-1.47 (2H, m, C*H*$_2$CH$_2$), 1.36-1.11 (8H, m, C$_4$*H*$_8$), 0.81 (3H, t, *J* = 6.5 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 88.8, 75.5, 64.1, 40.5, 35.2, 32.0, 30.0, 23.6, 22.9, 14.4, 8.8; IR (ATR) ν (cm^{-1}): 3330.0 (O-H), 1753.0 (C=O); HRMS (ESI): *m/z* calculated for $C_{12}H_{22}O_4$ requires 253.1416 for $[M+Na]^+$, found 253.1394.

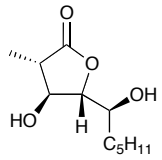
6.2.30 (3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 181i



Vanadyl acetyl acetonate (34.5 mg, 0.13 mmol) was added to a solution of aldol **163i** (450 mg, 1.25 mmol) in benzene (6 mL) followed by addition of *tert*-butyl hydroperoxide (0.28 mL, 1.38 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 181i** (174.1 mg, 0.925 mmol, 74%) as a pale oil.

Lit for (*ent*)-**181i** $[\alpha]_D^{25}$ = +25.4 (*c* = 0.66 in EtOH). [235]
Rf (7:3 DCM/EtOAc) = 0.53; $[\alpha]_D^{25}$ = -15.0 (*c* = 0.54 in $CHCl_3$); ^{1}H NMR (300 MHz, MeOD) δ 3.82 (1H, d, *J* = 9.0 Hz, C*H*OH), 3.62 (1H, dd, *J* = 10.2 and 2.6 Hz, C*H*OHCH$_2$), 2.74 (1H, dq, *J* = 9.0 and 7.5 Hz, C*H*CH$_3$), 1.64-1.38 (2H, m, C*H*$_2$CH$_3$), 1.30 (3H, s, CH$_3$), 1.15 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 0.91 (3H, t, *J* = 7.5 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, MeOD) δ 179.5, 87.7, 83.9, 76.9, 44.5, 25.5, 21.6, 14.3, 11.8; IR (ATR) ν (cm^{-1}): 3394.8 (O-H), 1747.5 (C=O); HRMS (ES): *m/z* calculated for $C_9H_{16}O_4$ requires 211.0941 for $[M+Na]^+$, found 211.0940.

6.2.31 (3*S*,4*S*,5*R*)-4-hydroxy-5-((*S*)-1-hydroxyhexyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181j

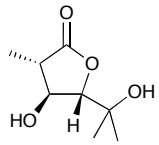


Vanadyl acetyl acetonate (33.9 mg, 0.128 mmol) was added to a solution of aldol **163j** (497.5 mg, 1.28 mmol) in benzene (6 mL) followed by addition of *tert*-butyl hydroperoxide (0.28 mL, 1.41 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-hydroxy-5-((*S*)-1-hydroxyhexyl)-3-methyl-dihydrofuran-2(3*H*)-one, 181j** (232.7 mg, 1.076 mmol, 84%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.41; $[\alpha]_D^{25}$ = +32.8 (*c* = 0.34 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (1H, br. t, *J* = 8.8 Hz, C*H*OH), 3.98 (1H, dd, *J* = 7.9 and 3.2 Hz, OC*H*), 3.69 (1H, br. s,

C*H*OHCH$_2$), 2.58 (1H, dq, *J* = 8.8 and 7.2 Hz, C*H*CH$_3$), 1.66-1.15 (11H, m, C$_4$*H*$_8$, CHC*H*$_3$), 0.83 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 177.78, 85.6, 74.5, 69.5, 44.0, 34.5, 32.1, 26.0, 23.0, 14.4, 12.7; IR (ATR) ν (cm^{-1}): 3379.9 (O-H), 1736.3 (C=O); HRMS (ESI): *m/z* calculated for $C_{11}H_{20}O_4$ requires 239.1259 for $[M+Na]^+$, found 239.1256.

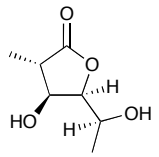
6.2.32 (3*S*,4*S*,5*S*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 181h



Vanadyl acetyl acetonate (12.9 mg, 0.049 mmol) was added to a solution of aldol **163h** (169.3 mg, 0.49 mmol) in benzene (3 mL) followed by addition of *tert*-butyl hydroperoxide (0.118 mL, 0.58 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 181h** (66.37 mg, 0.381 mmol, 78%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.24; $[\alpha]_D^{25}$ = +23.5 (*c* = 0.17 in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.11 (1H, ddd, *J* = 8.7, 6.8 and 4.6 Hz, C*H*OH), 3.88 (1H, d, *J* = 7.6 Hz, OC*H*), 2.61 (1H, dq, *J* = 8.4 and 6.5 Hz, C*H*CH$_3$), 2.32 (1H, br. d, *J* = 4.88 Hz, CHO*H*), 1.72 (1H, br. s, O*H*), 1.29-1.20 (9H, m, CHC*H*$_3$, C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.45, 88.2, 74.9, 71.1, 44.3, 26.4, 26.2, 12.9; IR (ATR) ν (cm^{-1}): 3398.8 (O-H), 1766.8 (C=O); HRMS (ESI): *m/z* calculated for $C_8H_{14}O_4$ requires 197.0789 for $[M+Na]^+$, found 197.0774.

6.2.33 (3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-1-hydroxyethyl)-3-methyldihydrofuran-2(3H)-one, 181fa



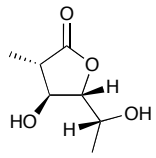
Vanadyl acetyl acetonate (16.2 mg, 0.061 mmol) was added to a solution of aldol **163f** (200.5 mg, 0.605 mmol) in benzene (5 mL) followed by addition of *tert*-butyl hydroperoxide (0.13 mL, 0.665 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-1-hydroxyethyl)-3-methyldihydrofuran-2(3H)-one, 181fa** (46.5 mg, 0.290 mmol, 48%) as a

pale oil. The minor diastereomer was also isolated as a white solid **(3*S*,4*S*,5*R*)-4-hydroxy-5-((*R*)-1-hydroxyethyl)-3-methyldihydrofuran-2(3H)-one, 181fb**, (21.2 mg, 0.132 mmol, 22%).

6.2.33.1 (3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-1-hydroxyethyl)-3-methyldihydrofuran-2(3H)-one, 181fa

Rf (7:3 DCM/EtOAc) = 0.17; $[\alpha]_D^{25}$ = -35.5 (*c* = 0.23 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (1H, app. t., *J* = 8.4 Hz, C*H*OH), 3.98 (1H, app. pent., *J* = 6.2 Hz, C*H*OHCH$_3$), 3.87 (1H, dd, *J* = 7.2 and 5.7 Hz, OC*H*), 2.61 (1H, dq, *J* = 8.4 and 6.5 Hz, C*H*CH$_3$), 2.55 (1H, br. s, O*H*), 1.98 (1H, br. s, O*H*), 1.29 (3H, d, *J* = 6.2 Hz, CHOHC*H*$_3$), 1.27 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 88.6, 76.1, 68.6, 43.9, 19.9, 12.9; IR (ATR) ν (cm^{-1}): 3391.2 (O-H), 1753.4 (C=O); HRMS (ESI): *m/z* calculated for $C_7H_{12}O_4$ requires 183.0633 for $[M+Na]^+$, found 183.0616.

6.2.33.2 (3*S*,4*S*,5*R*)-4-hydroxy-5-((*R*)-1-hydroxyethyl)-3-methyldihydrofuran-2(3H)-one, 181fb



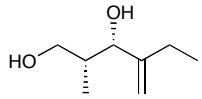
Rf (7:3 DCM/EtOAc) = 0.21; $[\alpha]_D^{25}$ = -36.4 (*c* = 0.71 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (1H, dd, *J* = 4.4 and 2.9 Hz, C*H*OH), 4.20 (1H, app. pent., *J* = 6.3 Hz, C*H*OHCH$_3$), 4.1 (1H, dd, *J* = 6.3 and 4.4 Hz, OC*H*), 2.64 (1H, qd, *J* = 7.7 and 3.0 Hz, C*H*CH$_3$), 1.35 (3H, d, *J* = 6.2 Hz, CHOHC*H*$_3$), 1.23 (3H, d, *J* = 7.7 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 83.1, 75.6, 67.1, 44.9, 20.1, 13.8; IR (ATR) ν (cm^{-1}): 3308.6 (O-H), 1751.8 (C=O); HRMS (ESI): *m/z* calculated for $C_7H_{12}O_4$ requires 183.0633 for $[M+Na]^+$, found 183.0624.

6.2.34 Solid phase *syn*-aldol reaction to afford polymer 227

N-Propionyl-oxazolidin-2-one resin **222** (500 mg, 0.90 mmol/g, 0.45 mmol) was sealed in an IRORI minikan® in an oven-dried round bottomed flask, and dichloromethane (8 mL) added to preswell the resin. The reaction flask was then cooled to 0 °C, 9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (4.5 mL, 0.5 M in dichloromethane, 2.25 mmol) added slowly and the reaction mixture stirred gently for one hour. The solvent was then removed *via* cannula and fresh pre-chilled dichloromethane (10 mL) added to resuspend the resin. *N*,*N*-diisopropylethylamine (0.391 mL, 2.25 mmol) was then added and the reaction stirred for a

further hour, before being cooled to -78 °C. 2-Ethylacrolein (0.308 mL, 3.15 mmol) was then added dropwise and the stirred reaction mixture allowed to warm to room temperature over a period of 12 hours. The reaction was then quenched *via* addition of phosphate buffer pH 7 (0.1 M) and the polymer filtered off and washed sequentially with dichloromethane (10 mL), dichloromethane/methanol (10 mL) and tetrahydrofuran (10 mL) to afford (*syn*)-aldol polymer **227** that was dried *in vacuo*.

6.2.34.1 (2*R*,3*S*)-2-methyl-4-methylenehexane-1,3-diol 228



(*syn*)-Aldol resin **227** was characterised *via* treatment of a small portion of resin (50 mg) that had been preswollen in tetrahydrofuran (2 mL) with a solution of sodium borohydride (6 mg, 0.15mmol) in water (0.2mL), that was then agitated on an orbital shaker for 4 hours. Polymer **221** was then filtered off and washed thoroughly with dichlromethane (5 mL) and tetrahydrofuran (5 mL), before all organic extracts were combined, dried (magnesium sulphate) and evaporated to dryness to afford a clean sample of (2*R*,3*S*)-2-methyl-4-methylenehexane-1,3-diol **228** (16.1 mg, 0.112 mmol, 62%) as a colourless oil.

$[\alpha]_D^{25}$ -26 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ 5.05 (1H, br. s, CH_AH$_B$C=C), 4.92 (1H, br. s, CH$_A$$H_B$C=C), 4.28 (1H, d, *J* = 3.0 Hz), 3.68 (2H, m), 2.64 (2H, s), 2.08-1.80 (3H, m), 1.05 (3H, t, *J* = 7.0 Hz), 0.84 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 108.5, 76.4, 67.0, 37.7, 25.6, 12.6, 9.9; IR (thin film): 3380 (broad OH); MS (CI+, NH_3) *m/z* (%) 162 (100) $[M+NH_4]^+$, 144 (23) $[M+H]^+$, 52 (23); HRMS (ES^+): *m/z* calculated for $C_8H_{16}O_2$ requires 162.1489 for $[M+NH_4]^+$; found 162.1491.

6.2.35 Solid phase epoxidation/lactonisation reaction for formation of lactone (3*S*,4*S*,5*S*)-181c

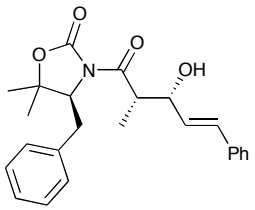
Vanadyl acetyl acetonate (24 mg, 0.09 mmol) was added to (*syn*)-aldol-resin **227** (200mg, 0.90 mmol/g, 0.18 mmol) pre-swollen in benzene (8 mL) at room temperature and the reaction mixture agitated on an orbital shaker for 30 minutes. *tert*-Butyl-hydroperoxide (5.0-6.0 M solution in decane) (0.098 mL, 5.5 M, 0.54 mmol) was then added and the reaction agitated for a further 16 hours at room temperature. The resin was then filtered off and washed thoroughly with dichloromethane (5 mL) and CH_2Cl_2/MeOH (5 mL, 1:1) with all organic extracts being combined and evaporated to dryness. The resulting crude product was dissolved in

dichloromethane (5 mL) and filtered through a plug of silica, before the solvent was removed *in vacuo* to afford (3*S*,4*S*,5*S*)-γ-butyrolactone **181c** (17 mg, 0.097 mmol) ($[\alpha]_D^{25}$ = -43.7 (*c* = 0.15, $CHCl_3$)) as a crystalline solid in 58% yield over two steps.

Characterisation matched that described for the solution phase synthesis of lactone **181c**.

6.3 Compounds for Chapter 4

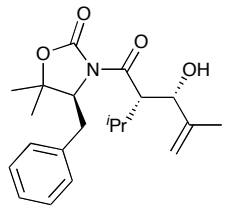
6.3.1 (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163g



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (10.1 mL, 5.1 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, **157** (1.2 g, 4.6 mmol) in dichloromethane (30 mL) followed by addition of *N,N*-diisopropylethylamine (1.0 mL, 6.0 mmol) and (*E*)-cinnamaldehyde (0.76 mL, 6.0 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **163g** (1.41 g, 3.58 mmol, 78 %) as a colourless oil.

R_f (CH_2Cl_2) = 0.21; $[\alpha]_D^{23}$ = +6.0 (c = 0.89 in $CHCl_3$); mp = 147 – 149 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.13 (10H, m, Ph), 6.59 (1H, dd, *J* = 16.0 and 1.5 Hz, CH =C*H*Ph), 6.12 (1H, dd, *J* = 16.0 Hz and 6.0 Hz, C*H*=CHPh), 4.54 (1H, m, C*H*OH), 4.47 (1H, dd, *J* = 9.0 and 5.0 Hz, CHN), 3.94 (1H, qd, *J* = 7.0 and 4.0 Hz, COCH), 3.00 (1H, dd *J* = 14.0 and 5.0 Hz, CH_AH$_B$Ph), 2.84 (1H, dd, *J* = 14.0 and 9.0 Hz, CH$_A$CH_BPh), 2.74 (1H, broad s, OH), 1.32 (3H, s, (CH_3)C(CH_3)), 1.30 (3H, s, (CH_3)C(CH_3)), 1.13 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 152.6, 137.7, 134.1, 129.3, 129.2, 129.1, 127.3, 82.7, 73.4, 63.8, 43.3, 35.9, 32.7, 32.2, 29.6, 29.5, 23.1, 14.5, 12.0; IR (ATR) ν (cm^{-1}): 3443.6 (O-H), 1768.0 (C=O), 1684.6 (C=O$_{ox}$); HRMS (ES): *m/z* calculated for $C_{24}H_{27}NO_4$: requires 416.1838 for $[M+Na]^+$; found: 416.1821.

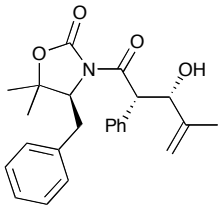
6.3.2 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-isopropyl-4-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163m



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (9.46 mL, 4.73 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-(3-methylbutanoyl)oxazolidin-2-one, **142b** (1.24 g, 4.29 mmol) in dichloromethane (100 mL) followed by addition of *N,N*-diisopropylethylamine (0.97 ml, 5.59 mmol) and methacrolein (0.96 mL, 5.59 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **163m** (1.22 g, 3.39 mmol, 79 %) as a colourless oil.

$[\alpha]_D^{25}$ = -40.0 (*c* = 1.0, $CHCl_3$); R_f (CH_2Cl_2) = 0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.11 (5H, m, Ph), 4.96 (1H, app. d, *J* = 1.0 Hz, C*H*$_{cis}$H$_{trans}$=C), 4.81 (1H, app. t, *J* = 1.5 Hz, CH$_{cis}$*H*$_{trans}$=C), 4.53 (1H, dd, *J* = 9.0 Hz and 4.5 Hz, CHN), 4.46 (1H, dd, *J* = 10.0 Hz and 3.5 Hz, C*H*OH), 4.38 (1H, d, *J* = 8.5 Hz, C*H*CH), 3.08 (1H, dd, *J* = 14.5 Hz and 4.5 Hz, C*H*$_A$H$_B$Ph), 2.78 (1H, dd, *J* =14.5 Hz and 10.0 Hz, CH$_A$*H*$_B$Ph), 2.23 (1H, m, C*H*(CH_3)$_2$) 1.90 (1H, broad s, OH), 1.71 (3H, s, C=CC*H*$_3$), 1.23 (6H, app. d, *J* = 5.5 Hz) (C*H*$_3$)C(CH_3)), 0.97 (6H, t, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 153.0, 146.2, 137.3, 129.4, 129.07, 127.2, 113.5, 82.2, 64.1, 51.0, 35.9, 28.6, 28.4, 22.7, 21.2, 19.1, 18.6; IR (thin film / cm^{-1}) 3499 (broad O-H), 1768 (C=O$_{ox}$), 1685 (C=O); HRMS (EI+) *m/z* calculated for $C_{21}H_{29}NO_4$: requires 360.2174 for $[M+H]^+$; found: 360.2165; requires 382.1994 for $[M+Na]^+$; found: 382.1984.

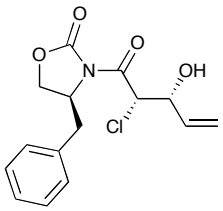
6.3.3 (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-4-methyl-2-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163L



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (0.45 mL, 0.912 mmol) was added to a solution of (*S*)-4-benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one, **142c** (267.9 mg, 0.83 mmol) in dichloromethane (70 mL) followed by addition of *N,N*-diisopropylethylamine (0.17 ml, 0.99 mmol) and methacrolein (0.083 mL, 0.99 mmol) according to General Procedure 2 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **163L** (244.8 mg, 0.62 mmol, 75 %) as a colourless oil.

$[\alpha]_D^{25}$ = -89.9 (*c* = 1.0, $CHCl_3$); R_f (CH_2Cl_2) = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.20 (5H, m, Ph), 7.14-6.98 (5H, m, Ph), 5.27 (1H, d, *J* = 7.0 Hz, PhC*H*) 4.92 (1H, m, C$H_{cis}H_{trans}$=C), 4.85 (1H, br. app. pent., *J* = 1.5 Hz, $CH_{cis}H_{trans}$=C), 4.69 (1H, d, *J* = 8.0 Hz, C*H*OH), 4.43 (1H, dd, *J* = 9.0 Hz and 4.0 Hz, CHN), 4.40 (1H, m, C*H*OH), 2.82 (1H, dd *J* = 14.0 Hz and 4.0 Hz, CH_AH_BPh), 2.63 (1H, dd, *J* = 14.0 Hz and 9.0 Hz, CH_ACH_BPh), 2.05 (1H, br. s, OH), 1.74 (3H, s, CH_2=CCH_3), 1.27 (3H, s, (CH_3)C(CH_3)), 1.24 (3H, s, (CH_3)C(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 152.5, 144.8, 136.9, 134.7, 130.26, 129.4, 129.1, 128.9, 128.4, 127.1, 114.2, 82.5, 63.7, 53.4, 35.3, 28.7, 22.5, 18.7; IR (ATR) ν (cm^{-1}): 3489.6 (O-H), 1768.2 (C=O), 1671.5 (C=O_{ox}); HRMS (ES): *m/z* calculated for $C_{24}H_{27}NO_4$ requires 394.2018 for $[M+H]^+$; found: 394.2019; requires 416.1838 for $[M+H]^+$; found: 416.1842.

6.3.4 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one, 274

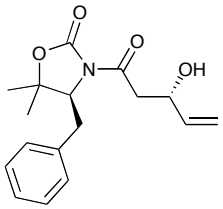


Dibutylboron trifluoromethanesulphonate (2.17 mL, 2.17 mmol) was added to a solution of (*S*)-4-benzyl-3-(2-chloroacetyl)oxazolidin-2-one **142d** (500 mg, 1.97 mmol) in dichloromethane (60 mL) followed by addition of *N,N*-diisopropylethylamine (0.41 mL, 2.34 mmol) and acrolein

(0.16 mL, 2.34 mmol) according to General Procedure 3 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **274** (362.2 mg, 1.172 mmol, 54%) as a colourless oil.

Rf (CH_2Cl_2) = 0.20; $[\alpha]_D^{24}$ = -12 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.05 (5H, m, Ph), 5.92 (1H, ddd, *J* = 17.2, 10.5, 5.5 Hz, C*H*CH_2), 5.73 (1H, d, *J* = 4.5 Hz, C*H*Cl), 5.46 (1H, dt, *J* = 17.2, 1.3 Hz, CHC$H_A$$CH_B$), 5.34 (1H, dt, *J* = 10.5, 1.3 Hz, $CHCH_ACH_B$), 4.81 – 4.57 (2H, m, C*H*OH & C*H*N), 4.37 – 4.19 (2H, m, CH_2O), 3.31 (1H, dd, *J* = 13.5, 3.3 Hz, C$H_A$$CH_B$Ph), 2.84 (1H, dd, *J* = 13.5, 9.4 Hz, CH_ACH_BPh); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.95, 153.03, 135.35, 134.91, 129.77, 129.40, 127.90, 119.06, 72.88, 66.88, 59.57, 55.77, 37.57; IR (ATR) ν_{max} (cm^{-1}): 3497 (broad O-H), 1759 (C=O_{ox}), 1711 (C=O); HRMS (ES+); *m/z* calculated for $C_{15}H_{16}ClNO_4$: requires 310.0846 for $[M+H]^+$; found: 310.0836; requires 332.0666 for $[M+Na]^+$; found: 332.0650.

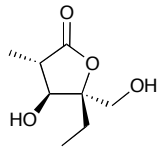
6.3.5 (*S*)-4-benzyl-3-((*S*)-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 275



(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one **274** (130 mg, 0.0.42 mmol), zinc dust (110 mg, 1.68 mmol), ammonium chloride (90 mg, 1.68 mmol) and methanol (1.82 mL, 14 mL/g) were mixed together and treated according to General Procedure 8. The clear oil was purified by column chromatography eluting with dichloromethane, to yield title compound, (*S*)-4-benzyl-3-((*S*)-3-hydroxypent-4-enoyl)oxazolidin-2-one **275** (65 mg, 0.24 mmol, 56%) as a colourless oil.

Rf (CH_2Cl_2) = 0.18; $[\alpha]_D^{25}$ = -5.0 (*c* = 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.02 (5H, m, Ph), 5.96 (1H, ddd, *J* = 17.2, 10.5, 5.4 Hz, C*H*CH_2), 5.37 (1H, dt, *J* = 17.2, 1.4 Hz, CHC$H_A$$CH_B$), 5.20 (1H, dt, *J* = 10.5, 1.4 Hz, $CHCH_ACH_B$), 4.82 – 4.59 (2H, m, C*H*OH & C*H*N), 4.29 – 4.15 (2H, m, CH_2O), 3.30 (1H, dd, *J* = 13.4, 3.3 Hz, C$H_A$$CH_B$Ph), 3.21 (2H, dd, *J* = 11.4, 6.1 Hz, CH_2CHOH), 2.81 (1H, dd, *J* = 13.5, 9.4 Hz, CH_ACH_BPh); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.48, 153.75, 139.09, 135.33, 129.76, 129.37, 127.80, 115.87, 69.22, 66.70, 55.43, 42.64, 38.16; IR (ATR) ν_{max} (cm^{-1}): 3300 (broad O-H), 1776 (C=O), 1698 (C=O_{ox}); HRMS (ESI); *m/z* calculated for $C_{15}H_{17}NO_4$: requires 298.1055 for $[M+Na]^+$; found: 298.1044.

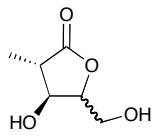
6.3.6 (3*S*,4*S*,5*R*)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240c



Osmium tetroxide (22.4 mg, 0.088 mmol) was added to a solution of aldol **163c** (304.5 mg, 0.88 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.2 mL, 0.97 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240c** (119.5 mg, 0.61 mmol, 69 %) as a pale oil.

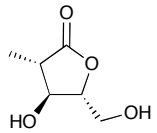
Rf (7:3 DCM/EtOAc) = 0.21; $[\alpha]_D^{24}$ = - 3.4 (*c* = 0.88 in $CHCl_3$); ^{1}H NMR (500 MHz, MeOD) δ 4.24 (1H, d, *J* = 9.4 Hz, C*H*OH), 3.74 (1H, d, *J* = 12.1 Hz, CH_AH_BOH), 3.52 (1H, d, *J* = 12.16 Hz, CH_AH_BOH), 2.68 (1H, qd, *J* = 9.4 Hz and 7.1 Hz, C*H*CO), 1.81 (1H, dq, *J* = 15.0 Hz and 7.5 Hz, C$H_AH_B$$CH_3$), 1.71 (1H, dq, *J* = 15.0 Hz and 7.5 Hz, $CH_AH_B$$CH_3$), 1.28 (1H, d, *J* = 7.5 Hz, CH_3), 1.01 (1H, t, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, MeOD) δ 179.59, 90.18, 76.48, 64.74, 44.16, 24.96, 13.86, 8.57; IR (ATR) ν (cm^{-1}): 3368 (broad O-H), 1751 (C=O); HRMS (ES+): *m/z* calculated for $C_8H_{14}O_4$: requires 175.0970 for $[M+H]^+$; found: 175.957; requires 197.0789 for $[M+Na]^+$; found: 197.0777.

6.3.7 (3*S*,4*S*)-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one,



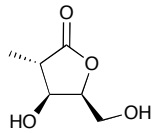
Osmium tetroxide (14.8 mg, 0.052 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one, **163a** (150 mg, 0.52 mmol) in acetone/water (8:1, 5 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.09 mL, 0.52 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded a diastereomeric mixture of **(3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one, 240a1** and **(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one, 240a2** (60.1 mg, 0.41 mmol, 79%) as a pale oil. The two diastereomers were analysed as a mixture.

6.3.7.1 (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one, 240a1



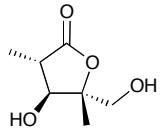
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 – 4.17 (1H, m, C*H*CH_2OH), 4.17 – 4.11 (1H, m, C*H*OH), 3.98 (1H, dd, *J* = 12.7 and 3.0 Hz, C$H_A$$CH_B$OH), 3.83 (1H, dd, *J* = 12.7 and 3.2 Hz, CH_ACH_BOH), 2.68 (1H, dq, *J* = 8.9 and 7.1, C*H*CH_3), 1.32 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.04, 83.59, 74.42, 60.85, 43.95, 12.70; IR (ATR) ν_{max} (cm^{-1}): 3377 (broad O-H), 2934 (broad O-H), 1763 (C=O); HRMS (ESI); *m/z* calculated for $C_6H_{10}O_4$: requires 147.0657 for $[M+H]^+$; found: 147.0650; requires 169.0477 for $[M+Na]^+$; found: 169.0466.

6.3.7.2 (3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one, 140a2



^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, dt, *J* = 6.9 and 3.6 Hz, C*H*CH_2O), 4.35 (1H, d, *J* = 6.0 Hz, C*H*OH), 4.06 (2H, d, *J* = 3.5 Hz, CH_ACH_BOH), 2.74 (1H, dt, *J* = 13.6 and 7.5 Hz, C*H*CH_3), 1.32 (3H, d, *J* = 7.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.42, 80.04, 76.08, 61.52, 44.18, 30.03, 13.89; IR and HRMS were the same as the other diastereomer.

6.3.8 (3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 240b

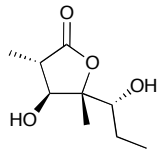


Osmium tetroxide (9.1 mg, 0.036 mmol) was added to a solution of aldol **163b** (120 mg, 0.36 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.08 mL, 0.40 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-**

hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 240b (43.2 mg, 0.27 mmol, 75%) as a white solid.

Rf (7:3 DCM/EtOAc) = 0.19; $[\alpha]_D^{23}$ = +5.3 (*c* = 1.78 in MeOH); ^{1}H NMR (500 MHz, MeOD) δ 4.10 (1H, d, *J* = 9.7 Hz, C*H*OH), 3.65 (1H, d, *J* = 12.4 Hz, CH_AH_BOH), 3.54 (1H, d, *J* = 12.2 Hz, CH$_A$*H*$_B$OH), 2.70 (1H, qd, *J* = 9.7 Hz and 7.0 Hz, C*H*CO), 1.28 (1H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.28 (3H, s, CC*H*$_3$); ^{13}C NMR (75 MHz, MeOD) δ 179.0, 88.6, 75.8, 66.5, 43.3, 16.9, 13.3; IR (ATR) ν (cm^{-1}): 3335.7 (broad O-H), 1736.5 (C=O); HRMS (ES+): *m/z* calculated for $C_7H_{12}O_4$: requires 161.0814 for $[M+H]^+$; found: 161.0810; requires 183.0633 for $[M+Na]^+$; found: 183.0621.

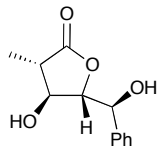
6.3.9 (3*S*,4*S*,5*R*)-4-hydroxy-5-((*R*)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 240i



Osmium tetroxide (14.7 mg, 0.058 mmol) was added to a solution of aldol **163i** (208.8 mg, 0.58 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.11 mL, 0.64 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-hydroxy-5-((*R*)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3*H*)-one, 240i** (89.4 mg, 0.48 mmol, 82%, >95 % de) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.22; $[\alpha]_D^{23}$ = -5.4 (*c* = 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (1H, dd, *J* = 9.8 Hz and 5.4 Hz, C*H*OH), 3.93 (1H, d, *J* = 5.39 Hz, O*H*), 3.57 (1H, d, *J* = 8.57 Hz, O*H*), 3.37 (1H, ddd, *J* = 10.8 Hz, 8.8 Hz and 2.24 Hz, C*H*OHCH$_2$), 2.62 (1H, dq, *J* = 9.9 Hz and 7.1 Hz, C*H*CH$_3$) 1.67 (1H, dqd, *J* = 15.1 Hz, 7.46 Hz and 2.42 Hz, CH_AH_BCH$_3$) 1.45 – 1.28 (1H, m, CH$_A$*H*$_B$CH$_3$), 1.23 (3H, s, C*H*$_3$CH$_2$), 1.18 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 0.97 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.02, 89.12, 75.56, 75.24, 41.56, 24.07, 16.41, 12.84, 11.30; IR (ATR) ν (cm^{-1}): 3356.5 (broad O-H), 1748.7 (C=O); HRMS (ES+): *m/z* calculated for $C_9H_{16}O_4$: requires 189.1127 for $[M+H]^+$; found: 189.1120; requires 211.0946 for $[M+Na]^+$; found: 211.0934.

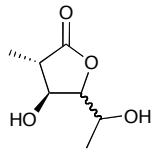
6.3.10 (3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-hydroxy(phenyl)methyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240g1



Osmium tetroxide (12.7 mg, 0.05 mmol) was added to a solution of aldol **163g** (198.2 mg, 0.50 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.1 mL, 0.55 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*S*)-4-hydroxy-5-((*S*)-hydroxy(phenyl)methyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240g1** (89.9 mg, 0.41 mmol, 81 %) as a pale oil.

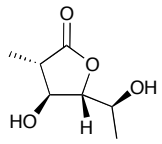
Rf (7:3 DCM/EtOAc) = 0.34; $[\alpha]_D^{23}$ = +44.0 (*c* = 1.62 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.25 (5H, m, Ar*H*), 4.76 (1H, d, *J* = 5.7, C*H*Ph), 4.22 (1H, dd, *J* = 9.2 Hz and 7.5 Hz), 3.95 (1H, dd, *J* = 9.2 Hz and 7.5 Hz, C*H*OH), 2.56 (1H, dq, *J* = 9.2 Hz and 7.2 Hz, C*H*CO), 1.19 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 134.5, 129.1, 128.7, 127.4, 80.1, 74.9, 70.9, 43.1, 14.1; IR (ATR) ν (cm^{-1}): 3358.5 (broad O-H), 1753.2 (C=O); HRMS (ES+): *m/z* calculated for $C_{12}H_{14}O_4$: requires 223.0970 for $[M+H]^+$; found: 223.0964; requires 245.0790 for $[M+Na]^+$; found: 245.0767.

6.3.11 (3*S*,4*S*)-4-hydroxy-5-(1-hydroxyethyl)-3-methyl-dihydrofuran-2(3*H*)-one



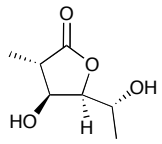
Osmium tetroxide (12.7 mg, 0.05 mmol) was added to a solution of aldol **163f** (164.3 mg, 0.50 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.09 mL, 0.54 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded a diastereotopic mixture of diastereomeric mixture of **(3*S*,4*S*,5*R*)-4-hydroxy-5-((*S*)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240f1** and **(3*S*,4*S*,5*S*)-4-hydroxy-5-((*R*)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240f2** (65.6 mg, 0.41 mmol, 83%) as a pale oil. The two diastereomers were analysed as a mixture.

6.3.11.1 (3*S*,4*S*,5*R*)-4-hydroxy-5-((*S*)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240f1



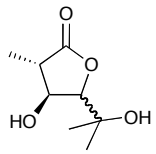
Rf (7:3 DCM/EtOAc) = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (1H, dd, *J* = 8.8 Hz and 7.0 Hz, C*H*OH), 4.04 – 3.95 (2H, m, C*H*OCO and C*H*OHCH$_3$), 2.68 (1H, dq, *J* = 9.1 Hz and 7.1 Hz, C*H*CO), 1.37 (3H, d, *J* = 6.5 Hz, C*H*$_3$CHOH), 1.32 (3H, d, *J* = 7.1 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 86.4, 74.9, 66.6, 44.17, 19.9, 12.8; IR (ATR) ν (cm^{-1}): 3356.6 (broad O-H), 1754.5 (C=O); HRMS (ES+): *m/z* calculated for $C_7H_{12}O_4$: requires 183.0628 for $[M+Na]^+$; found: 183.0613.

6.3.11.2 (3*S*,4*S*,5*S*)-4-hydroxy-5-((*R*)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3*H*)-one, 240f2



Rf (7:3 DCM/EtOAc) = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 - 4.32 (1H, m, C*H*OH), 4.32 – 4.27 (2H, m, C*H*OCO and C*H*OHCH$_3$), 2.76 (1H, dq, *J* = 7.7 Hz and 5.3 Hz, C*H*CO), 1.39 (3H, d, *J* = 6.7 Hz, C*H*$_3$CHOH), 1.32 (3H, d, *J* = 7.5 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 82.9, 76.3, 67.1, 44.6, 19.8, 14.0; IR and HRMS were the same as **240f1**.

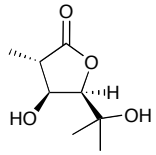
6.3.12 (3*S*,4*S*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one



Osmium tetroxide (13.5 mg, 0.053 mmol) was added to a solution of aldol **163h** (184.0 mg, 0.53 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.10 mL, 0.59 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 240h1** (37.8 mg,

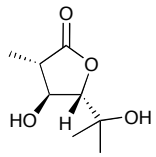
0.22 mmol, 41%) as a pale oil. The minor diastereomer was also isolated as a white solid **(3*S*,4*S*,5*S*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 240h2**, (27.7 mg, 0.16 mmol, 30%)

6.3.12.1 (3*S*,4*S*,5*R*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 240h1



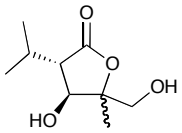
Rf (7:3 DCM/EtOAc) = 0.32; $[\alpha]_D^{23}$ = -55.6 (*c* = 0.99 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (1H, d, *J* = 4.1 Hz, O*H*), 4.26 (1H, app. dt, *J* = 3.9 Hz and 1.5 Hz, C^4*H*OH), 4.09 (1H, d, *J* = 4.1 Hz, C*H*OCO), 2.96 (1H, br. s, O*H*), 2.68 (1H, qd, *J* = 7.8 Hz and 1.5 Hz), 1.38 (3H, s, (CH_{3A})C(CH_{3B})), 1.36 (3H, s, (CH_{3A})C(CH_{3B})), 1.19 (3H, d, *J* = 7.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.52, 84.04, 76.30, 73.03, 46.85, 28.74, 25.01, 13.50; IR (ATR) ν (cm^{-1}): 3295.1 (broad O-H), 1754.3 (C=O); HRMS (ES+): *m/z* calculated for $C_8H_{14}O_4$: requires 175.0970 for $[M+H]^+$; found: 175.0970; requires 197.0790 for $[M+Na]^+$; found: 197.0784.

6.3.12.2 (3*S*,4*S*,5*S*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3*H*)-one, 240h2



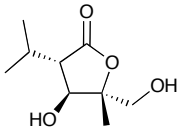
Rf (7:3 DCM/EtOAc) = 0.24; $[\alpha]_D^{23}$ = +25.0 (*c* = 0.53 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (1H, ddd, *J* = 9.1 Hz, 7.4 Hz and 4.4 Hz, C*H*OH), 3.88 (1H, d, *J* = 7.5 Hz, C*H*OCO), 2.61 (1H, dq, *J* = 9.3 Hz and 7.5 Hz, C*H*CO), 2.32 (1H, d, *J* = 4.4 Hz, O*H*), 1.72 (1H, s, O*H*), 1.30 – 1.19 (9H, m, CH_3CH and (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 88.5, 74.7, 71.0, 44.4, 26.6, 25.9, 12.9; IR (ATR) ν (cm^{-1}): 3398.8 (O-H), 1766.8 (C=O); HRMS (ES+): *m/z* calculated for $C_8H_{14}O_4$ requires 197.0789 for $[M+Na]^+$, found 197.0774.

6.3.13 (3*S*,4*S*)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3*H*)-one



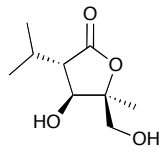
Osmium tetroxide (14.5 mg, 0.057 mmol) was added to a solution of aldol **163m** (206.4 mg, 0.57 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.11 mL, 0.63 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3*H*)-one, 240m1** (46.3 mg, 0.24 mmol, 43%) as a pale oil. The slightly minor diastereomer was also isolated as a white solid **(3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3*H*)-one, 240m2** (34.5 mg, 0.18 mmol, 32%)

6.3.13.1 (3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3*H*)-one, 240m1



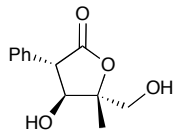
Rf (7:3 DCM/EtOAc) = 0.33; $[\alpha]_D^{23}$ = +39.1 (*c* = 0.69 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (1H, app. br. d, *J* = 7.5 Hz, C*H*OH), 3.87 (1H, d, *J* = 12.6 Hz, CH_AH_BOH), 3.75 Hz (1H, d, *J* = 12.6 Hz, CH$_A$*H*$_B$OH), 2.67 (1H, dd, *J* = 8.3 Hz and 4.9 Hz, C*H*CO), 2.19 (1H, d sept., *J* = 6.9 Hz and 4.9 Hz, C*H*(CH$_3$)$_2$), 1.29 (3H, s, CH_3), 1.03 (3H, d, *J* = 6.8 (CH_3^A)CH(CH$_3^B$)), 0.94 (3H, d, *J* = 6.8 (CH$_3^A$)CH(CH_3^B)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 85.9, 69.6, 65.9, 52.1, 27.2, 20.1, 19.3, 17.3; IR (ATR) ν (cm^{-1}): 3333.6 (broad O-H), 1736.7 (C=O);); HRMS (ES+): *m/z* calculated for $C_9H_{16}O_4$: requires 189.1127 for $[M+H]^+$; found: 189.1124: requires 211.0946 for $[M+Na]^+$; found: 211.0938

6.3.13.2 (3*S*,4*S*,5*S*)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3*H*)-one, 240m2



Rf (7:3 DCM/EtOAc) = 0.42; $[\alpha]_D^{23}$ = -17.0 (*c* = 0.53 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (1H, app. br. d, *J* = 7.5 Hz, C*H*OH), 3.87 (1H, d, *J* = 12.6 Hz, CH_AH$_B$OH), 3.75 Hz (1H, d, *J* = 12.6 Hz, CH$_A$$H_B$OH), 2.67 (1H, dd, *J* = 8.3 Hz and 4.9 Hz, C*H*CO), 2.19 (1H, d.sept., *J* = 6.9 Hz and 4.9 Hz, C*H*(CH$_3$)$_2$), 1.29 (3H, s, CH_3), 1.03 (3H, d, *J* = 6.8 (CH_3^A)CH(CH$_3^B$)), 0.94 (3H, d, *J* = 6.8 (CH$_3^A$)CH(CH_3^B)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 85.8, 66.8, 56.1, 28.1, 22.6, 20.1, 19.1; IR (ATR) ν (cm^{-1}): 3308.0 (broad O-H), 1744.9 (C=O); HRMS (ES): *m/z* calculated for $C_9H_{16}O_4$: requires 189.1127 for $[M+H]^+$; found: 189.1115: requires 211.0946 for $[M+Na]^+$; found: 211.0927.

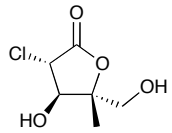
6.3.14 (3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-5-methyl-3-phenyl-dihydrofuran-2(3*H*)-one, 240l



Osmium tetroxide (6.3 mg, 0.025 mmol) was added to a solution of aldol **163l** (94 mg, 0.25 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.05 mL, 0.26 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-5-methyl-3-phenyl-dihydrofuran-2(3*H*)-one, 240l** (42 mg, 0.19 mmol, 75%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.34; $[\alpha]_D^{25}$ = -9.1 (*c* = 0.83 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.23 (3H, m, Ph*H*), 7.18 – 7.13 (2H, m, Ph*H*), 4.62 (1H, d, *J* = 10.5 Hz, C*H*OH), 3.80 (1H, d, *J* = 10.5 Hz, C*H*CO), 3.70 (1H, d, *J* = 12.6 Hz, CH_AH$_B$OH), 3.58 (1H, d, *J* = 12.6 Hz, CH$_A$$H_B$OH), 1.32 (3H, s, C$H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.33, 135.10, 129.42, 128.95, 128.42, 86.51,75.28, 65.47, 53.75, 16.87; IR (ATR) ν (cm^{-1}): 3308.3 (broad O-H), 1745.7 (C=O); HRMS (ES): *m/z* calculated for $C_{12}H_{14}O_4$: requires 223.0970 for $[M+H]^+$; found: 223.0961: requires 245.0790 for $[M+Na]^+$; found: 245.0767.

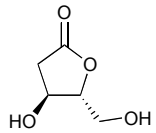
6.3.15 (3*S*,4*R*,5*R*)-3-chloro-4-hydroxy-5-(hydroxymethyl)-5-methyl-dihydrofuran-2(3*H*)-one, 240k



Osmium tetroxide (13.7 mg, 0.054 mmol) was added to a solution of aldol **163k** (175.2 mg, 0.54 mmol) in acetone/water (8:1, 3 mL) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.1 mL, 0.59 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded **(3*S*,4*R*,5*R*)-3-chloro-4-hydroxy-5-(hydroxymethyl)-5-methyl-dihydrofuran-2(3*H*)-one, 240k** (74.1 mg, 0.41 mmol, 76%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.13; $[\alpha]_D^{23}$ = +12.7 (*c* = 0.85 in MeOH); ^{1}H NMR (500 MHz, MeOD) δ 4.82 (1H, d, *J* = 9.6 Hz, C*H*Cl), 4.50 (1H, d, *J* = 9.6 Hz, C*H*OH), 3.66 (1H, d, *J* = 13.5 Hz, CH_AH$_B$OH), 3.55 (1H, d, *J* = 13.5 Hz, CH$_A$$H_B$OH), 1.33 (3H, s, C$H_3$); ^{13}C NMR (75 MHz, MeOD) δ 174.5, 91.6, 72.9, 68.0, 59.0, 18.1; IR (ATR) ν (cm^{-1}): 3331.0 (broad O-H), 1755.1 (C=O); HRMS (ES): *m/z* calculated for $C_6H_9ClO_4$: requires 203.0087 for $[M+Na]^+$; found: 203.0073.

6.3.16 (4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one, 272a

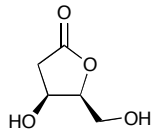


Osmium tetroxide (7.5 mg, 0.024 mmol) was added to a solution of aldol **275** (165 mg, 0.24 mmol) in acetone/water (0.07 mL, 0.24 mmol) followed by addition of *N*-methylmorpholine-*N*-oxide (60% by weight in water, 0.1 mL, 0.59 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification *via* column chromatography afforded a mixture of diastereomers **(*S*)-4-benzyl-3-((*S*)-3-hydroxypent-4-enoyl)oxazolidin-2-one, 272a** and **(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one, 272b** (14.5 mg, 0.11 mmol, 47%) as a pale oil.

^{1}H NMR (300 MHz, MeOD): δ 4.47 (1H, dt, *J* = 6.7, 2.3 Hz, C*H*OH), 4.43 – 4.37 (1H, m, C*H*CH$_2$OH), 3.81 (1H, dd, *J* = 12.4, 3.3 Hz, CH_ACH$_B$OH), 3.73 (1H, dd, *J* = 12.4, 3.6 Hz,

$CH_AC\mathit{H}_B$OH), 2.94 (1H, dt, *J* = 17.6, 6.2 Hz, $C\mathit{H}_ACH_BC$=O), 2.51 – 2.32 (1H, m, $CH_AC\mathit{H}_B$C=O); ^{13}C NMR (75.5 MHz, MeOD): δ 179.5, 91.1, 70.6, 63.4, 40.1; IR (ATR) ν_{max} (cm^{-1}): 3329 (broad O-H), 2941 (broad O-H), 1793 (C=O); HRMS (ESI); *m/z* calculated for $C_5H_8NO_4$: requires 155.0320 for $[M+Na]^+$; found: 155.0325.

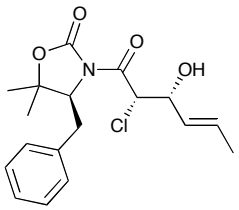
6.3.16.1 (4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one, 272b



^{1}H NMR (300 MHz, MeOD): δ 4.62 – 4.50 (1H, m, C*H*OH & C*H*CH_2OH), 3.91 (1H, dd, *J* = 5.4, 1.6 Hz, $C\mathit{H}_AC\mathit{H}_B$OH), 2.94 (2H, dt, *J* = 17.6, 6.2 Hz, $C\mathit{H}_ACH_BC$=O), 2.52 – 2.32 (1H, m, $CH_AC\mathit{H}_B$C=O); ^{13}C NMR (75.5 MHz, MeOD): δ 179.4, 87.4, 69.9, 62.1, 40.9; IR (ATR) ν_{max} (cm^{-1}): 3329 (broad O-H), 2941 (broad O-H), 1793 (C=O); HRMS (ESI); *m/z* calculated for $C_5H_8NO_4$: requires 155.0320 for $[M+Na]^+$; found: 155.0325.

6.4 Compounds from Chapter 5

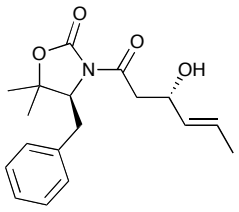
6.4.1 (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163p



9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (6.40 mL, 3.20 mmol) was added to a solution of (S)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one, **142d** (750.0 mg, 2.67 mmol) in dichloromethane (70 mL) followed by addition of *N,N*-diisopropylethylamine (0.58 ml, 3.335 mmol) and methacrolein (0.28 mL, 3.335 mmol) according to General Procedure 3 to afford the crude product as a pale yellow oil. Purification *via* column chromatography afforded **163p** (610.5 mg, 1.73 mmol, 65 %) as a colourless oil.

Rf = 0.21 (DCM); $[\alpha]_D^{24}$ = -20 (*c* = 1.20 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.10 (5H, m, Ph), 5.80 (1H, ddd, *J* = 15.5 Hz, 6.5 Hz and 1Hz, C*H*=CHCH$_3$), 5.66 (1H, d, *J* = 5.5 Hz, C*H*Cl), 5.47 (1H, dqd, *J* = 15.5 Hz, 6.5Hz and 1Hz, CH=C*H*CH$_3$), 4.51– 4.40 (2H, m, C*H*OH and C*H*N), 3.09 (1H, dd, *J* = 14.5Hz and 4.0 Hz, CH_AH$_B$Ph), 2.85 (1H, dd, *J* = 14.5 Hz and 9.5 Hz, CH$_A$$H_B$Ph) 2.61 (1H, br d, *J* = 4.0 Hz, O*H*), 1.65 (3H, d, *J* = 6.5 Hz, CH=CHCH_3), 1.34 (3H, s, C(CH_3)), 1.29 (3H, s, C(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 152.3, 136.7, 131.8, 129.5, 129.2, 128.1, 127.4, 83.4, 73.4, 64.4, 59.6, 35.3, 28.8, 22.6, 18.2; IR (ATR) ν (cm^{-1}): 3451 (broad O-H) 1772 (C=O), 1652 (C=O$_{ox}$); HRMS (ES): *m/z* calculated for $C_{18}H_{22}ClNO_4$: requires 374.1135 for $[M+Na]^+$; found 374.1147.

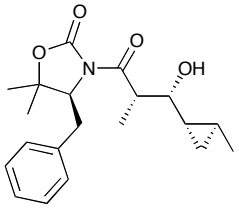
6.4.2 (*S*)-4-benzyl-3-((*S*,*E*)-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 296



According to General Procedure 8, Zinc dust (234 mg, 3.60 mmol) was added in one portion to a stirred mixture of aldol **163p** (314 mg, 0.89 mmol), solid NH_4Cl (191 mg, 3.60 mmol) and methanol (20 mL). The crude reaction product was purified by chromatography (CH_2Cl_2) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 296** (210 mg, 0.66 mmol) as a colourless oil in 74% yield.

$[\alpha]_D^{23}$ = -51.5 (*c* = 1.23, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.11 (5H, m, *Ar*H), 5.68 (1H, dqd, *J* = 15.5, 6.5, 1Hz, C*H*=CHCH$_3$), 5.47 (1H, ddq, *J* = 15.5, 6.5, 1Hz, CH=C*H*CH$_3$), 4.50–4.39 (2H, m, C*H*OH and C*H*N), 3.1-3.0 (3H, m, CH_2CHOH and CH_AH$_B$Ph), 2.8 (1H, dd, *J* = 14.5, 6.5 Hz, CH$_A$$H_B$Ph), 1.63 (3H, dt, *J* = 6.5 Hz, CH=CHCH_3), 1.32 (3H, s, C(CH_3)), 1.30 (3H, s, C(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 153.0, 137.2, 132.1, 129.4, 129.2, 127.8, 127.3, 82.9, 69.1, 63.8, 53.8, 43.3, 35.9, 28.8, 18.1; IR (KBr / cm^{-1}) 3502 (broad OH) 1777 (C=O), 1695 (C=O$_{ox}$); HRMS (ES+): *m/z* calculated for $C_{18}H_{23}NO_4$ requires $[M+Na]^+$ for 340.1524; found 374.1514.

6.4.3 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoyl))-5,5-dimethyloxazolidin-2-one, 295f

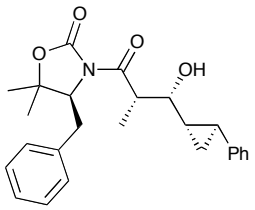


According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **163f** (200 mg, 0.658 mmol) in dichloromethane (10 mL) was treated with diethylzinc (3.29 mL, 3.289 mmol, 1.0 M in hexane) and diiodomethane (0.26 mL, 3.289 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-**

methylcyclopropyl)propanoyl))-5,5-dimethyloxazolidin-2-one, 295f as a white solid in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.20 (5H, m, Ph), 4.53 (1H, dd, *J* = 9.2, 4.3 Hz, C*H*OH), 3.99 (1H, dq, *J* = 14.0, 3.7 Hz, COC*H*), 3.20 (1H, dd, *J* = 8.4, 3.6 Hz, C*H*N), 3.08 (1H, dd, *J* = 14.3, 4.3 Hz, CH_AH$_B$Ph), 2.90 (1H, dd, *J* = 14.3, 9.2 Hz, CH$_A$$H_B$Ph), 2.46 (1H, s, O*H*), 1.38 (3H, s, (CH_3)C(CH$_3$)), 1.37 (3H, s, (CH$_3$)C(CH_3)), 1.25 (3H, d, *J* = 7.0 Hz, CHCH$_2$CHCH_3), 1.03 (3H, d, *J* = 6.0 Hz, CH_3CH), 0.77-0.63 (2H, m, CHCH_2CH), 0.55-0.49 (1H, m, C*H*CH$_2$CHCH$_3$), 0.35-0.29 (1H, m, CHCH$_2$C*H*CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.0, 11.8, 18.4, 22.3, 23.2, 28.6, 35.6, 43.0, 63.6, 76.2, 77.4, 82.4, 127.0, 128.8, 129.2, 136.9, 152.6, 176.9; IR (ATR) ν (cm^{-1}) = 3485.31 (O-H), 1775.98 (C=O$_{ox}$), 1685.41 (C=O); HRMS (ES): *m/z* calculated for $C_{20}H_{27}NO_4$: requires 368.1837 for $[M+Na]^+$; found: 368.1827.

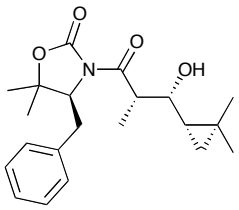
6.4.4 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295g



According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one **163g** (355 mg, 0.901 mmol) in dichloromethane (10 mL) was treated with diethylzinc (4.535 mL, 4.54 mmol, 1.0 M in hexane) and diiodomethane (0.36 mL, 4.535 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295g** as a white solid in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.04 (10H, m, Ph and CH$_2$*Ph*), 4.44 (1H, dd, *J* = 9.2, 4.3 Hz, C*H*N), 4.04 (1H, qd, *J* = 7.0, 4.4 Hz, COC*H*), 3.47 (1H, m, C*H*OH), 3.08 (1H, dd, *J* = 14.3, 4.2 Hz, CHCH_AH$_B$Ph), 2.87 (1H, dd, *J* = 14.3, 9.3 Hz, CHCH$_A$$H_B$Ph), 1.91 (1H, m, C*H*CH$_2$CHPh), 1.35 (3H, s, (C$H_3$)C(CH$_3$)), 1.25 (3H, d, *J* = 7.0 Hz, (CH_3CH), 1.16 (3H, s, (CH$_3$)C(CH_3)), 1.12-1.05 (1H, m, CHCH$_2$C*H*Ph), 1.03-0.83 (2H, m, CHCH_2CHPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 152.5, 142.3, 136.9, 129.2, 128.8, 128.5, 127.0, 125.9, 125.8, 82.3, 75.5, 63.5, 43.5, 35.5, 28.3, 26.6, 22.4, 21.3, 14.0, 12.4; IR (ATR) ν (cm^{-1}) = 3488.90 (O-H), 1769.80 (C=O$_{ox}$), 1692.60 (C=O); HRMS (ES): *m/z* calculated for $C_{25}H_{29}NO_4$: requires 430.1994 for $[M+Na]^+$; found: 430.1982.

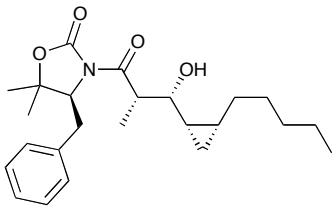
6.4.5 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295h



According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, **163h** (430 mg, 1.25 mmol) in dichloromethane (10 mL) was treated with diethylzinc (6.23 mL, 6.23 mmol, 1.0 M in hexane) and diiodomethane (0.5 mL, 6.23 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295h** as a white solid in quantitative yield.

$[\alpha]_D^{24}$ = +12.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.10 (5H, m, Ph) 4.48 (1H, dd, *J* = 9.2 Hz and 4.5 Hz, C*H*N), 3.91 (1H, qd, *J* = 7.0 Hz and 3.4 Hz, COC*H*), 3.47 (1H, dd, *J* = 9.5 Hz and 3.5 Hz, C*H*OH), 3.03 (1H, dd, *J* = 14.0 Hz and 4.5 Hz, CH_AH_BPh), 2.83 (1H, dd, *J* = 14.0 and 9.2 Hz, CH_ACH_BPh), 2.69 (1H, broad s, OH), 1.32 (3H, s, $(CH_3)C(CH_3)$), 1.31 (3H, s, $(CH_3)C(CH_3)$), 1.18 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.01 (3H, s, $(CH_3)C(CH_3)$-cyclopropane), 0.98 (3H, s, $(CH_3)C(CH_3)$-cyclopropane), 0.77 (1H, app. td, *J* = 8.3 Hz and 5.6 Hz, C*H*CH_2C), 0.51 (1H, dd, *J* = 8.3 Hz and 4.2 Hz, $CHCH_AH_BC$), 0.25 (1H, app. t, *J* = 5 Hz, CH_AH_BC); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 152.5, 137.1, 129.5, 129.0, 127.3, 82.5, 73.5, 64.2, 43.3, 35.8, 28.8, 28.1, 27.5, 23.1, 22.0, 19.5, 18.6, 11.4; IR (ATR) ν (cm^{-1}): 3483.7 (O-H), 1776.9 (C=O), 1686.4 ($C=O_{ox}$); HRMS (ES): *m/z* calculated for $C_{21}H_{29}NO_4$: requires 382.1994 for $[M+Na]^+$; found: 382.1979.

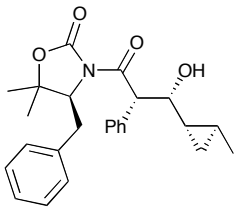
6.4.6 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295j



According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*Z*)-3-hydroxy-2-methyldec-4-enoyl)-5,5-dimethyloxazolidin-2-one, **163j** (363 mg, 0.938 mmol) in dichloromethane (10 mL) was treated with diethylzinc (4.68 mL, 4.68 mmol, 1.0 M in hexane) and diiodomethane (0.37 mL, 4.68 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)-propanoyl)-5,5-dimethyloxazolidin-2-one, 295j** as a white solid in quantitative yield.

$[\alpha]_D^{24}$ = -19.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (5H, m, Ph), 4.50 (1H, dd, *J* = 9.3 Hz and 4.3 Hz, C*H*N), 3.95 (1H, qd, *J* = 7.0 and 3.0 Hz, COC*H*), 3.55 (1H, app. dt, *J* = 9.2 Hz and 3.0 Hz, C*H*OH), 3.09 (1H, dd, *J* = 14.5 and 4.3 Hz, CH_AH_BPh), 2.91 (1H, dd, *J* = 14.5 and 9.3 Hz, CH_ACH_BPh), 2.65 (1H, d, *J* = 2.1 Hz, O*H*), 1.65-1.20 (8H, obs. m, $(CH_2)_4$), 1.40 (3H, s, $(CH_3)C(CH_3)$), 1.37 (3H, s, $(CH_3)C(CH_3)$), 1.29 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.07-0.93 (2H, m, $CHCH_2CH$), 0.88 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 0.86-0.76 (1H, m, $CHCH_2CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 152.7, 137.1, 129.5, 129.1, 127.3, 82.6, 72.4, 63.9, 43.3, 35.8, 32.1, 30.2, 29.3, 28.8, 23.1, 22.6, 19.4, 16.7, 14.5, 11.6, 10.2; IR (ATR) ν (cm^{-1}): 3510.7 (O-H), 1774.4 (C=O), 1694.4 ($C=O_{ox}$); HRMS (ES): *m/z* calculated for $C_{24}H_{35}NO_4$: requires 424.2464 for $[M+Na]^+$; found: 424.2449.

6.4.7 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295o

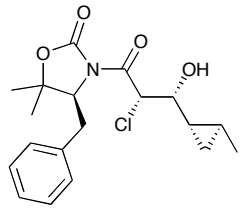


According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-phenylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, **163o** (915 mg, 2.33 mmol) in dichloromethane (10 mL) was

treated with diethylzinc (11.6 mL, 11.6 mmol, 1.0 M in hexane) and diiodomethane (0.935 mL, 11.6 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295o** as a white solid in quantitative yield.

$[\alpha]_D^{24}$ = -6.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.10 (10H, m, Ph), 5.17 (1H, br. d, *J* = 5.2 Hz, C*H*Ph), 4.56 (1H, dd, *J* = 9.7 Hz and 3.0 Hz, C*H*N), 3.59 (1H, dd, *J* = 7.4 Hz and 5.2 Hz, C*H*OH), 2.98 (1H, dd, *J* = 14.9 Hz and 3.7 Hz, CH_AH_BPh), 2.69 (1H, dd, *J* = 14.9 Hz and 10.4 Hz, CH_AH_BPh), 1.36 (3H,s, (CH_3)C(CH_3)), 1.29 (3H, s, (CH_3)C(CH_3)), 1.01 (3H, d, *J* = 5.9, CHCH_3), 0.80 – 0.64 (1H, m, C*H*CH_2CHMe), 0.63 – 0.45 (2H, m, CHCH_2CHMe), 0.34 – 0.19 (1H, m, $CHCH_2$C*H*Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 152.2, 137.1, 134.5, 130.5, 129.4, 129.1, 128.9, 128.1, 127.2, 82.4, 76.7, 63.9, 55.1, 35.1, 29.1, 24.1, 22.7, 18.7, 12.0, 11.8; IR (ATR) ν (cm^{-1}): 3511.9 (O-H), 1771.6 (C=O), 1690.3 ($C=O_{ox}$); HRMS (ES): *m/z* calculated for $C_{25}H_{29}NO_4$: requires 430.1994 for $[M+H]^+$; found: 430.1989.

6.4.8 (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295p

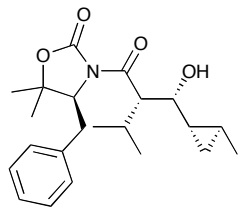


According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, **163p** (599 mg, 1.70 mmol) in dichloromethane (10 mL) was treated with diethylzinc (8.5 mL, 8.5 mmol, 1.0 M in hexane) and diiodomethane (0.682 mL, 8.5 mmol) to afford **(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295p** as a white solid in quantitative yield.

$[\alpha]_D^{24}$ = -18.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.11 (5H, m, Ph), 5.72 (1H, d, *J* = 4.1 Hz, C*H*Cl), 4.45 (1H, dd, *J* = 9.5 Hz and 3.5 Hz, C*H*N), 3.39 (1H, dd, *J* = 7.9 Hz and 4.1 Hz, C*H*OH), 3.15 (1H, dd, *J* = 14.5 Hz and 3.5 Hz, CH_AH_BPh), 2.84 (1H, dd, *J* = 14.5 Hz and 9.8 Hz, CH_AH_BPh), 1.33 (3H, s, (CH_3)C(CH_3)), 1.29 (3H, s, (CH_3)C(CH_3)), 0.97 (3H, d, *J* = 5.7, CHCH_3), 0.86 – 0.68 (2H, m, CHCH_2CHMe), 0.62 – 0.53 (1H, m, C*H*CH_2CHMe), 0.37 – 0.27 (1H, m, $CHCH_2$C*H*Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.69, 152.3, 136.8, 129.4, 129.2, 127.4, 83.5, 75.5, 64.6, 60.7, 35.1, 28.9, 23.1, 22.7, 18.6, 12.18, 11.34; IR (ATR) ν (cm^{-1}): 3509.8 (O-H), 1774.9 (C=O), 1711.8 ($C=O_{ox}$); HRMS (ES): *m/z* calculated for $C_{19}H_{24}ClNO_4$:

requires 366.1472 for $[M+H]^+$; found: 366.1472; requires 388.1291for $[M+Na]^+$; found: 388.1282.

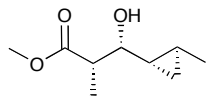
6.4.9 (*S*)-4-benzyl-3-((*S*)-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one, 295q



According to General Procedure 9, (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-isopropylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, **163q** (810 mg, 2.28 mmol) in dichloromethane (10 mL) was treated with diethylzinc (11.4 mL, 11.4 mmol, 1.0 M in hexane) and diiodomethane (0.92 mL, 11.4 mmol) to afford **(*S*)-4-benzyl-3-((*S*)-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)-methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one, 295q** as a white solid in quantitative yield.

$[\alpha]_D^{24}$ = -8.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.15 (5H, m, Ph), 4.63 (1H, dd, *J* = 10.4 Hz and 3.2 Hz, C*H*N), 4.24 (1H, dd, *J* = 8.5 Hz and 6.4 Hz, C*H*$(CH_3)_2$), 3.67 (1H,dd, *J* = 8.9 Hz and 6.4 Hz, C*H*OH), 3.24 (1H, dd, *J* = 14.3 Hz and 3.2 Hz, CH_AH_BPh), 2.87 (1H, dd, *J* = 14.5 Hz and 10.0 Hz, CH_AH_BPh), 2.29 (1H, m, C*H*$(CH_3)_2$), 1.36 (3H, s, (CH_3)C(CH_3)), 1.34 (3H, s, (CH_3)C(CH_3)), 1.06 (3H, d, *J* = 6.1 Hz, CHCH_3), 1.03 (3H, d, *J* = 6.8 Hz, (CH_3^A)C(CH_3^B)), 0.95 (3H, d, *J* = 6.8 Hz, (CH_3^A)C(CH_3^B)), 0.85 – 0.67 (2H, m, CHCH_2CHMe), 0.60 – 0.39 (1H, m, C*H*CH_2CHMe), 0.37 – 0.23 (1H, m, $CHCH_2$C*H*Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 153.7, 137.4, 129.4, 129.1, 127.2, 82.2, 75.8, 64.3, 54.5, 35.8, 28.9, 28.7, 23.5, 22.8, 21.3, 21.0, 18.8, 14.7, 13.1, 10.7; IR (ATR) ν (cm^{-1}): 3511.1 (broad O-H), 1771.7 (C=O), 1689.4 ($C=O_{ox}$); HRMS (ES): *m/z* calculated for $C_{22}H_{31}NO_4$: requires 396.2150 for $[M+Na]^+$; found: 396.2154.

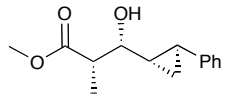
6.4.10 (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 309f



According to General Procedure 10, (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)-propanoyl)-5,5-dimethyloxazolidin-2-one **295f** (152 mg, 0.440 mmol) in dichloromethane (8.8 mL) was treated with sodium methoxide (0.88 mL, 0.440 mmol, 0.5 M in methanol). The crude product was purified using flash chromatography. Pure fractions were evaporated to afford **(2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 309f** (42 mg, 55%) as a colourless liquid.

R_f = 0.24 (1:4, EtOAc:Hexane); $[\alpha]_D^{24}$ = -8.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s, OC*H*$_3$), 3.13-3.08 (1H, m, C*H*OH), 2.70 (1H, dq, *J* = 14.2 Hz and 5.2 Hz, COC*H*), 2.19 (1H, s, O*H*), 1.26 (3H, d, *J* = 7.1 Hz, C*H*$_3$CH), 1.01 (3H, d, *J* = 5.7 Hz, CHCH$_2$CHC*H*$_3$)), 0.71-0.58 (2H, m, CH(C*H*$_2$)CHCH$_3$), 0.54-0.49 (1H, m, C*H*(CH$_2$)CHCH$_3$), 0.34-0.28 (1H, m, CH(CH$_2$)C*H*CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 76.8, 52.0, 45.6, 23.9, 18.3, 12.3, 11.5, 11.3; IR (ATR) ν (cm^{-1}) = 3444.07 (O-H), 1718.01 (C=O); HRMS (ES+): *m/z* calculated for $C_9H_{16}O_3$: requires 195.0997 for $[M+Na]^+$; found: 195.0995

6.4.11 (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate, 309g

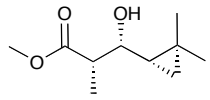


According to General Procedure 10, (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)-propanoyl)-5,5-dimethyloxazolidin-2-one **295g** (168 mg, 0.412 mmol) in dichloromethane (8.2 mL) was treated with sodium methoxide (0.82 mL, 0.412 mmol). The crude product was purified using flash chromatography. The pure fractions were concentrated under reduced pressure to afford **(2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate, 309g** (86 mg, 89%) as a colourless liquid.

R_f = 0.49 (3:7, EtOAc:Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.14 (2H, m, Ph), 7.10-7.04 (1H, m, Ph), 6.98-6.95 (2H, m, Ph), 3.53 (3H, s, OC*H*$_3$), 3.35 (1H, dd, *J* = 8.0Hz and 4.7 Hz, C*H*OH), 2.68 (1H, dq, *J* = 14.2 and 4.7 Hz, COC*H*), 2.43 (1H, s, O*H*), 1.79-1.72 (1H, m, CH(CH$_2$)C*H*Ph), 1.30-1.23 (1H, m, C*H*(CH$_2$)CHPh), 1.20 (3H, d, *J* = 7.2 Hz, C*H*$_3$CH), 1.03-

0.97 (1H, m, CH(CH_AH$_B$)CHCH$_3$), 0.93-0.87 (1H, m, CH(CH$_A$$H_B$)CHCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 142.1, 128.5, 125.9, 125.8, 75.8, 51.8, 45.3, 26.4, 21.2, 13.9, 12.1; IR (ATR) ν (cm^{-1}) = 3439.46 (O-H), 1730.03 (C=O); HRMS: *m/z* calculated for $C_{14}H_{18}O_3$: requires 257.1153 for $[M+Na]^+$; found: 257.1148.

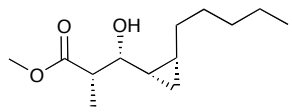
6.4.12 (2*S*,3*R*)-methyl 3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate, 309h



According to General Procedure 10, (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **295h** (272 mg, 0.75 mmol) in dichloromethane (7 mL) was treated with sodium methoxide (2.3 mL, 1.15 mmol). The crude product was purified using flash chromatography. The pure fractions were concentrated under reduced pressure to afford **(2*S*,3*R*)-methyl 3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate, 309h** (99.0 mg, 71 %) as a colourless oil.

Rf (3:1, Petrol:EtOAc) = 0.5; $[\alpha]_D^{23}$ = -11 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s, OCH_3), 3.50 (1H, dd, *J* = 9.4 Hz and 4.1 Hz C*H*OH), 2.64 (1H, dq, *J* = 7.1 Hz and 3.9 Hz, COC*H*), 1.27 (3H, d, *J* = 7.5 Hz, CH_3CH), 1.07 (3H, s, *CH$_3$*), 1.03 (3H, s, *CH$_3$*), 0.83-0.74 (1H, m, CH(CH_AH$_B$)C), 0.57 (1H, dd, *J* = 8.4 Hz and 4.3 Hz, CH(CH$_A$$H_B$)C), 0.33 (1H, app t, *J* = 5.1 Hz, C*H*(CH$_2$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 73.5, 52.2, 45.7, 28,6, 27.5, 21.0, 18.8, 17.1, 11.5; IR (ATR) ν (cm^{-1}): 3451.9 (O-H), 1721.4 (C=O); HRMS (ES): *m/z* calculated for $C_{10}H_{18}O_3$: requires 209.1153 for $[M+Na]^+$; found: 209.1134.

6.4.13 (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)propanoate, 309j

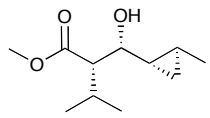


According to General Procedure 10, (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, **295j** (340.1 mg, 0.848 mmol) in dichloromethane (7 mL) was treated with sodium methoxide (2.54 mL, 1.27 mmol). The crude product was purified using flash chromatography. The pure fractions were concentrated under

reduced pressure to afford **(2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)propanoate, 309j** (157.0 mg, 81%) as a colourless liquid

Rf (3:1, Petrol:EtOAc); $[\alpha]_D^{23}$ = +8.0 (*c* =0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s, OC*H*$_3$), 3.58 (1H, dd, *J* = 9.3 Hz and 3.2 Hz C*H*OH), 2.66 (1H, dq, *J* = 7.3 Hz and 3.2 Hz, COC*H*), 1.63-1.46 (2H, m, C*H*$_2$-alkyl), 1.46-1.16 (9H, m, (C*H*$_2$)$_3$ and C*H*$_3$CH) 0.93 (2H, m, CH(C*H*$_A$H$_B$)CH), 0.88 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 0.80 (1H, m, CH(CH$_A$*H*$_B$)CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 72.6, 52.2, 45.3, 32.1, 30.2, 29.2, 23.0, 19.8, 16.9, 14.4, 10.8, 10.2; IR (ATR) ν (cm^{-1}): 3335.1 (O-H), 1715.1 (C=O); HRMS (ES): *m/z* calculated for $C_{13}H_{24}O_3$: requires 251.1623 for $[M+H]^+$; found: 251.1612.

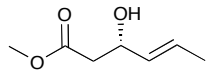
6.4.14 (*S*)-methyl 2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate, 309q



According to General Procedure 10, (*S*)-4-benzyl-3-((*S*)-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one **295q** (900 mg, 2.5 mmol) in dichloromethane (10 mL) was treated with sodium methoxide (5.5 mL, 2.75 mmol). The crude product was purified using flash chromatography. The pure fractions were concentrated under reduced pressure to afford **(*S*)-methyl 2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate, 309q** (375 mg, 75%) as a colourless liquid

Rf (3:1, Petrol:EtOAc) = 0.6; $[\alpha]_D^{24}$ = -13.0 (*c* = 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (3H, s, OC*H*$_3$), 3.18 (1H, app. t, *J* = 8.2 Hz, C*H*OH), 2.53 (1H, dd, *J* = 7.9 Hz and 6.1 Hz, COC*H*), 2.21 (1H, m, C*H*(CH$_3$)$_2$), 1.00 (3H, app. s, CHC*H*$_3$), 0.98 (3H, d, *J* = 2.77 Hz, C*H*$_3$CH), 0.97 (3H, d, *J* = 2.7 Hz, C*H*$_3$CH), 0.80-0.63 (2H, m, CH(C*H*$_2$)CHCH$_3$), 0.55-0.41 (1H, m, C*H*(CH$_2$)CHCH$_3$), 0.33-0.21 (1H, m, CH(CH$_2$)C*H*CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 75.2, 58.6, 51.4, 27.5, 25.5, 21.8, 19.2, 18.6, 12.8, 11.1; IR (ATR) ν (cm^{-1}): 3451.0 (broad O-H), 1731.8 (C=O); HRMS (ES): *m/z* calculated for $C_{11}H_{20}O_3$: requires 223.1315 for $[M+Na]^+$; found: 223.1305.

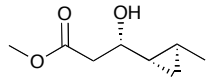
6.4.15 (*S*)-methyl 3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 297



According to General Procedure 10, (*S*)-4-benzyl-3-((*S*,*E*)-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, **296** (242 mg, 0.76 mmol) in dichloromethane (10 mL) was treated with sodium methoxide (0.5 M in methanol, 1.54 mL, 0.77 mmol). The crude product was purified using flash chromatography. The pure fractions were concentrated under reduced pressure to afford **(*S*)-methyl 3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 297** (78 mg, 0.54 mmol, 71%) as a colourless oil.

$[\alpha]_D^{22}$ = -22.2 (*c* = 0.72 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, dqd, *J* = 15.0 Hz, 6.0 Hz and 1.0 Hz, CH=C*H*CH_3), 5.43 (1H, ddq, *J* = 15.0 Hz, 6.0 Hz and 1.0 Hz, C*H*=$CHCH_3$), 4.42 (1H, app. q, *J* = 6.5 Hz, C*H*OH), 3.62 (3H, s, OCH_3), 2.78 (1H, br. s, CHO*H*), 2.47 (2H, m, CH_2), 1.63 (3H, t, *J* = 6.5 Hz, CH=CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 132.2, 127.9, 69.3, 52.1, 41.8, 18.0; IR (KBr / cm^{-1}) 3431 (broad O-H), 1734 (C=O); HRMS (ES+): *m/z* calculated for $C_7H_{12}O_3$ requires 167.0684 for $[M+Na]^+$; found 167.0683.

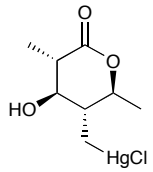
6.4.16 (*S*)-methyl 3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 298



According to General Procedure 9, diethylzinc (1.9 mL) and diiodomethane (510 mg, 1.9 mmol) were added to (*S*)-methyl 3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, **297** (56 mg, 0.39 mmol) in dichloromethane (5 mL) to afford the crude reaction product that was purified by column chromatography to afford the **(*S*)-methyl 3-hydroxy-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, 298** (258 mg, 0.65 mmol) as a yellow oil in 95% yield.

$[\alpha]_D^{25}$ = +6.0 (*c* = 0.60 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (3H, s, OCH_3), 3.25 (1H, m, C*H*OH), 2.56 (1H, m, CH_AH_B), 2.54 (1H, d, m, CH_AH_B), 0.96 (3H, d, *J* = 5.5 Hz, CH_3), 0.57 (2H, m, C*H*-cyclopropyl), 0.49 (1H, m, cyclopropyl-CH_AH_B), 0.25 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 71.2, 50.7, 40.5, 24.6, 17.2, 10.5, 9.6; IR (KBr / cm^{-1}) 3435 (broad O-H), 1739 (C=O); HRMS (ES+): *m/z* calculated for $C_8H_{14}O_3$ requires 181.0840 for $[M+Na]^+$; found 181.0834.

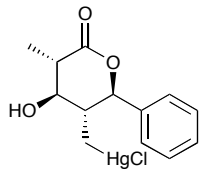
6.4.17 (((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-2,5-dimethyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, 313f



Mercury trifluoroacetate (371 mg, 0.87 mmol) was added in one portion to a stirring solution of (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate, **309f** (60 mg, 0.35 mmol) in dichloromethane (5 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford crude product, which was purified over a column of silica gel eluting with DCM/EtOAc (9:1). The pure fractions were concentrated under reduced pressure to afford **(((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-2,5-dimethyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, 313f** (107.6 mg, 0.27 mmol, 78%) as a colourless oil

Rf (10:1 DCM/EtOAc) = 0.12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (1H, dq, *J* = 9.9 Hz and 6.3 Hz, OC*H*CH_3), 3.39 (1H, br. d, *J* = 5.6 Hz, O*H*), 3.30 (1H, app. dt, *J* = 10.1 Hz and 5.1 Hz, C*H*OH), 2.48 (1H, dq, *J* = 9.8 Hz and 7.1 Hz, C*H*CH_3), 2.09 – 1.98 (2H, m, C*H*CHOH and CH_AH_BHg), 1.48 (3H, d, *J* = 6.3 Hz, C*H*$_3$CO), 1.43 (3H, d, *J* = 7.1 Hz, C*H*$_3$CH), 1.38 (1H, app. t, *J* = 9.9 Hz, CH_AH_BHg); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 80.1, 74.8, 47.1, 45.2, 27.1, 20.6, 14.3; ^{199}Hg NMR (89 MHz, $CDCl_3$) δ -933.9 ppm; IR (ATR) ν (cm^{-1}): 3335.4 (broad O-H), 1682.1 (C=O); HRMS (ES+): *m/z* calculated for $C_8H_{13}ClHgO_3$: requires 395.0338 for $[M+H]^+$; found: 395.0338; requires 417.0157 for $[M+Na]^+$; found: 417.0148.

6.4.18 (((2*R*,3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-6-oxo-2-phenyltetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, 313g

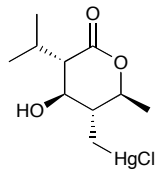


Mercury trifluoroacetate (64 mg, 0.273 mmol) was added in one portion to a stirring solution of (2*S*,3*R*)-methyl-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)-propanoate **309g** (290

mg, 0.683 mmol) in dichloromethane (5 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford crude product **(((2*R*,3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-6-oxo-2-phenyltetrahydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 313g**. The product was not purified due to its potential toxicity.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (3H, m, Ph), 7.32-7.28 (2H, m, Ph), 4.76 (1H, d, J = 10.5 Hz, OC*H*Ph), 3.45-3.39 (1H, m, C*H*OH), 3.19 (1H, d, J = 4.5 Hz, O*H*), 2.62 (1H, m, COC*H*CH_3), 2.35 (1H, m, C*H*CH_2HgCl), 1.49-1.43 (5H, m, CHC*H*$_3$ and CHC*H*$_2$HgCl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 129.9, 129.4, 127.7, 85.5, 75.4, 46.7, 45.3, 29.8, 26.9, 14.0.

6.4.19 (((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-5-isopropyl-2-methyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, 313h

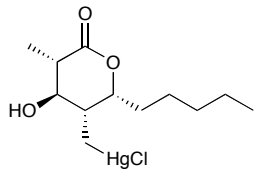


Mercury trifluoroacetate (585 mg, 1.37 mmol) was added in one portion to a stirring solution of (*S*)-methyl-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate, **309h** (110 mg, 0.55 mmol) in dichloromethane (5 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford crude product, which was purified over a column of silica gel eluting with DCM/EtOAc (9:1). The pure fractions were concentrated under reduced pressure to afford **(((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-5-isopropyl-2-methyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 313h** (193.0 mg, 0.46 mmol, 83%) as a colourless oil

Rf (10:1 DCM/EtOAc) = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (1H, dq, *J* = 9.9 Hz and 6.3 Hz, OC*H*CH_3), 3.44 (1H, app. dt, *J* = 10.2 Hz and 6.6 Hz, C*H*OH), 3.25 (1H, br. d, *J* = 6.3 Hz, O*H*), 2.55 (1H, dd, *J* = 6.9 Hz and 3.9 Hz, C*H*COO), 2.41 – 2.31 (2H, m, C*H*$(CH_3)_2$), 2.05 (1H, dd, *J* = 12.0 Hz and 3.9 Hz, CH_AH_BHg), 1.95 (1H, dq, *J* = 10.5 Hz and 3.9 Hz, C*H*CH_2Hg), 1.44 (3H, d, *J* = 6.0 Hz, CH_3CH), 1.35 (1H, t, *J* = 11.7 Hz, CH_AH_BHg), 1.27 (1H, d, *J* = 6.9 Hz, (CH_3^A)C(CH_3^B)), 1.08 (1H, d, *J* = 6.9 Hz, (CH_3^A)C(CH_3^B)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 78.6, 72.1, 57.3, 47.1, 30.6, 27.1, 20.8, 20.1, 19.9; ^{199}Hg NMR (89 MHz, $CDCl_3$) δ -

937.7 ppm; IR (ATR) ν (cm^{-1}): 3334.9 (broad O-H), 1681.8 (C=O); HRMS (ES+): *m/z* calculated for $C_{10}H_{17}ClHgO_3$: requires 423.0650 for $[M+H]^+$; found: 423.0637.

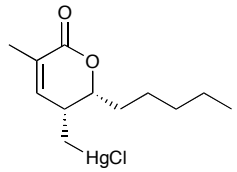
6.4.20 (((2*R*,3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-6-oxo-2-pentyltetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, 313j



Mercury trifluoroacetate (692 mg, 1.625 mmol) was added in one portion to a stirring solution of (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentylcyclopropyl)propanoate, **309j** (149.0 mg, 0.65 mmol) in dichloromethane (5 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford a mixture of lactone products, which were purified over a column of silica gel eluting with DCM/EtOAc (9:1). The pure fractions were concentrated under reduced pressure to afford **(((2*R*,3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-6-oxo-2-pentyltetrahydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 313j** (160.5 mg, 0.36 mmol, 55%) as a colourless oil and **(((2*R*,3*R*)-5-methyl-6-oxo-2-pentyl-3,6-dihydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 323 (**92.5 mg, 0.214 mmol, 33%) as a white solid.

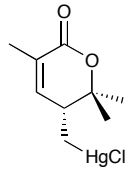
Rf (10:1 DCM/EtOAc) = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (1H, dq, 1H, *J* = 8.0 Hz and 4.0 Hz, C*H*O), 3.44 (1H, dd, *J* = 9.3 Hz and 5.6 Hz, C*H*OH), 2.65 (1H, dq, *J* = 13.3 Hz and 6.8 Hz), 2.42 – 2.33 (1H, m, C*H*CH_2Hg), 1.97 (1H, dd, *J* = 11.6 Hz and 3.6 Hz, CH_AH_BHg), 1.69 (1H, app. t, 11.6 Hz, CH_AH_BHg), 1.70 – 1.46 (2H m, CH_2CHO), 1.36 (3H, d, *J* = 6.8 Hz, CH_3CH), 1.36 – 1.27 (6H, m, (CH_2)$_3$), 0.91 (3H, t, *J* = 6.4, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 79.8, 45.1, 43.3, 31.9, 31.4, 29.1, 26.0, 22.9, 14.4, 13.7; ^{199}Hg NMR (89 MHz, $CDCl_3$) δ -958.1 ppm; IR (ATR) ν (cm^{-1}): 3438.4 (broad O-H), 1702.9 (C=O).

6.4.20.1 (((2*R*,3*R*)-5-methyl-6-oxo-2-pentyl-3,6-dihydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 323



Rf (DCM) = 0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (1H, dq, *J* = 6.27 Hz and 1.39 Hz), 4.45 (1H, ddd, *J* = 8.9 Hz, 5.1 Hz and 3.5 Hz, C*H*O), 2.73 (1H, m, C*H*CH_2Hg), 2.02 (1H, dd, *J* =11.6 Hz and 4.7 Hz, C$H_A$$H_B$Hg), 1.92 (3H, s, C$H_3$C=C), 1.82 (1H, dd, *J* = 11.6 Hz and 8.9 Hz, $CH_A$$H_B$Hg); 1.62 – 1.48 (2H, m, CHOCH_2), 1.43 – 1.2 (6H, m, $(CH_2)_3$), 0.90 (3H, t, *J* = 6.8 Hz, C$H_3$$CH_2$); ^{199}Hg NMR (89 MHz, $CDCl_3$) δ -937.6 ppm; IR (ATR) ν (cm^{-1}): 1697.9 (C=O); HRMS (ES): *m/z* calculated for $C_{12}H_{19}HgClO_2$: requires 433.0858 for $[M+H]^+$; found: 433.0836.

6.4.21 (*R*)-((2,2,5-trimethyl-6-oxo-3,6-dihydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 324

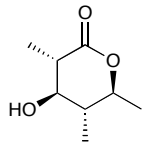


Mercury trifluoroacetate (607.0 mg, 1.42 mmol) was added in one portion to a stirring solution of (*S*)-methyl-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate, **309h** (106 mg, 0.57 mmol) in dichloromethane (5 mL). The reaction was stirred at ambient temperature for 24 hours, before being quenched with brine (5 mL) and stirred for one hour. The solution was extracted with dichloromethane, washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated to afford crude product, which was purified over a column of silica gel eluting with DCM/EtOAc (9:1). The pure fractions were concentrated under reduced pressure to afford **(*R*)-((2,2,5-trimethyl-6-oxo-3,6-dihydro-2*H*-pyran-3-yl)methyl)mercury(II) chloride, 324** (195.0 mg, 0.47 mmol, 83%) as a colourless oil

Rf (DCM) = 0.15; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (1H, br. d, *J* = 5.1 Hz), 2.14 (1H, dd, *J* = 11.3 Hz and 3.9 Hz, C$H_A$$H_B$Hg), 1.94 (3H, s, CH_3C=C), 1.91 (1H, dd, *J* = 12.5 Hz and 10.2 Hz, C$H_A$$H_B$Hg), 1.49 (3H, s, (C$H_3$)C($CH_3$)), 1.44 (3H, s, ($CH_3$)C(C$H_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 144.3, 128.0, 83.2, 42.6, 32.3, 28.2, 24.6, 17.4; IR (ATR) ν (cm^{-1}): 1695.8

(C=O); HRMS (ES): *m/z* calculated for $C_9H_{13}HgClO_2$: requires 391.0389 for $[M+H]^+$; found: 391.0387; requires 413.0208 for $[M+H]^+$; found: 413.0190.

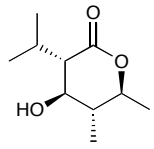
6.4.22 (3*S*,4*R*,5*R*,6*S*)-4-hydroxy-3,5,6-trimethyltetrahydro-2*H*-pyran-2-one, 326



Sodium borohydride (1 mL, 0.5M in $NaOH_{(aq)}$) was added dropwise to a stirring solution of (((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-2,5-dimethyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, **313f** (30.0 mg, 0.075 mmol) in methanol (1 mL) and aqueous sodium hydroxide (2.5M, 0.8 mL). After 5 minutes the reaction was washed with 2.0 M HCl and 5% sodium hydrogen carbonate, the resulting organics were dried over magnesium sulphate and concentrated under reduced pressure to yield **(3*S*,4*R*,5*R*,6*S*)-4-hydroxy-3,5,6-trimethyltetrahydro-2*H*-pyran-2-one, 326** in quantitative yield.

$[\alpha]_D^{25}$ = -27.1 (*c* = 0.48 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 4.01 (1H, dq, *J* = 10.5 Hz and 7.1 Hz, C*H*OCH_3), 3.31 (1H, app. t, *J* = 9.9 Hz, C*H*OH), 2.41 (1H, dq, *J* = 10.49 Hz and 7.06 Hz, C*H*CO), 1.71-1.60 (1H, m, C*H*CHOH), 1.42 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.41 (3H, d, *J* = 6.1 Hz, CHCH_3), 1.11 (3H, d, *J* = 6.3 Hz, CHCH_3), ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 79.0, 75.6, 44.9, 43.4, 20.2, 14.2, 13.6; IR (ATR) ν (cm^{-1}): 3423.6 (broad O-H), 1711.8 (C=O); HRMS (ES): *m/z* calculated for $C_8H_{14}O_3$: requires 159.1021 for $[M+H]^+$; found: 159.1026; requires 181.0841 for $[M+Na]^+$; found: 181.0834.

6.4.23 (3*S*,4*R*,5*R*,6*S*)-4-hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2*H*-pyran-2-one, 327



Sodium borohydride (0.63 mL, 0.325 mmol, 0.5M in $NaOH_{(aq)}$) was added dropwise to a stirring solution of (((2*S*,3*R*,4*S*,5*S*)-4-hydroxy-5-isopropyl-2-methyl-6-oxotetrahydro-2*H*-pyran-3-yl)methyl)-mercury(II) chloride, **313h** (70.0 mg, 0.17 mmol) in methanol (0.42 mL) and aqueous sodium hydroxide (2.5M, 0.8 mL). After 5 minutes the reaction was washed with 2.0 M HCL and 5% sodium hydrogen carbonate, the resulting organics were dried over magnesium

sulphate and concentrated under reduced pressure to yield **((3*S*,4*R*,5*R*,6*S*)-4-hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2*H*-pyran-2-one, 327** in quantitative yield.

$[\alpha]_D^{25}$ = -30.1 (*c* = 0.76 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (1H, dq, *J* = 9.6 Hz and 5.7 Hz, C*H*OCH_3), 3.49 (1H, dd, *J* = 9.6 Hz and 7.4 Hz, C*H*OH), 2.47 (1H, dd, *J* = 7.9 Hz and 3.9 Hz, C*H*CO), 2.44-2.33 (1H, m, C*H*$(CH_3)_2$), 1.66-1.54 (1H, m, C*H*CHOH), 1.38 (3H, d, *J* = 6.2, C*H*$_3$CHCO), 1.12 (3H, d, *J* = 6.8 Hz, (C*H*$_3$)$CH(CH_3)$), 1.09 (3H, d, *J* = 6.8 Hz, (CH_3)CH(C*H*$_3$)), 1.07 (3H, d, *J* = 7.4 Hz, C*H*CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 77.8, 72.38, 56.6, 43.2, 30.1, 20.8, 20.0, 19.9, 13.6; IR (ATR) ν (cm^{-1}): 3434.4 (broad O-H), 1706.1 (C=O); HRMS (ES): *m/z* calculated for $C_{10}H_{18}O_3$: requires 187.1335 for $[M+H]^+$; found: 187.1315; requires 209.1154 for $[M+Na]^+$; found: 209.1130.

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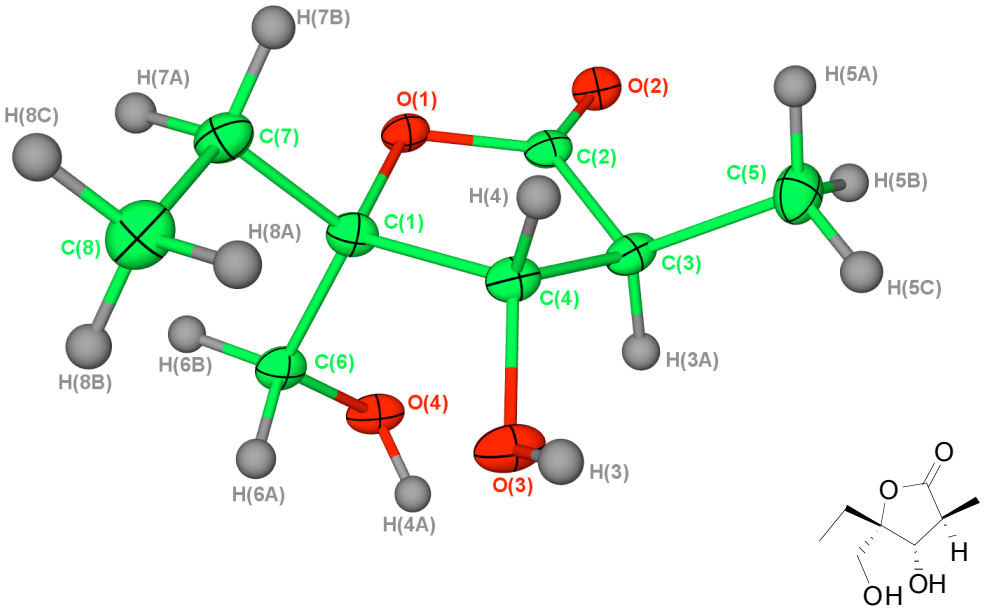
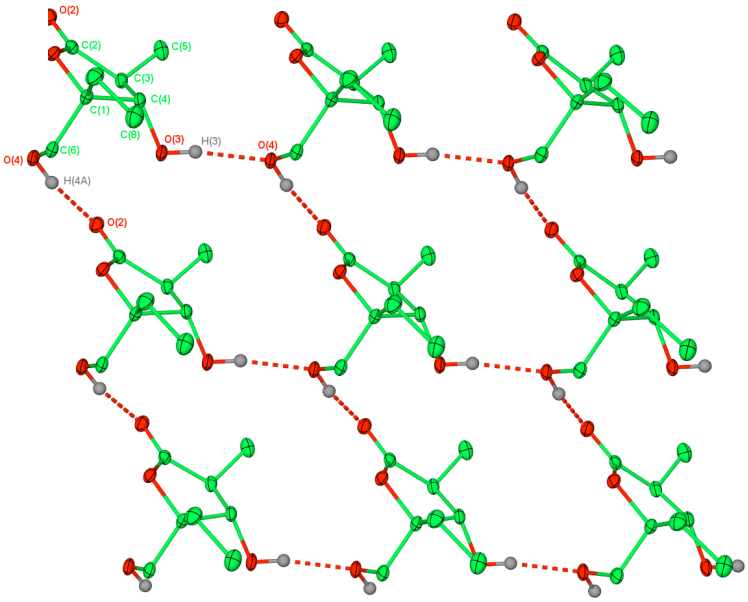
Appendix 1:

Crystal structure of lactone 163c



Crystal structure of (*S*,*S*,*S*)-lactone **163c**



Crystal packing of (*S*,*S*,*S*)-lactone **163c**

Table 1. Crystal data and structure refinement for (*S*,*S*,*S*)-lactone **163c**.

Identification code	c:\x-ray\kappa\k05rg1\maxus\k05rg1
Empirical formula	C8 H14 O4
Formula weight	174.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 5.4370(2)Å α = 90°
	b = 14.1610(6)Å β = 101.723(2)°
	c = 5.9280(2)Å γ = 90°
Volume	446.90(3) Å^3
Z	2
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	188
Crystal size	0.18 x 0.18 x 0.03 mm
Theta range for data collection	5.46 to 27.47°
Index ranges	-6<=h<=7; -18<=k<=18; -7<=l<=7
Reflections collected	8674
Independent reflections	2025 [R(int) = 0.0559]
Reflections observed (>2σ)	1779
Data Completeness	0.989
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2025 / 1 / 116
Goodness-of-fit on F^2	1.149
Final R indices [I>2σ(I)]	R^1 = 0.0554 wR$_2$ = 0.0926
R indices (all data)	R^1 = 0.0679 wR$_2$ = 0.0959
Absolute structure parameter	0.3(13)
Largest diff. peak and hole	0.191 and -0.154 eÅ^{-3}

Notes: absolute configuration assigned on basis of known stereochemistry at one chiral centre. Lattice dominated by hydrogen bonded sheets in *ac* plane.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O3-H3	0.840	1.897	169.72	2.728	O4 [x, y, z+1]
O4-H4A	0.840	1.924	167.70	2.750	O2 [x-1, y, z]
O4-H4A	0.840	2.621	134.98	3.269	O1 [x-1, y, z]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	8345(3)	8800(1)	9406(2)	31(1)
O(2)	9941(3)	7395(1)	8907(3)	37(1)
O(3)	3756(3)	8476(2)	12861(2)	41(1)
O(4)	3461(3)	8491(1)	7400(2)	39(1)
C(1)	6453(4)	9224(2)	10561(4)	32(1)
C(2)	8566(4)	7873(2)	9808(3)	31(1)
C(3)	6985(4)	7555(2)	11478(4)	33(1)
C(4)	6210(4)	8485(2)	12435(3)	31(1)
C(5)	8376(5)	6859(2)	13253(4)	45(1)
C(6)	4074(4)	9335(2)	8710(4)	35(1)
C(7)	7494(5)	10172(2)	11493(4)	40(1)
C(8)	5845(5)	10676(2)	12916(5)	47(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(2)	1.335(3)	O(1)-C(1)	1.474(2)
O(2)-C(2)	1.210(3)	O(3)-C(4)	1.407(2)
O(4)-C(6)	1.427(3)	C(1)-C(7)	1.517(3)
C(1)-C(6)	1.525(3)	C(1)-C(4)	1.550(3)
C(2)-C(3)	1.506(3)	C(3)-C(5)	1.526(3)
C(3)-C(4)	1.527(3)	C(7)-C(8)	1.527(3)
C(2)-O(1)-C(1)	111.29(17)	O(1)-C(1)-C(7)	106.57(17)
O(1)-C(1)-C(6)	106.11(16)	C(7)-C(1)-C(6)	111.7(2)
O(1)-C(1)-C(4)	103.15(18)	C(7)-C(1)-C(4)	114.57(19)
C(6)-C(1)-C(4)	113.71(19)	O(2)-C(2)-O(1)	120.8(2)
O(2)-C(2)-C(3)	127.5(2)	O(1)-C(2)-C(3)	111.6(2)
C(2)-C(3)-C(5)	112.2(2)	C(2)-C(3)-C(4)	102.95(18)
C(5)-C(3)-C(4)	115.90(18)	O(3)-C(4)-C(3)	113.69(19)
O(3)-C(4)-C(1)	110.93(18)	C(3)-C(4)-C(1)	104.21(16)
O(4)-C(6)-C(1)	112.0(2)	C(1)-C(7)-C(8)	113.45(19)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	28(1)	40(1)	28(1)	0(1)	12(1)	-5(1)
O(2)	38(1)	44(1)	31(1)	-7(1)	11(1)	-3(1)
O(3)	34(1)	71(1)	19(1)	-2(1)	9(1)	-13(1)
O(4)	33(1)	65(1)	20(1)	-2(1)	9(1)	-9(1)
C(1)	31(1)	43(1)	24(1)	0(1)	12(1)	-1(1)
C(2)	28(1)	41(2)	22(1)	-4(1)	3(1)	-8(1)
C(3)	33(1)	42(2)	22(1)	-2(1)	5(1)	-12(1)
C(4)	31(1)	44(1)	19(1)	-2(1)	5(1)	-7(1)
C(5)	59(2)	43(2)	31(1)	5(1)	5(1)	-5(1)
C(6)	34(1)	47(2)	26(1)	5(1)	13(1)	-3(1)
C(7)	38(1)	44(2)	42(1)	-3(1)	14(1)	-8(1)
C(8)	57(2)	49(2)	39(1)	-6(1)	17(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(3)	3822	8436	14286	60(8)
H(4A)	2238	8224	7801	41(7)
H(3A)	5445	7238	10591	39
H(4)	7423	8644	13891	38
H(5A)	9903	7157	14124	67
H(5B)	8828	6297	12464	67
H(5C)	7289	6676	14311	67
H(6A)	2658	9506	9449	41
H(6B)	4312	9856	7662	41
H(7A)	7681	10581	10186	48
H(7B)	9185	10075	12464	48
H(8A)	5700	10286	14248	71
H(8B)	4172	10782	11963	71
H(8C)	6606	11285	13450	71

Appendix 2

Publications