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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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[Signature] [Date]
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.
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Abbreviations

A<sup>1,2</sup> 1,2-Allylic Strain
A<sup>1,3</sup> 1,3-Allylic Strain
Ac Acetyl
acac Acetylacetonate
app. Apparent
9-BBN 9-Borabicyclo[3.3.1]nonane
BINAP 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn Benzyl
Boc/BOC <i>tert</i>-Butyloxycarbonyl
br. Broad
Bu Butyl
<sup>1</sup>Bu <i>normal</i>-Butyl
<sup>2</sup>Bu <i>sec</i>-Butyl
<sup>3</sup>Bu <i>tert</i>-butyl
BVMO Baeyer Villiger Mono Oxygenase
CAN Ceric ammonium nitrate
Cp. Pentamethylcyclopentadienyl
δ Chemical Shift
d Doublet
DCE Dichloroethane
DCM Dichloromethane
d<sub>e</sub> diastereomeric excess
DIPEA <i>N</i>,<i>N</i>-Diisopropylethylamine
DMAP 4-Dimethylaminopyridine
DMD Dimethyl dioxirane
DME 1,2-Dimethoxy-ethane
DMF <i>N</i>,<i>N</i>′-Dimethylformamide
DMSO Dimethylsulfoxide
ds Diastereoselectivity
<sub>e</sub>e enantiomeric excess
<i>E</i> Entegen (opposite, trans)
EI Electron Impact
Et Ethyl
ether Diethyl ether
g Grams
h Heptet
Hz Hertz
IR Infra red
<i>J</i> Coupling Constant
L Ligand
Lindlar's Pd on CaCO₃/PbO
M Molar
m Multiplet
M+ Molecular Ion
Me Methyl
Mg Milligrams
MOM Methoxymethyl
MTO Metyltrioxo rhenium (MeReO₃)
MPEG550 Polyethylene-Methoxy-glycol
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-(N)-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluromethanesulfonic acid / Triflate</td>
</tr>
<tr>
<td>p</td>
<td>Pentet</td>
</tr>
<tr>
<td>Petrol</td>
<td>Petroleum Ether (fraction at 40-60 °C)</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>(p)-Methoxybenzyl</td>
</tr>
<tr>
<td>PMHS</td>
<td>Polymethylhydrogensiloxane</td>
</tr>
<tr>
<td>PPL</td>
<td>Lipase</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>‘Pr</td>
<td>(iso)-Propyl</td>
</tr>
<tr>
<td>psi</td>
<td>Pounds per square inch</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>RAMP</td>
<td>(R)-1-amino-2-(methoxymethyl) pyrrolidine</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring closing metathesis</td>
</tr>
<tr>
<td>Rf</td>
<td>Retention factor</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-1-amino-2-(methoxymethyl) pyrrolidine</td>
</tr>
<tr>
<td>sept.</td>
<td>Septet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-(n)-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>(tert)-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethyl silyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetra-(N)-propylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>(p)-Toluene sulfonic acid / Tosyl</td>
</tr>
<tr>
<td>UHP</td>
<td>Urea hydrogen peroxide</td>
</tr>
<tr>
<td>WSC</td>
<td>(N)-(3-Dimethylaminopropyl)-(N)(^{\prime})-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>(X_{\chi})</td>
<td>Chiral Auxiliary</td>
</tr>
<tr>
<td>(X_{\psi})</td>
<td>((S))-4-benzyl-5,5-dimethyl-2-oxazolidinone</td>
</tr>
<tr>
<td>Z</td>
<td>Zusamen (together, (cis))</td>
</tr>
</tbody>
</table>
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

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. 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). 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 H₂ 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 BBr₃, and addition of NaOMe in methanol to yield the desired 1-deoxymannojirimycin 6 in an overall 35% yield.
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.
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. 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). Treatment of ketone under optimised reaction conditions of copper(II) triflate, bisoxazoline ligand and Hantzsch ester (which is the hydrogen source) resulted in an almost clean conversion to the alcohol 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.
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 1.2: Selective reduction of β-keto-ester 7.
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. 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). 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.\textsuperscript{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.

![Chemical structures](image)

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,\textsuperscript{9} with well over 1000 reports of these methodologies having been reported to date.
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. 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.

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. 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 $\alpha$-chloro-$\beta$-keto-ethyl ester 15.\(^{18}\) Treatment with engineered *Escherichia coli* (Over expressing YOR120w) under acidic conditions furnished the $\alpha$-chloro-$\beta$-hydroxy-ethyl ester 16 in excellent yield and 98% ee.

\[
\text{Scheme 1.6: Whole cell reduction of $\alpha$-chloro-$\beta$-ketoethyl ester 15.}
\]

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.

\[
\text{Scheme 1.7: Asymmetric reduction of 4-phenylbutan-2-one using secondary alcohol dehydrogenase.}
\]

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.\(^{20-22}\)
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. 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 (2R,3R)-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.

Reagents and conditions: (i) H₂O/HOAc, 90 °C to 5 °C; (ii) K₂CO₃ (2 equiv), H₂O/EtOH

Scheme 1.9: Physical resolution of racemic diamine 17.
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](image)

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.

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

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%), Cul (1 mol%), 24 (0.5 equiv), Cy₂NMe (0.5 equiv) CH₂Cl₂, 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

![Diagram of dynamic kinetic resolution](image)

**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.

![Scheme 1.13](image)

**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.\textsuperscript{33-35}

![Scheme 1.14: Representative selection of widely used kinetic resolution strategies](image)

### 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.
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). 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.

**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).

![Lactone nomenclature](image)

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 cytotoxic activity as well as being of great use in the perfume and flavouring industries.
γ-Butyrolactones have also been shown to be valuable synthetic precursors for the synthesis of a wide number of natural products.\textsuperscript{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-enzyme 49. Finally, removal of the silyl protecting group using tetra-butylamine fluoride gave the natural product trans-(+)-laurediol 50.\textsuperscript{41}
The diverse range of biological activity and synthetic versatility observed for \( \gamma \)-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 \( \gamma \)-butyrolactone, with most strategies being directed towards the synthesis of a specific class of \( \gamma \)-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 \( \gamma \)-butyrolactone frameworks in enantiopure form.

### 2.3 Oxidative and Reductive Strategies

One of the simplest strategies for accessing \( \gamma \)-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 \( \gamma \)-lactones having been widely investigated.\(^{45-48}\) For example, Malkov and co-workers have reported the palladium catalysed Baeyer-Villiger oxidative desymmetrisation of prochiral cyclobutanone 51 in the presence of a
chiral phosphine ligand 53, using urea-H$_2$O$_2$ complex as a stoichiometric oxidant,\textsuperscript{49} which gave (S)-4-phenylidihydrofuran-2(3H)-one 52 in high ee.

![Diagram of ligand 53](image)

Reagents and conditions: (i) (NH$_2$)$_2$CO-H$_2$O$_2$ (1.3 equiv), (PhCN)$_2$PdCl$_2$ (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 cyclobutane 51.

Another simple strategy to access γ-lactones is via regioselective oxidation of chiral tetrahydrofurans.\textsuperscript{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).\textsuperscript{51}

![Diagram of reaction](image)

Reagents and conditions: (i) RuCl$_3$-nH$_2$O, NaHCO$_3$, NaIO$_4$, CCl$_4$, MeCN, H$_2$O, 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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{55}
Complementary to this approach, are strategies that rely on the stereoselective reduction of a substrate containing a \( \gamma \)-ketone functionality to afford a chiral \( \gamma \)-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.\(^{62}\)

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

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 \([\text{(OEP)}\text{Cr(THF)}_2][\text{Co(CO)}_4] \) that can ring open chiral epoxides with concomitant C1-homologation to afford \( \beta \)-lactones which in the presence of an appropriate internal ester nucleophile can undergo further ring expansion to yield chiral \( \gamma \)-butyrolactone skeletons \(62,63\). Mechanistic studies revealed that the Lewis acid catalysed ring expansion of \( \beta \)-lactone \( 63 \) was occurring, whereby coordination of \([\text{(OEP)}\text{Cr(THF)}_2]^+\) to the carbonyl of \( \beta \)-lactone (\( \text{R} \))-\( 63 \) resulted in intramolecular nucleophilic attack of its ester group at its \( \beta \)-position to afford a
dioxycarbenium ion intermediate 66, that then undergoes a further ring opening reaction at its \(\gamma\)-position to give the stable \(\gamma\)-lactone (S)-64.

![Chemical diagram]

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.

![Chemical diagram]

**Figure 2.3:** Proposed mechanism of carbonylation of epoxide 62 and ring expansion to access \(\gamma\)-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.\(^6^4\) 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-\(\gamma\)-lactone 68 in good yield (Scheme 2.7).\(^6^5\)
Chiral epoxides can also be used as substrates in ‘formal’ carbonylation reactions to directly afford chiral γ-butyrolactones.\cite{66,67} Therefore, Jacobsen and co-workers have shown that treatment of terminal epoxide (S)-2-(phenoxy)methyl)oxirane 69 with a Lewis acid and ynamine 73 results in clean conversion to γ-butyrolactone 72 with complete retention of configuration.\cite{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.
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)-ally alanine 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

![Scheme 2.9: Stereoselective iodolactonisation.](image)

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.

![Scheme 2.10: Selenolactonisation reaction α-hydroxy-β,γ-unsaturated carboxylic acid 77.](image)
Further to this, Reiser has utilised cyclopropanes for the synthesis of $\beta,\gamma$-disubstituted-$\gamma$-butyrolactones (Scheme 2.11). 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 allytrimethylsilane 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 retros-aldol reaction that resulted in cleavage of the strained cyclopropane ring to afford an unstable open chain derivative (85) that cyclised to afford $\gamma$-lactone 86 in 64% yield and $>95\%$ de.

Scheme 2.11: Enantioselective synthesis of $\beta,\gamma$-disubstituted $\gamma$-butyrolactone 86.

A number of protocols for the synthesis of $\gamma$-lactones have been developed which rely on the intramolecular addition of a carboxylic acid nucleophile onto an activated alkyne functionality. This type of cyclisation reaction is normally carried out using gold catalysis, 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.\(^8^6\)

![Scheme 2.12: Cycloisomerisation of acetylenic acid 89.](image)

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.\(^8^7\)

![Figure 2.4: Proposed mechanism for the gold catalysed cycloisomerisation of acetylenic acids.](image)

### 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.\(^4^0,8^8,8^9\) For example, the intramolecular Alder-ene reaction has been demonstrated as a strategy to access a range of
alkyldene-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 \([\text{RhCOCl}_2]/\text{BINAP}/\text{AgSbF}_6\) as a catalytic system to enable access to the desired enantiopure alkyldene-γ-lactone \((S)-94\) and enantioenriched \((R)-93\). 40

![Scheme 2.13: Intramolecular Alder-ene reaction for the synthesis of γ-butyrolactone 94.](image)

Reagents and conditions: (i) \([\text{Rh(COD)Cl}]_2\), \((R)-\text{BINAP}, \text{AgSbF}_6, \text{CICH}_2\text{CH}_2\text{Cl}, \text{RT}\).

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 96 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 alkyldene-γ-lactone 94 with regeneration of the rhodium(I) catalyst for further reaction.

![Figure 2.5: Mechanism of the rhodium catalysed intramolecular alderene reaction.](image)

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.\textsuperscript{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).\textsuperscript{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.

![Scheme 2.14: Tandem ring-closing/cross metathesis for the formation of α,β-unsaturated-γ-lactone 100.](image)

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).\textsuperscript{94}

![Figure 2.6: Mechanism of tandem ring-closing/cross metathesis.](image)
There are many examples in the literature where radicals have been used to construct lactone functionalities via intramolecular cyclisation onto unsaturated functionalities. For example, Naito has described free radical-mediated methodology for cyclisation of oxime ether substrates via a conjugate addition-cyclisation strategy (Scheme 2.15).

![Scheme 2.15: Radical mediated cyclisation of oxime ether 104.](image)

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 boran-γ-lactone 109 which on aqueous workup affords the α,β-disubstituted-γ-lactone 105 as the major product.

![Figure 2.7: Radical mediated cyclisation of oxime-ether 104.](image)

Another, interesting reaction for the generation of carbon-carbon bonds involves ring formation via carbene insertion into an unactivated C-H bond. 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

![Scheme 2.16: Intramolecular C-H insertion reaction generating β,γ-disubstituted-γ-butyrolactone 110.](image)

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.](image)

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 syntheses 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.
In recent years there has been an ever-increasing interest in organocatalysis and its applications for organic synthesis,\textsuperscript{9,105} with its use for the asymmetric synthesis of lactone moieties having attracted much interest.\textsuperscript{106} The application of nucleophilic heterocyclic carbenes (NHC) for reaction catalysis has been widely investigated.\textsuperscript{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 \(\gamma\)-butyrolactones (Scheme 2.18).

Initially the carbene is generated by treatment of IMes-HCl with a base (DBU) to generate catalytic species 121 \textit{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 \(\gamma\)-hydroxy-carbonyl 125, with concomitant cyclisation/elimination to afford the desired \(\gamma\)-butyrolactone.\textsuperscript{108}
Clearly, there are a wide range of synthetic strategies available to construct a range of different \( \gamma \)-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 \( \gamma \)-butyrolactone still remains a challenge with most strategies being target driven aiming at a particular class of \( \gamma \)-butyrolactone natural products. Here in we shall discuss our attempts to access highly functionalised \( \alpha,\beta,\gamma \)-substituted-\( \gamma \)-butyrolactones utilising an aldol/epoxidation/lactonisation strategy upon unsaturated-aldol systems.

**Figure 2.9**: Mechanism of NHC catalysed annulation of enals and carbonyl compounds to generate spiro-\( \gamma \)-butyrolactones.

### 2.8 Conclusions

Clearly, there are a wide range of synthetic strategies available to construct a range of different \( \gamma \)-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 \( \gamma \)-butyrolactone still remains a challenge with most strategies being target driven aiming at a particular class of \( \gamma \)-butyrolactone natural products. Here in we shall discuss our attempts to access highly functionalised \( \alpha,\beta,\gamma \)-substituted-\( \gamma \)-butyrolactones utilising an aldol/epoxidation/lactonisation strategy upon unsaturated-aldol systems.

### Chapter 2: Synthesis of \( \gamma \)-lactones
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;\textsuperscript{110} ent-Clavilactone B (131) isolated from the \textit{Clitocybe clavipes} fungus demonstrates antibacterial activity;\textsuperscript{111} and peroxylactone Plakortolide 132 (isolated from a Jamaican sponge) has been shown to inhibit protein kinase enzymes.\textsuperscript{112}

![Figure 3.1: Naturally occurring γ-butyrolactones](image)

Moreover, trisubstituted γ-butyrolactones have proven to be powerful synthetic precursors, and have been used in many natural product syntheses.\textsuperscript{40,113} One such example is in the synthesis of cryptophycin A (Scheme 3.1).\textsuperscript{114} Initially (\textit{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$_2$)$_2$(OMe)$_2$, RT, 2d, 88% yield; (ii)Dibal-H, CH$_2$Cl$_2$, -78 °C, 3h; (iii) 136, MgBr$_2$.Et$_2$O, 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$_2$O$_3$ (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, Weinreb amides, thioesters and oxazolines that allow direct access to chiral aldehyde motifs. Oxidations from chiral primary alcohols are also viable, although often limited by the potential of racemisation of the α-stereocentre. Alternatively, oxidative cleavage of chiral diols and ozonolysis of chiral alkenes or hydrazones have also been widely reported. 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, rearrangement reactions, 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. 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. 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, CH₂Cl₂, 0 °C; (b) α,β-Unsaturated aldehyde, -78 °C to RT; (ii) Et₂Zn, CH₂Cl₂, CH₂Cl₂, -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 diastereocentrol (See Scheme 3.4). Hydrogenation of anti-aldol 146 with
Wilkinson’s catalyst in dichloromethane generated the saturated \((2R,3R,4S)\)-anti-aldol 147 in 96% de. Subsequent treatment of \((2R,3R,4S)\)-anti-aldol 147 with LHMDS at 0 °C, resulted in a clean retro-aldol reaction to afford \((S)\)-\(\alpha\)-methyl-octanal 148 in >95% ee.

![Chemical structures](image)

Reagents and conditions: (i) (a) MgCl₂, Et₃N, Hexylacrolein, TMSOTf, EtOAc; (b) TFA, MeOH; (ii) 17.5 mol% Wilkinson’s catalyst, 5 bar H₂, CH₂Cl₂; (iii) LHMDS, toluene, 0 °C

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

\(\gamma,\delta\)-Unsaturated-\(N\)-acyl-oxazolidin-2-ones have previously been shown to undergo epoxidation reactions. For example, Trova *et al* previously demonstrated that epoxidation of \(\gamma,\delta\)-unsaturated \(N\)-acyl-oxazolidin-2-one 149 with \(m\)CPBA and NaHCO₃ in dichloromethane yielded a 50:50 mixture of the diastereomeric epoxides 150a and 150b (Scheme 3.5).

![Chemical structures](image)

Reactions and conditions: (i) \(m\)CPBA, NaHCO₃, CH₂Cl₂

**Scheme 3.5**: Synthesis of 50:50 diastereotopic mixture of \(\gamma,\delta\)-epoxy \(N\)-acyl-oxazolidin-2-one 150.
With this precedent in mind, it was decided to investigate the hydroxyl-directed epoxidation reactions of \( \beta \)-hydroxy-\( \beta \)-vinyl-\( N \)-acyl-oxazolidin-2-ones, with the aim of developing a ‘temporary stereocentre’ methodology for the synthesis of chiral \( \alpha \),\( \beta \)-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 \textit{retro}-aldol cleavage affording the desired \( \alpha \),\( \beta \)-\textit{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 \textit{et al}, starting from naturally occurring (\( S \))-Phenylalanine (Scheme 3.7).\(^{132,133}\)
(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.

Scheme 3.7: Synthesis of SuperQuat auxiliary 57.

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 hydrogen carbonate 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.

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.
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 °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) tBuLi, acid chloride, CH₂Cl₂, -78 °C to RT, 2 hours.

**Scheme 3.8:** Acylation of N-H SuperQuat auxiliary 157.
Table 3-1: Acylation of SuperQuat auxiliary 157 with various acid chlorides; a isolated yield after recrystallisation from Et₂O:Petroleum ether; b isolated yield after column chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chloride</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHOCl</td>
<td>142a</td>
<td>93% a</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₂</td>
<td>142b</td>
<td>75% a</td>
</tr>
<tr>
<td>3</td>
<td>CH₃C(O)Ph</td>
<td>142c</td>
<td>71% b</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>142d</td>
<td>69% b</td>
</tr>
</tbody>
</table>

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 (S₁ and S₂ vs. A₁ and A₂) and the enantioselectivity (S₁ vs. S₂ or A₁ vs. A₂) of the reaction.¹³⁴
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). The resultant rigid Zimmerman-Traxler transition states allow us to rationalise the stereochemical outcome of the Lewis acid mediated 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. 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.](image)

The SDB group has previously optimised Caddick’s conditions for the synthesis of racemic Evans’ syn-aldol products. 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.
As such, it was decided to apply these conditions to the synthesis of unsaturated syn-aldol products.\textsuperscript{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 $\alpha,\beta$-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.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>de&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td><img src="image" alt="Structure 163a" /></td>
<td>71%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td><img src="image" alt="Structure 163b" /></td>
<td>81%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>3</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td><img src="image" alt="Structure 163c" /></td>
<td>82%</td>
<td>&gt;95%</td>
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<tr>
<td>4</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;Pr</td>
<td><img src="image" alt="Structure 163d" /></td>
<td>79%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td><img src="image" alt="Structure 163e" /></td>
<td>83%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>6</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td><img src="image" alt="Structure 163f" /></td>
<td>93%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>7</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
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</tr>
<tr>
<td>8</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>83%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>9</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td><img src="image" alt="Structure 163i" /></td>
<td>86%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography eluting with CH<sub>2</sub>Cl<sub>2</sub>; <sup>b</sup> de determined from examination of crude 300 MHz<sup>1</sup>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

![Mannich-type reaction diagram]

Reagents and conditions: (i) Formaldehyde (37% solution in water), Me₂NH.

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).
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).

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.
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.

Reagents and conditions: (i) Hexylacrolein (1.2 equiv), MgCl$_2$ (10 mol%), Et$_3$N (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.\(^\text{143}\) 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](image.png)

**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.\(^\text{144}\) *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.
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 diastereocntrol. These include the use of metal catalysed approaches such as VO(acac)$_2$, Ti(OiPr)$_4$ or Mo(CO)$_6$ activation of tert-butylhydroperoxide, MTO/UHP (Methyl trioxo-rhenium/Urea hydrogen peroxide) and non metal peroxides such as mCPBA and DMD (Dimethyl-dioxirane).\textsuperscript{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 \textit{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).\textsuperscript{145,148}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.10.png}
\caption{Possible stereochemical outcomes from epoxidation of allylic alcohols.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.11.png}
\caption{Proposed transition-state structures for the epoxidation of chiral allylic alcohols by various oxidants.}
\end{figure}
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 d¹ complex 172 to the catalytically active d⁶ vanadate ester 173. 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.\textsuperscript{150}

![Scheme 3.15: Mechanism of the VO(acac)$_2$/BuOOH epoxidation of allylic alcohols.](image)

Both Sharpless and Adam have investigated the stereoselectivity of the homogenous vanadium catalysed epoxidation of allylic alcohols.\textsuperscript{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 \textit{et al} have shown that the presence of an $\alpha$-substituent favours an \textit{erythro}-epoxy alcohol, whilst the presence of a \textit{cis}-$\beta$-substituent results in a \textit{threo}-epoxy alcohol being formed as the favoured product (See Table 3.4).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic alcohol</th>
<th>Major epoxy-alcohol product</th>
<th>Erythro/threo selectivity</th>
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</thead>
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<tr>
<td>1</td>
<td><img src="image1" alt="Allylic Alcohol" /></td>
<td><img src="image2" alt="Epoxy Alcohol" /></td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Allylic Alcohol" /></td>
<td><img src="image4" alt="Epoxy Alcohol" /></td>
<td>95:05</td>
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<td><img src="image6" alt="Epoxy Alcohol" /></td>
<td>29:71</td>
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<td>4</td>
<td><img src="image7" alt="Allylic Alcohol" /></td>
<td><img src="image8" alt="Epoxy Alcohol" /></td>
<td>71:29</td>
</tr>
<tr>
<td>5</td>
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<td><img src="image10" alt="Epoxy Alcohol" /></td>
<td>14:86</td>
</tr>
<tr>
<td>6</td>
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<td><img src="image12" alt="Epoxy Alcohol" /></td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Allylic Alcohol" /></td>
<td><img src="image14" alt="Epoxy Alcohol" /></td>
<td>67:33</td>
</tr>
</tbody>
</table>

Reagents and conditions: VO(acac)$_2$, $^1$BuOOH, 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-$\beta$-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 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 $\alpha$-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 $cis$-$\beta$-substituent, with a $threo$-epoxy alcohol $178b$ being formed as the favoured product.

Adam observed that $cis$-$\beta$-functionalities are more sterically dominant than $trans$-$\beta$-substituents. This can be observed by comparison of the epoxidation selectivities of $trans$- and $cis$-3-methylpent-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 diastereoc祝l for epoxidation of simple $trans$-$\beta$-allylic alcohols may also be rationalised by consideration of the transition states shown in Figure 3.3.
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.

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 $\gamma$-butyrolactone 181c, in high de. The gross structure of this $\gamma$-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 ¹H 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 ¹³C 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 C₈H₁₄O₄.

![Scheme 3.17: Synthesis of γ-lactone 181c via epoxidation of β-hydroxy-β-vinyl-N-acyl-oxazolidin-2-one 163c.](image)

The stereochemical determination of five-membered cyclic systems is more complicated than their six-membered counterparts. Normally, ¹H NMR spectroscopy can be used to assign relative stereochemistry to vicinal chiral centres because of the correlation of coupling constants to the dihedral angle. 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). 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.](image)

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 C₅ position. The C₃ hydrogen is shown to strongly interact
with the CH$_2$OH 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 2S,3S 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.

**Figure 3.16:** X-ray crystal structure of (35S,45S,55S)-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.
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.\textsuperscript{153,154} For example, Jenkins \textit{et al} showed that treatment of amide-diene 182 with \textit{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\textsubscript{2}SO\textsubscript{4}) or basic (NaOH) conditions according to the mechanism shown in Figure 3.19.
Applying this mechanistic rationale to our substrate, it is proposed that aldol 163c is stereoselectively epoxidised to generate an unstable (2S,3S,4R)-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 $\beta$-hydroxy-$\beta$-vinyl-$N$-acyl-oxazolidin-2-one 163c.

A similar mechanism has been proposed for the iodolactonisation of $\gamma,\delta$-unsaturated oxazolidin-2-one functionalities which aldol afforded $\gamma$-butyrolactones.\textsuperscript{155} Shibuya \textit{et al} showed that treatment of bis-$\gamma,\delta$-unsaturated oxazolidin-2-one 189 with \textit{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 $\gamma$-stereocentre.

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

Scheme 3.21: Iodolactonisation of bis-$\gamma,\delta$-unsaturated oxazolidin-2-one 189 via a neighbouring group participation mechanism to afford iodo-$\gamma$-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 1H 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](image)

**Scheme 3.23:** Cleavage of \(N\)-H oxazolidin-2-one 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 \(\text{syn-aldol} 198\) was prepared via reaction of the boron enolate of \(N\)-propionyl oxazolidin-2-one 142a with \(\text{iso-valeraldehyde}\) in 81% yield and >95% de. Subsequent treatment of aldol 198 with vanadyl acetylacetonate and \(\text{tert-butyl hydroperoxide}\) 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 \(\text{exo-cyclic cleavage}\) of their oxazolidin-2-one fragments under these epoxidation conditions, however their vanadium alkoxides do appear to have a slight propensity to undergo \(\text{retro-aldol cleavage}\) (\textit{vide supra}).

![Scheme 3.24](image)

**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 \(\text{syn-aldol esters}\), 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 \(\text{syn-aldol esters}\) via an epoxide intermediate has been reported previously in the literature.\(^{157,158}\) For example, Nakata had reported that epoxidation of \(\text{syn-aldol benzyl ester} 200\) 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.


 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 1H NMR spectra. Methyl ester 202 was subsequently treated with vanadyl acetylacetonylactonate 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 1H 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.

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 occurred. 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 on the epoxidation/lactonisation reactions of syn-aldol 163c.](image)

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.
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.

Reagents and conditions: (i) 1BuOOH (1.1 equiv), VO(acac)₂ (10 mol%), benzene, 1 hour; (ii) 0.1 mL H₂O, 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.

<table>
<thead>
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<th>Entry</th>
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<th>Unstable erythro-epoxide intermediate</th>
<th>γ-butyrolactone</th>
<th>Yield(^a) (de(^b))</th>
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</thead>
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<td><img src="181b.png" alt="Image" /></td>
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<td>2</td>
<td><img src="163c.png" alt="Image" /></td>
<td><img src="180.png" alt="Image" /></td>
<td><img src="181c.png" alt="Image" /></td>
<td>78%, (&gt;95%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="163d.png" alt="Image" /></td>
<td><img src="180d.png" alt="Image" /></td>
<td><img src="181d.png" alt="Image" /></td>
<td>78%, (&gt;95%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="163e.png" alt="Image" /></td>
<td><img src="180e.png" alt="Image" /></td>
<td><img src="181e.png" alt="Image" /></td>
<td>74%, (&gt;95%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="163i.png" alt="Image" /></td>
<td><img src="180i.png" alt="Image" /></td>
<td><img src="181i.png" alt="Image" /></td>
<td>83%, (&gt;95%)</td>
</tr>
</tbody>
</table>

Reagents and Conditions: 10 mol% VO(acac)_2, 1 equiv BuOOH, Benzene, 24 hrs, RT; \(^a\) All reported yields are after column chromatography eluting with CH\(_2\)Cl\(_2\)-EtOAc (7:3); \(^b\) Determined from \(^1\)H 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 C₅ stereocentres of the γ-butyrolactones 181b-e,i were assigned according to the proposed neighbouring group participation mechanism with (S)-configuration of the C₆-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 diasterecontrol 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).

![Scheme 3.29: Epoxidation/Lactonisation of anti-aldol 146.](image_url)

The (S)-configuration of the C₅ position was confirmed from examination of its NOESY spectra. A favoured conformation is shown in Figure 3.28, which positions the vicinal C₄OH and C₅-alkyl groups in axial positions on opposite faces of the lactone ring. With this in mind, the C₃ proton gave a strong correlation to the proton on C₄, which in turn gave a strong interaction with the protons on C₆. Further to this, the C₃ proton and the C₅ 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.](image_url)
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 5S stereocentre.

![Scheme](image)

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 C5-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).
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 C₅ 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 C₅ stereocentre, whereas 5-exo cyclisation manifold would proceed with inversion of configuration at C₅ (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 C₃ methyl group interacting with the C₆-dimethyl functionality, and further strong interactions between the C₃ and C₅ 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 5R 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 C₅ position to afford the lactone 181j.

Reagents and conditions: (i) VO(acac)₂, ²BuOOH, Benzene, H₂O

**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-diastereocntrol. 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 (3S,4S,5S)-181fa and (3S,4S,5R)-181fb respectively.
The configuration of the \((3S,4S,5S,6S)\)-\(\gamma\)-butyrolactone \(\text{181fa}\) and \((3S,4S,5R,6R)\)-\(\gamma\)-butyrolactone \(\text{181fb}\) were assigned from comparison of their \(^1\text{H}\) NMR and NOESY spectra. One key difference in the \(^1\text{H}\) NMR spectra was the \(C_3\) proton signal, which in the \text{erythro}-product \(\text{181fa}\) was observed as a quartet of doublets, however in the \text{threo}-product \(\text{181fb}\) 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.

**Scheme 3.33:** Epoxidation/lactonisation reaction of \(\text{trans-aldol 163f}\) via the epoxy alcohol intermediates.

![Chemical structures](image.png)

**Figure 3.22:** Observed interactions from NOESY of both \(\text{erythro-181fa}\) and \(\text{threo-181fb}\).
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.\textsuperscript{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 $\gamma$-lactones on solid supports. Procter \textit{et al} reported the use of a solid supported chiral ephedrine\textsuperscript{211} for use in asymmetric radical reactions of alkenes with aldehydes using samarium iodide as a reductive catalyst.\textsuperscript{161,162} In this case, the chiral ephedrine resin was readily esterified with crotonyl chloride and the resultant unsaturated $O$-acyl resin\textsuperscript{212} was treated with samarium iodide and cyclohexanecarboxaldehyde, resulting in an asymmetric radical reaction with self-cleavage to afford the disubstituted $\gamma$-lactone\textsuperscript{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.
Schore et al reported that iodolactonisation of polymer supported γ,δ-unsaturated chiral pyrrolidine derivative 215.\textsuperscript{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) (R,2S)-ephedrine, DMF, 85 °C; (ii) Crotonyl chloride, NEt\textsubscript{3}, Et\textsubscript{2}O, RT; (iii) Cyclohexanecarboxaldehyde, \textsuperscript{1}BuOH, RT to -15 °C, then Sml\textsubscript{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.\textsuperscript{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\textsubscript{3}N; (ii) LDA, THF, 0 °C; (b) CH\textsubscript{3}I; (iii) I\textsubscript{2}, THF/H\textsubscript{2}O (1.5:1).

**Scheme 3.35:** Solid supported chiral iodolactonisation.
The high levels of diastereoccontrol 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 oxazolidin-2-one.\textsuperscript{165} Initially, L-tyrosine derived oxazolidin-2-one 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.\textsuperscript{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 oxazolidin-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) \(^{6}\)BuLi, propionyl chloride, DCM, -78 °C to RT, 2 hours; (ii) (a) 9-BBN-OTf, DIPEA, \(\text{CH}_3\text{Cl}_2\), 0 °C; (b) iso-propylacrolein 164, -78 °C to RT; (iii) VO(acac)\(_2\), \(^{6}\)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.
Reagents and conditions: (i) $K_2CO_3$ (3.0 equiv), 18-crown-6, DMF, 60°C, 18 hours; (ii) Propionic anhydride, LiCl, Et$_3$N, 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$_2$Cl$_2$ 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 $N$,$N$-disopropylethylamine 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$_2$Cl$_2$ 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$_2$O to afford a clean sample of chiral diol 228 in >95% de whose structure was confirmed by spectroscopic analysis.

Reagents and conditions: (i) (a) 9-BBN-OTf (5.0 equiv), CH$_2$Cl$_2$, 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$_2$Cl$_2$; (ii) NaBH$_4$, THF/H$_2$O.

**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.

Reagents and conditions: (i) VO(acac)$_2$, $^1$BuOOH, Benzene, filtered.

**Scheme 3.40:** Solid phase lactonisation of $\beta$-hydroxy-$\beta$-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 $\gamma$-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 C₅ 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.
Chapter 4: An alternative dihydroxylation protocol for the asymmetric synthesis of chiral β-butylactones

![Chemical structure diagram]

Reagents and conditions: (i) NMO, OsO₄, Acetone-H₂O (8:1), 0 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol</th>
<th>Major Lactone</th>
<th>Yield (%)</th>
<th>dr (%)</th>
</tr>
</thead>
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<td><img src="229a" alt="Lactone structure" /></td>
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<td>78:22</td>
</tr>
<tr>
<td>2</td>
<td><img src="228b" alt="Aldol structure" /></td>
<td><img src="229b" alt="Lactone structure" /></td>
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<td>95:05</td>
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<tr>
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<tr>
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<td><img src="229e" alt="Lactone structure" /></td>
<td>44</td>
<td>75:25</td>
</tr>
</tbody>
</table>

* 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 (5S) derivative. The reported (5S)-configuration of 232 was identical to that described for the OTBS protective aldol derivatives 228a-e, which were also described to afford monoprotected (5S)-O-silyl lactones 229a-e in comparable 43-47% yields.

\[
\text{Reagents and conditions: (i) NMO, OsO}_4, \text{Acetone-H}_2\text{O (8:1), 0 }^\circ\text{C}
\]

**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 C4/C5 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, (5S)-229b and (5R)-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 C5 carbon centre.

Although, the stereochemical outcomes of the dihydroxylation reactions reported were inferred from 1H 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.\(^\text{168}\)

(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.
Given the aldol chemistry used to prepare the aldol precursors used as substrates for dihydroxylation, it is unlikely that Dias’ reaction proceeded from a \textit{cis}-alkenyl system. However, it was possible that an \textit{anti}-dihydroxylation product could potentially have been accessed \textit{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\textsubscript{4} of the osmate ester by intramolecular nucleophilic attack of the \textit{exo}-cyclic carbonyl of the \textit{N}-acyl fragment could potentially occur with resultant inversion of the C\textsubscript{4} stereocentre. The resultant imminium intermediate 236 would then be hydrolysed on workup to yield the parent \textit{N-H} oxazolidin-2-one 225 and the \(\gamma\)-lactone with an \textit{(anti)}-diol-configuration.
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 C₄ stereocentres. This was surprising because it would be expected that their stereogenic C₄ 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 C₅.
(e) Finally, there were concerns over the spectroscopic data reported for O-TMS-lactone \(229a\) \((Entry\ I)\). 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 \((5S)\)-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.

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

Treatment of unsaturated aldol \(163c\) with osmium tetroxide (10 mol%) and \(N\)-methylmorpholine-\(N\)-oxide under Dias’ conditions gave a new \(\gamma\)-lactone, whose spectroscopic...
data was clearly different to that of the lactone (3S,4S,5S)-181c produced in our previous epoxidation reaction. Therefore it follows that its newly formed C₅ stereochemistry must in fact have an (R)-configuration opposite to the (5S)-configuration observed in our epoxidation/lactonisation reactions.

![Chemical structures](image)

Reagents and conditions: (i) VO(acac)₂ (10 mol%), ¹⁸BuOOH, Benzene, H₂O₂; (ii) OsO₄ (10 mol%), NMO, Acetone-H₂O (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 (3S,4S,5R)-lactone 240c in a comparative 78 % yield and >95% de to that obtained previously using SuperQuat derived β-vinyl-syn-aldol 163c.
The dihydroxylation of simple 1,1-disubstituted-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). 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 hydroxybutyrolactone (3S,4S,5R)-(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.
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 (5R), which is opposite to the (5S)-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 1H 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 (5R) lactone product.
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.\textsuperscript{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 that is subsequently hydrolysed to generate a cis-vicinal diol (248) and reduced osmium oxide (Figure 4.7).\textsuperscript{171} The catalyst is subsequently regenerated in the presence of a stoichiometric amount of an oxidant such as N-methylmorpholine-N-oxide (UpJohn), H\textsubscript{2}O\textsubscript{2}, or trimethylamine-N-oxide (Poli).\textsuperscript{168,172}
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). In 1977, Sharpless challenged this concerted mechanism in favour of a step-wise process. 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).

The debate over the mechanism of the addition pathway was subsequently solved by computational studies and detailed experimental investigation. 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).\(^{180}\)

![Scheme 4.5: Dihydroxylation of 1,1-disubstituted system 255](image)

Reagents and conditions: (i) OsO\(_4\) cat., NMO, Acetone-H\(_2\)O (20:1), RT, 3 days, (91 \% yield).

Similarly, Donohoe described that dihydroxylation of \(O-H\) allylic alcohol 257 occurs with good \((anti)\)-selectivity to afford triol 258 in 80\% de.\(^{181}\)
There are several examples in the literature of the dihydroxylation of acrolein derived allylic systems.\textsuperscript{169,181} Blechert has demonstrated the osmium catalysed dihydroxylation reaction of the free allylic alcohol \textsuperscript{259} was shown to proceed in 70\% de in favour of the \textit{anti}-addition product, with the silyl protected species \textsuperscript{261} also proceeding with (\textit{anti})-selectivity in a reduced 50\% de.\textsuperscript{182}

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

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). 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.
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.\textsuperscript{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.\textsuperscript{187} Houk used \textit{ab initio} calculations to show that TS3 which positions the hydroxyl functionality in an \textit{inside} conformation (Figure 4.11), was lower in energy than the alternative TS4, thus predicting \textit{anti}-stereoselectivity in the dihydroxylation reaction.\textsuperscript{188,189}

![Figure 4.10: Kishi’s model to rationalise the stereoselectivity for osmium catalysed dihydroxylation of allylic systems.](image)

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.\textsuperscript{170}

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![Figure 4.11: Houk model proposed for the protected and O-H allylic alcohol systems.](image)
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 \textit{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.](image)

\textbf{4.4.2} \textit{syn}-Dihydroxylation

Both Evans and Donohoe have shown that both the Vedejs and Houk models are consistent with the observed stereochemical trends for \textit{anti}-dihydroxylation of O-H 1,1-disubstituted and \textit{trans}-1,2-allylic systems.\(^{169,170}\)

However, Donohoe has shown that this is not the case for allylic alcohol systems containing \textit{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 favour of its \textit{syn}-triol 267.\(^{169}\)
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. 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 4.13). 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.

\[ \text{Scheme 4.9: Dihydroxylation 1,2,2-trisubstituted allylic alcohol 266.} \]

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-trisubstituted allylic alcohols is limited, Chakraborty reported that dihydroxylation of allylic alcohol 268 proceeds with syn-selectivity to yield triol 269.\(^{102}\)
However, Evans has shown that treatment of the trisubstituted allylic alcohol methyl ester 270 proceeds with anti-selectivity in >95% de.170

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 diastereocntrol. 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 C₃ of lactone 229a (Scheme 4.14).

![Scheme 4.14: Proposed dihydroxylation/lactonisation of 1,1-disubstituted alkenyl systems](image)

Reagents and conditions: (i) OsO₄ (10 mol%), NMO, Acetone-H₂O (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’ (5S)-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).

![Scheme 4.12: Dihydroxylation/lactonisation of methacrolein derived aldol 163b](image)

Reagents and conditions: (i) OsO₄ cat., NMO, Acetone-H₂O (8:1), RT.

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

Comparison of the ^1H NMR spectra of the previously prepared (5S)-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 (5R)-
configuration. As such the lactone generated in the dihydroxylation procedure was assigned as (3S,4S,5R)-240b, which was confirmed by examination of its NOE spectra. This showed a strong interaction between the methyl substituent of C₅ interacting with the C₃ proton, with the C₅ CH₂OH methylene resonance interacting strongly with the C₃ methyl functionality and the C₄ hydrogen. This confirms the syn relationship of these functionalities, thus providing further evidence of its (5R) 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 C₅, which is opposite to the (anti)-stereoselectivity reported in the literature for dihydroxylation of this class of substrate.

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/H₂O, and left to stir for forty-eight hours. ¹H 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.
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 (3S,4S,5R)-$240a1$, 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$_2$OH methylene protons. In turn, the minor diastereomer was assigned as (3S,4S,5S)-$240a2$ which was confirmed by the presence of a large interaction between its C$_3$ proton and its C$_5$ CH$_2$OH methylene protons.

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.
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!

![Chemical structure of 228a and 229b]

Reagents and conditions: (i) OsO₄ (10 mol%), NMO, Acetone-H₂O (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.

![Chemical structure of 163g, 157, 240g₁, and 240g₂]

Reagents and conditions: (i) OsO₄ (10 mol%), NMO, Acetone-H₂O (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 C₅-proton interacts strongly with the C₃-proton, whilst the C₄ proton interacts strongly with both the C₃ methyl group and the C₅ HC(OH)Ph, thus indicating a syn relationship between these substituents. The stereochemistry of the major diastereomeric lactone was therefore inferred as (3S,4S,5S)-240g₁, which is
consistent with the osmylation reaction proceeding with \textit{anti}-selectivity to the hydroxyl functionality, as previously established from literature precedent.\textsuperscript{169,183}

![Diagram](image)

\textbf{Figure 4.17}: Major lactone product \textbf{240g1}, with observed NOE interactions.

In relation to this, a \textit{trans}-crotonaldehyde derived aldol \textbf{163f} was also treated under catalytic UpJohn dihydroxylation conditions. The resulting lactone products were inseparable from one another, however analysis of the \textsuperscript{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 \textit{anti}-dihydroxylation had occurred to afford (3S,4S,5S)-lactone \textbf{240f1} as the major diastereomer.

![Diagram](image)

Reagents and conditions: (i) OsO\textsubscript{4} (10 mol\%), NMO, Acetone-H\textsubscript{2}O (8:1), 67 \% de.

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

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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.

\[
\text{Reagents and conditions: (i) OsO}_4 \, (10 \text{ mol\%}), \text{NMO, Acetone-H}_2\text{O (8:1).}
\]

**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-\(\gamma\)-butyrolactone 240i in >95 % de.

\[
\text{Reagents and conditions: (i) OsO}_4 \, (10 \text{ mol\%}), \text{NMO, Acetone-H}_2\text{O (8:1), 88% yield, } >95 \% \text{ de.}
\]

**Scheme 4.18: - Dihydroxylation/lactonisation of trisubstituted alkene 163i yielding \(\gamma\)-butyrolactone 240i.**

The observed high diastereoselectivity is consistent with that previously discussed for (\textit{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\(_5\) CH-OH substituent, thus confirming the (5\(R\)) stereochemistry. Therefore, given the \textit{syn}-dihydroxylation mechanisms we are able to infer that the configuration of the newly formed C\(_6\) stereocentre is also (\(R\)).
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.  

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 C3 methyl group and the C5 hydrogen indicating the syn relationship of these functionalities, which implies a (5R) configuration. Minor diastereomer 240h2 was also isolated; with analysis of its NOE spectra indicating a large interaction between its C3 hydrogen and C5 hydrogen indicating a syn relationship, which is consistent with its expected (5S) 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 $^3J_{4,5} = 4.0$Hz 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.

![Diagram](image)

**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 $\alpha$-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 $\alpha$-substituent might have on the dihydroxylation reaction. As such a range of methacrolein derived aldol products 163b and 163k-n containing different $\alpha$-substituents were synthesised in $>70$ % yield and $>95$ % de using our standard boron aldol protocol (See Table 4.2).
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 164a were shown to consistently generate the predicted anti-dihydroxylation products in reasonable diastereocntrol 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.](image)

### 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. In the case of oxidatively damaged DNA, reactions involving reactive oxygen species are an unavoidable consequence of respiration.
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.](image)

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-ribose 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.

![Scheme 4.20: Synthesis of 1,2-dideoxy-1-β-aryl-D-ribose derivatives 275 from deoxyribonolactone derivative 273.](image)

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, CH2Cl2, -78 °C to RT, then acrolein -78 °C to RT, 24 hr, 57 % yield, > 95 % de; (ii) Zn (s), NH4Cl, MeOH, 90 % yield; (iii) OsO4, NMO, Acetone/H2O (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.

![Diagram of lactones 272a and 272b](image)

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

This mixture of diastereomeric $\gamma$-lactones is currently being subjected to preparative HPLC chromatography to obtain a pure sample of 2-deoxyribonolactone.

### 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.\textsuperscript{169,170} We have shown that Dias’ literature precedent for osmylation/lactonisation of related $\beta$-vinyl-*syn*-aldol systems was flawed; however, in their defence it should be noted that assignment of stereochemistry for $\gamma$-lactone systems is notoriously problematic.\textsuperscript{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. 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), (-)-baconipyrene 277 (antimicrobial and cytotoxicity) and (+)-superstolide A 278 (cytotoxic against several cancer cell lines) all represent potentially important medicinal agents for the treatment of disease.

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, 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. 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, BF₃OEt₂, CH₂Cl₂; (ii) Bu₃BOTf, DIPEA, CH₂Cl₂, -78 °C followed by Bu₂SnH, Et₃B, -78 °C; (iii) BrONC(NH)Cl₂, TFOH, CH₂Cl₂; (iv) LiAlH₄, THF; (v) Oxalyl chloride, DMSO, CH₂Cl₂, -78 °C; (vi) 287, TiCl₄(O'Pr), CH₂Cl₂, -78 °C; (vii) Bu₃BOTf, DIPEA, CH₂Cl₂, -78 °C followed by Bu₂SnH, Et₃B, -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. 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 trifluoroacetate 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).
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 C₃ stereocentre.

Reagents and conditions: (i) Hg(OCOCF₃)₂, CH₂Cl₂ then NaCl; (ii) ^Bu₃SnH, cat. AIBN, THF, RT then 60 °C

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

![Scheme 5.2](image)

Reagents and conditions: (i) BH₃·THF, THF, -30 °C to RT then NaOH, H₂O₂, 64%, 1:1 dr, separated by column chromatography; (ii) (a) cat. TPAP, NMO, CH₂Cl₂, MeCN, 0 °C to RT; (b) EtMgBr, THF, -30 °C, 77:23 dr separated by column chromatography; (iii) Ac₂O, cat. DMAP, Et₂O, 92%; (iv) (a) Hg(OCOCF₃)₂, CH₂Cl₂ then NaCl; (b) ^Bu₃SnH, cat. AIBN, THF, RT then 60 °C, 65%; (v) LiAlH₄, 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, \( \text{N-acyl-oxazolidin-2-one 142a} \) was treated under standard boron mediated aldol conditions to generate a \( \text{syn-aldol product in high de} \). Treatment of \( \text{syn-aldol 143} \) with diethyl zinc and diiodomethane in dichloromethane at \(-10^\circ \text{C}\) resulted in a highly diastereoselective cyclopropanation reaction to yield cyclopropyl aldol \( \text{144 in 99% yield and > 95% de} \). Subsequent treatment of cyclopropyl-syn-aldol \( \text{144} \) with LHMDS at \( 0^\circ \text{C} \) resulted in a clean \textit{retro-aldol} reaction to yield the chiral cyclopropane carboxaldehyde \( \text{145} \).

Reagents and conditions: (i) (a) 9-BBN-OTf, DIPEA, \( \text{CH}_2\text{Cl}_2 \), \( 0^\circ \text{C} \); (b) \( \alpha,\beta\)-Unsaturated aldehyde, -78 \(^\circ\) \text{C} \) to RT; (ii) \( \text{Et}_2\text{Zn, CH}_2\text{Cl}_2, \text{CH}_2\text{Cl}_2, -10 \) to \( 0^\circ \text{C} \); (iii) LHMDS, toluene, \( 0^\circ \text{C} \).

\textbf{Scheme 5.3:} Temporary stereocentre approach for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

Since this methodology had established that a wide range of \( \beta\)-vinyl-syn-aldols \( \text{143} \) 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 \( \text{294} \) 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.
Cyclopropanes have been widely reported in the literature as compounds that can readily undergo ring opening reactions of use in organic synthesis.\textsuperscript{206} The cyclopropane moiety is found in numerous natural products,\textsuperscript{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.\textsuperscript{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.\textsuperscript{210,211} Since these initial studies, several modifications have been made to this cyclopropanation protocol,\textsuperscript{212-214} with application of these conditions to allylic systems having been widely investigated.\textsuperscript{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.\textsuperscript{216-218}
Reagents and conditions: (i) Et₂Zn (5.0equiv), CH₂I₂ (5.0 equiv), CH₂Cl₂, -10 to 0 °C, 2hours

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<tr>
<td>6</td>
<td>OH</td>
<td>96</td>
<td>&gt;200:1</td>
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**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 diastereoocontrol.\(^{219}\) 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 “ZnCH₂I” 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).\(^{223}\)
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).\textsuperscript{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 $\Delta^{1,2}$ strain can be considered to be negligible. As a consequence, minimisation of $\Delta^{1,3}$ 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 $\Delta^{1,3}$ 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 $\Delta^{1,3}$ strain present in TS2 upon approach at the anti-face.\textsuperscript{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.
Reagents and conditions: (i) Et₂Zn (5.0equiv), CH₂Cl₂ (5.0 equiv), CH₂Cl₂, -10 to 0 °C, 2hours

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<th>de (%)</th>
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<td><img src="163i.png" alt="Image" /></td>
<td><img src="295i.png" alt="Image" /></td>
<td>96</td>
<td>0</td>
</tr>
</tbody>
</table>

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;\textsuperscript{141,226} b Isolated yields after column chromatography; c Diastereoisomeric excess determined from analysis of their crude \textsuperscript{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 diastereoccontrol 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 aldel
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$_2$Zn (5.0equiv), CH$_2$I$_2$ (5.0 equiv), CH$_2$Cl$_2$, -10 to 0 °C, 2hours

<table>
<thead>
<tr>
<th>Entry</th>
<th>syn-Aldol</th>
<th>Cyclopropane</th>
<th>Yield (%)$^{a}$</th>
<th>de (%)$^{b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="" /> 163o</td>
<td><img src="image2" alt="" /> 295o</td>
<td>92</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="" /> 163p</td>
<td><img src="image4" alt="" /> 295p</td>
<td>93</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="" /> 163q</td>
<td><img src="image6" alt="" /> 295q</td>
<td>90</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

$^{a}$ 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 diastereoccontrol. 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. 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.

![Diagram of the reaction](image)

Reagents and conditions: (i) Zn, NH₄Cl, MeOH; (ii) Et₂Zn (5.0 equiv), CH₂Cl₂ (5.0 equiv), CH₂Cl₂, -10 to 0 °C, 2 hours; (iii) NaOMe, CH₂Cl₂, 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 diastereosecontrol. 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 \(\psi_1\) (Figure 5.4).\(^{227}\) This can be used to rationalise the concept of \(\sigma\)-aromaticity, which arises from occupation of the \(\psi_1\) 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](image)

The presence of \(\sigma\)-aromaticity within its ring system accounts for the reactivity of cyclopropanes toward electrophiles and the upshift in the cyclopropane protons in their \(^1\)H NMR spectra.\(^{206,209}\) Cyclopropanes employ their \(\sigma\)-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 \(\gamma\)-lactone products.\(^{205}\) Collum and co-workers previously reported that treatment of cyclopropane methyl ester \(\text{299}\) with mercury(II) trifluoroacetate generates both a \(\gamma\)-lactone \(\text{300}\) and \(\delta\)-lactone \(\text{301}\). 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.\textsuperscript{229,230}

\[
\begin{align*}
\text{299} & \quad \xrightarrow{\text{(i), (ii), (iii)}} \quad \text{300} + \quad \text{301}
\end{align*}
\]

Reagents and conditions: (i) Hg(OOCF\(_3\))\(_2\), (ii) KBr (aq), (iii) \text{^6}Bu\(_3\)SnH

**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 \textit{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 \(^1\)H NMR spectrum of the crude reaction product indicated that cleavage had occurred to afford the parent \textit{N}-H oxazolidin-2-one 157 and a new product which was tentatively assigned as \(\alpha,\beta\)-unsaturated-\(\delta\)-lactone 302. This was proposed from the indicative resonance of its vinyl proton at \(\delta 6.34\) ppm, an infra-red carbonyl absorption at 1684 cm\(^{-1}\), and a molecular ion with a multiple isotope pattern for C\(_8\)H\(_{11}\)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.
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 iminium intermediate 302, whose β-hydroxyl group can potentially coordinate to the mercury atom to trigger an elimination reaction that generates the alkene functionality of iminium species 306. Subsequent hydrolysis of iminium species 306 then generates the N-H oxazolidin-2-one 157 and α,β-unsaturated-δ-lactone 302.

Reagents and conditions: (i) Hg(OCOCF₃)₂, CH₂Cl₂, RT, the NaCl (aq)

Scheme 5.8: Observed oxymercuration reaction.

---

**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. 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.

![Erythronolide I](image1.png)

**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 CH₂Cl₂ 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.
Reagents and conditions: (i) NaOMe (1.1 equiv), CH₂Cl₂ (c. 0.5 M), 5 mins.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropane Aldol</th>
<th>Methyl ester</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="295" /></td>
<td><img src="image" alt="309" /></td>
<td>80</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="295" /></td>
<td><img src="image" alt="309" /></td>
<td>89</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="295" /></td>
<td><img src="image" alt="309" /></td>
<td>71</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="295" /></td>
<td><img src="image" alt="309" /></td>
<td>81</td>
<td>&gt;95</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="163" /></td>
<td><img src="image" alt="309" /></td>
<td>75</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

* Isolated yields reported after column chromatography; † de determined from crude ¹H 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 ¹H NMR spectra of the methanolation 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), CH₂Cl₂ (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.
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.
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 \(\alpha\)- 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 \(C_{8}H_{13}O_{3}ClHg\).

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 (2S,3S)- 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 \(^1J_{4,5} = 10.1\) Hz also indicating a \(trans\) relationship.
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-alcohol. 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 trifluoroacetate 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).  

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.

![Diagram](image)

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. 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 322.

![Diagram](image)

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 diastereoccontrol. 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 $\delta$-stereocentre to generate (3S,4S,5R,6R)-313g and (3S,4S,5R,6S)-313q.

Reagents and conditions: (i) Hg(OCCF$_3$)$_2$, CH$_2$Cl$_2$, RT, then NaCl (aq)

**Scheme 5.11:** Generation of tetrasubstituted-$\delta$-mercuriolactones 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 (3S,4S,5R,6R)-lactone 313j and $\alpha$,\$-unsaturated-$\delta$-lactone (5R,6R)-323 had been formed in a 3:1 ratio. Chromatographic purification of this mixture allowed access to both the purified tetrasubstituted lactone (3S,4S,5R,6R)-313j in 55 % yield.
and >95% de and the α,β-unsaturated derivative (5R,6R)-323 in 30 % yield and >95 % de, whose structures were assigned via $^1$H NMR and NOE spectroscopic analysis as described previously.

![Chemical Structure](image1)

Reagents and conditions: (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, RT, then NaCl (aq)

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

![Chemical Structure](image2)

**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-$\delta$-lactone substrate 324 with no tetrasubstituted-$\delta$-lactone having been formed after 24 hours. The stereochemistry of this α,β-unsaturated lactone was inferred as (5R) from consideration of the mechanism previously determined for these lactonisation reactions.

![Chemical Structure](image3)

Reagents and conditions: (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, 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\(_2\)-substituent which is less stable and more prone to elimination (Figure 4.14).

\[
\begin{align*}
\text{trans-alkene} & \quad \text{cis-alkene} \\
\begin{array}{c}
\text{MeO} \quad \text{OH} \quad R \quad \text{H} \quad \text{R} \\
\text{O} \quad \text{H} \quad \text{R} \quad \text{Me} \quad \text{R} \quad \text{OH} \quad \text{HgCl} \\
\text{R} \quad \text{Me} \quad \text{H} \quad \text{R} \quad \text{OH} \quad \text{Me} \quad \text{R} \quad \text{HgCl}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{All functionality arranged equatorially, Favoured configuration} & \quad \text{Three groups arranged equatorially and one axially, Disfavoured configuration, more strained than trans-equivalent} \\
\text{All functionality arranged axially, Disfavoured conformation} & \quad \text{Three groups arranged axially, Disfavoured conformation}
\end{align*}
\]

\[\text{Figure 5.14: Conformers of lactones derived from both cis and trans allylic systems.}\]

### 5.5 Demercuration

With a range of mercuro-\(\delta\)-lactones accessed, it was now necessary to develop a demercuration strategy to access the desired highly functionalised chiral-\(\delta\)-lactones. Initially it was decided to investigate the tin mediated radical demercuration methodology developed by Cossy and co-workers.\(^{205}\) As such, mercuro-\(\delta\)-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 \(325\).
Although crude $^1$H 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 $\delta$-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 revealed that mercuro lactones of this type could be readily demercurated utilising sodium borohydride. Therefore, mercuro-$\delta$-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 °C. 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.

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 $^1$H NMR spectra indicated; a dq at 2.43 ppm, which was indicative of a CH $\alpha$- to the lactone.
carbonyl, a dq at 4.06 ppm assigned to the C₆ proton which is adjacent to an electron withdrawing lactone oxygen. The ¹³C 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 C₈H₁₄O₃.

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 C₃ hydrogen atom strongly interacts with the C₅ hydrogen (Figure 5.5) indicating a syn relationship between these substituents. Further to this, the C₄ hydrogen atom strongly interacts with the C₆ hydrogen atom indicating that these functionalities are on the same face of the six-membered ring. Given the known (2S,3S)-configuration of the syn-aldol 163f that was initially cyclopropanated, these NOE’s indicated the generated δ-lactone as (3S,4R,5R,6S)-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](image)

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 (3S,4R,5R,6S)-327.
However, attempts to demercurate the $\alpha,\beta$-unsaturated-$\delta$-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 $\beta$-vinyl-syn-aldols can be used as efficient precursors to access both tetrasubstituted $\delta$-lactones and $\alpha,\beta$-unsaturated-$\delta$-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-$\delta$-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 \( \delta \)-lactones

Scheme 5.18: General five-step strategy to access \( \alpha,\beta \)-unsaturated-\( \delta \)-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 Bruker Avance 300 spectrometer or at 500 MHz on a Bruker 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; dqq, 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. $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded at 75 MHz on a Bruker 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 Bruker 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 $F^2$ 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 Na₂PO₄/NaH₂PO₄ (pH7 buffer solution, 10 cm³) and was stirred for 10 minutes, followed by the addition of hydrogen peroxide/methanol solution (1:2 mixture, 10 cm³) 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-diisopropylethylenamine (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 Na₂PO₄/NaH₂PO₄ (pH7 buffer solution, 10 cm³), methanol (10 mL) and was stirred for 30 minutes. After which hydrogen peroxide (20 cm³) 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 hydrogen carbonate 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 hydrogen carbonate 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 hydrogen carbonate 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 MgSO₄ 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. 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 \text{ (c = 1.0 in MeOH); } ^1H \text{ NMR (300 MHz, MeOD) } \delta 7.43 - 7.20 \text{ (5H, m, Ph), 4.32 (1H, dd, CHN, } J = 8.1 \text{ and } 5.0 \text{ Hz), 3.78 (3H, s, } CH_2O), 3.20 \text{ (1H, dd, } CH_3H_2Ph, J = 14.0 \text{ and } 5.0 \text{ Hz), 3.25 (1H, dd, } CH_3H_2Ph, J = 14.0 \text{ and } 5.0 \text{ Hz); } ^13C \text{ (75 MHz, MeOD) } \delta 170.9, 135.7, 130.9, 130.6, 129.4, 55.6, 54.0, 37.8; \text{ IR (ATR) } \nu \text{ (cm}^{-1})= 1740.7 \text{ (C=O); HRMS (ES+) : } m/z \text{ calculated for } C_{10}H_{13}NO_2 \text{ requires 180.1024 for [M+H]^+}, \text{ found 180.1016; requires 202.0843 for [M+Na]^+}, \text{ 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. Boc₂O (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 cm³). The mixture was filtered through a pad of Celite® with diethyl ether as eluent (3 x 20 cm³). 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. The crude product was carried on to the next step without further purification.

\([\alpha]_D^{23} = -42 \text{ (c = 1.0 in CHCl}_3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.31-7.10 \text{ (5H, m, Ph,)}\), 4.97 (1H, broad d, \(J = 6.0 \text{ Hz, NH})\), 4.61 (1H, dd, \(J = 14.0 \text{ Hz and 6.0 Hz NCH}_2\)), 3.73 (3H, s, OCH\(_3\)), 3.10 (2H, m, CH\(_2\)Ph), 1.40 (9H, s, Boc); \(^{13}\)C (75 MHz, CDCl\(_3\)) \(\delta 172.5, 156.0, 137.3, 129.3, 128.6, 127.4, 80.2, 54.2, 52.3, 38.2, 28.5\); IR (ATR) \(\nu \text{ (cm}^{-1}\): 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

![Structure of (S)-tert-butyl 3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate](image)

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 Grignard 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 cm³). 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; \([\alpha]_D^{24} = -45.1 \text{ (c = 1.0 in CHCl}_3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.10 – 7.29 \text{ (5H, m, Ph,)}\), 4.52 (1H, d, NH, \(J = 8.9 \text{ Hz})\), 3.60 (1H, m, CHN), 3.02 (1H, dd, CH\(_A\)H\(_B\)Ph, \(J =

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13.5 and 3.5 Hz), 2.53 (1H, m, CH₄H₃Ph), 1.23 (6H, s, (CH₃)₂), 1.20 (9H, s, t-Bu); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₅NO₃ 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 cm³) under nitrogen and stirred for two hours at room temperature. The reaction mixture was quenched with saturated ammonium chloride (10 cm³), extracted with diethyl ether (3 x 20 cm³) washed with saturated sodium hydrogen carbonate solution (10 cm³), brine (10 cm³) 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, [α]D²⁵ = -103.0 (c = 1.0 in CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.08 (5H, m Ph), 5.09 (1H, broad s, NH), 3.63 (1H, dd, J = 10.5 Hz and 4.0 Hz, CH=N), 2.77 (1H, dd, J = 13.5 Hz and 4.0 Hz, CH₄H₃Ph), 2.62 (1H, dd, J = 13.5 Hz and 10.0 Hz, CH₄H₃Ph), 1.39 (3H, s, (CH₃)C(CH₃)), 1.38 (3H, s, (CH₃)C(CH₃)); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₅NO₂ requires 206.1184 for [M+H]⁺, found 206.1168; requires 228.1000 for [M+Na]⁺, found 228.0985.
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; [α]D24 = -21.0 (c = 1.0 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.20-7.35 (5H, m, Ph), 3.65 (1H, dd, J = 10.5 Hz and 3.4 Hz, CHAHOH), 3.40 (1H, dd, J = 10.5 Hz and 7.4 Hz, CHAHOH), 3.10 (1H, m, CHN), 2.80 (1H, dd, J = 13.5 Hz and 5.5 Hz, CHAHP), 2.55 (1H, dd, J = 13.5 Hz and 8.7 Hz, CHAHP), 1.68 (3H, br. s, OHA, NH2); 13C NMR (75 MHz, CDCl3) 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; [α]D 24 = 5.5 (c = 0.66 in EtOH); 1H NMR (300 MHz, CDCl3) δ 7.27-7.38 (3H, m, Ph), 7.20 (2H, app. d, J = 7.0 Hz, Ph), 5.05 (1H, br. s, NH), 4.50 (1H, app. t, J = 8.5 Hz CHA,HB,OH), 4.20 (1H, m, CHA,HB,OH), 4.10 (1H, m, CHN), 2.90 (1H, m, CH2Ph); 13C NMR (75 MHz, CDCl3) 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 C10H11NO2: 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%).

[α]D 24 = -46.0 (c = 1.0 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.33-7.21 (5H, m, Ph), 4.50 (1H, dd, J = 9.5, 4.0 Hz, NCH), 3.15 (1H, dd, J = 14.5, 4.0 Hz, CHA,HBPh), 2.96-2.84 (3H, m, CHA,HBPh, CH2CH3), 1.37 (3H, s, CCH3), 1.36 (3H, s, CCH3), 1.14 (3H, t, J = 7.5 Hz, CH3CH2); 13C NMR (75 MHz, CDCl3) δ 174.3, 137.0, 129.1, 128.6, 128.6, 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 C15H20N requires [M+H]+ requires 262.1438; found 261.1442;
6.2.8 (S)-4-benzyl-3-(2-chloroacyl)-5,5-dimethyl-oxazolidin-2-one, 142d

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-oxazolidin-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-chloroacyl)-5,5-dimethyl-oxazolidin-2-one, 142d as a pale yellow solid (2.87 g, 10.21 mmol, 69%).

Rf (CH2Cl2) = 0.74; [α]D25 = +40 (c = 1.0 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.34-7.19 (5H, m, Ph), 4.56 (1H, d, J = 12.5 Hz, CHAHAbr), 4.49 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 4.42 (1H, dd, J = 12.5 Hz, CHAHAbr), 3.18, (1H, dd, J = 14.5 Hz and 4.0 Hz, PHAHAbr), 2.89 (1H, dd, J = 14.5 Hz and 10.0 Hz, PhCHAHAbr), 1.38 (3H, s, (CH3)C(CH3)), 1.37 (3H, s, (CH3)C(CH3)); 13C NMR (75 MHz, CDCl3) 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 C14H16ClNO3 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-dimethyl-oxazolidin-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%).

Rf (CH2Cl2) = 0.45; [α]D25 = -17.0 (c = 0.73 in CHCl3); 1H NMR (300 MHz, CDCl3) 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, COCH2), 3.18
(1H, dd, \( J = 14.5 \) Hz and 10.0 Hz, \( CH_AH_BPh \)), 2.85 (1H, dd, \( J = 14.5 \) Hz and 4.0 Hz, \( CH_AH_BPh \)), 1.37 (3H, s, \( (CH_3)C(CH_3) \)), 1.32 (3H, s, \( (CH_3)C(CH_3) \)); \(^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 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) \( \nu \) (cm\(^{-1}\)): 1766.4 (C=O); 1712.7 (C=O\text{ox}); HRMS (ES\(^{+}\)): \( m/z \) calculated for C\(_{28}\)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 \((S)-4\text{-benzyl-3-propionyloxazolidin-2-one, 241}\)

The title compound was prepared according to General Procedure 1 \((S)-4\text{-benzyl-oxazolidin-2-one, 225}\) (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 \((S)-4\text{-benzyl-3-propionyloxazolidin-2-one, 241}\) 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\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 7.25-7.19 (5H, m, Ph), 4.65 (1H, m, NCH), 4.10 (2H, m, CH\(_2\)O), 3.25 (1H, dd, \( J = 13.5 \) Hz, \( CH_AH_BPh \)), 2.88 (2H, m, CH\(_2\)CH\(_3\)), 2.72 (1H, dd, \( J = 13.5 \) Hz, \( CH_AH_BPh \)), 1.14 (3H, t, \( J = 7.3 \) Hz, \( CH_2CH_3 \)); \(^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 174.6, 154.1, 135.6, 129.7, 129.3, 127.9, 66.5, 55.4, 38.3, 29.1, 8.8; IR (ATR) \( \nu \) (cm\(^{-1}\)): 1782.0 (C=O), 1699.3 (C=O\text{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-[(2S,3R)-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-((2S,3R)-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; 1H 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, CH=CH_2), 5.25 (1H, dt, J = 1.5 Hz, CH=CH_2H_{trans}=C), 5.13 (1H, dt, J = 10.5 Hz and 1.5 Hz, CH=CH_2H_{cis}=C), 4.49 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 4.38 (1H, m, CHO), 3.85 (1H, dq, J = 7.0 Hz and 4.0 Hz, CHCH_3), 3.0 (1H, dd, J = 14.5 Hz and 4.5 Hz, CH=CH_2Ph), 2.85 (1H, dd, J =14.5 Hz and 9.0 Hz, CH=CH_2Ph), 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); 13C 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) v (cm⁻¹): 3501.1 (broad OH), 1754.2 (C=O), 1702.2 (C=O), HRMS: 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.
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-((2S,3S)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one, 163c (1.187 g, 3.44 mmol, 80 %) as a colourless oil.

\[ \text{[\alpha]}_{D}^{21} = -36 \] (c = 1.0 in CHCl₃); \(^1\)H NMR (300 MHz, CDCl₃) δ 7.34-7.20 (5H, m, Ph), 5.16 (1H, app. t, J = 1.0 Hz, CH₃Htrans=C), 4.98 (1H, app. t, J = 1.0 Hz, CH₃Htrans=C), 4.53 (1H, dd, J = 9.0 Hz and 4.0 Hz, CHN), 4.40 (1H, d, J = 3.5 Hz, ChoH), 3.96 (1H, dd, J =14.0 Hz and 4.0 Hz, CH₂H₉Ph), 2.91 (1H, dd, J =14.0 Hz and 9.5 Hz, CH₂H₉Ph), 2.91 (1H, br. s, OH), 2.02 (2H, m, CH₂CH₃) 1.40 (3H, s, (CH₃)C(CH₃)), 1.38 (3H, s, (CH₃)C(CH₃)), 1.11 (3H, d, J = 7.0 Hz, CH₃CH), 1.07 (3H, t, J = 7.0, CH₃CH₂); \(^13\)C NMR (75 MHz, CDCl₃) 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\textsubscript{ox}), 1700 (C=O); HRMS (ES+): m/z calculated for C\textsubscript{20}H\textsubscript{27}NO\textsubscript{4}: requires 346.2013 for [M+H]\textsuperscript{+}; found: 346.2014.
6.2.13 (S)-4-benzyl-3-((2S,3S)-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-((2S,3S)-3-hydroxy-2,4-dimethylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 163b (1.084 g, 3.27 mmol, 81%) as a colourless oil.

$[\alpha]_D^{20} = -34 \ (c = 1.0 \text{ in CHCl}_3)$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.19 (5H, m, Ph), 5.12 (1H, app. t, $J = 1.1$ Hz, CH$_{cis}$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, CH$_{cis}$), 4.43 (1H, m, CHO$_{cis}$), 3.95 (1H, m, CH$_{cis}$), 3.08 (1H, dd, $J = 14.5$ Hz and 4.5 Hz, CH$_{cis}$), 2.91 (1H, dd, $J = 14.5$ Hz and 9.0 Hz, CH$_{cis}$), 2.84 (1H, broad s, OH), 2.40 (3H, s, CH$_3$), 1.42 (3H, s, (CH$_3$)$_2$C(CH$_3$)), 1.39 (3H, s, (CH$_3$)$_2$C(CH$_3$)), 1.29 (3H, d, $J = 7.0$ Hz, CH$_3$), $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 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), 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}\mathrm{H}\ NMR\ (300\ \text{MHz,}\ \text{CDCl}_3)\ \delta\ 9.50\ (1\text{H},\ \text{s, CHO}),\ 6.18\ (1\text{H},\ \text{s, C=CH}_2\text{H}_3),\ 5.93\ (1\text{H},\ \text{s, C=CH}_2\text{H}_3),\ 2.20\ (1\text{H},\ J = 7.5\ \text{Hz, CH}_2\text{C}=\text{CH}_2),\ 1.17-1.27\ (8\text{H},\ \text{br. m, (CH}_2\text{)}_3),\ 0.87\ (3\text{H, CH}_2\text{CH}_2);\ ^{13}\mathrm{C}\ NMR\ (75\ \text{MHz,}\ \text{CDCl}_3)\ \delta\ 196.0,\ 150.7,\ 134.2,\ 30.5,\ 20.3,\ 27.4,\ 26.7,\ 23.1,\ 14.7;\ \text{IR\ (thin\ film/ cm}^{-1}\text{)}\ 1725.4\ (\text{C}=\text{O}).\n
6.2.15\ \text{(S)-4-benzyl-3-((2S,3S)-3-hydroxy-2-methyl-4-methylene decanoyl)-5,5-dimethyl oxazolidin-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-((2S,3S)-3-hydroxy-2-methyl-4-methylene decanoyl)-5,5-dimethyl oxazolidin-2-one, 163e (1.174 g, 2.92 mmol, 75 %) as a colourless oil.

\([\alpha]_D^{25} = -27.8\ (c = 1.15\ \text{in CHCl}_3);\ ^{1}\mathrm{H}\ NMR\ (300\ \text{MHz,}\ \text{CDCl}_3)\ \delta\ 7.33-7.19\ (5\text{H, m, Ph}),\ 5.15\ (1\text{H, app. s, CH}_\text{cis}H_\text{trans}=\text{C}),\ 4.96\ (1\text{H, m, CH}_\text{cis}H_\text{trans}=\text{C}),\ 4.53\ (1\text{H, dd, J = 9.0\ Hz and 4.5 Hz, CHN}),\ 4.38\ (1\text{H, d, J = 3.4 Hz, CHO}),\ 3.95\ (1\text{H, q, J = 7.2 Hz and 3.4 Hz, CHCO}),\ 3.08\ (1\text{H, dd, J = 14.5 Hz and 4.5 Hz, CH}_2\text{H}_3\text{Ph}),\ 2.90\ (1\text{H, dd, J = 14.5 Hz and 9.0 Hz, CH}_2\text{H}_3\text{Ph}),\ 2.76\ (1\text{H, br. s, OH}),\ 1.98\ (2\text{H, m, CH}_2\text{C}=\text{C})\ 1.45\ (2\text{H, m, CH}_2\text{CH}_3)\ 1.39\ (3\text{H, s, (CH}_3C(CH}_3)),\ 1.37\ (3\text{H, s, (CH}_3C(CH}_3)),\ 1.28\ (6\text{H, m, (CH}_2\text{)}_3),\ 1.11\ (3\text{H, d, J = 7.2 Hz, CH}_2\text{CH})\ 0.87\ (3\text{H, t, J = 7.0, CH}_2\text{CH}_2);\ ^{13}\mathrm{C}\ NMR\ (75\ \text{MHz,}\ \text{CDCl}_3)\ \delta\ 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;\ \text{IR\ (thin\ film/ cm}^{-1}\text{)}\ 3499\ (\text{broad O-H}),\ 1780\ (\text{C}=\text{O}_{\text{oxy}}),\ 1700\ (\text{C}=\text{O});\ \text{HRMS\ (ES): m/z\ calculated\ for\ C}_{24}H_{35}NO_4:\ \text{requires\ 402.2639\ for\ [M+H]^+};\ \text{found:}\ 402.2637.
6.2.16 \((S)-4\text{-}\text{benzyl}-3\text{-}((2R,3S)-3\text{-}\text{hydroxy}-2\text{-}\text{methyl}-4\text{-}\text{methylene}d\text{ecanoyl})\text{-}5,5\text{-}\text{dimethyl}\text{oxazolidin}2\text{-}\text{one}, 146\)

According to General Procedure 4, to a stirring mixture of \((S)-4\text{-}\text{benzyl}-5,5\text{-}\text{dimethyl}3\text{-}\text{propionyloxazolidin}2\text{-}\text{one} (100 mg, 0.38 mmol) in dry ethyl acetate (2 mL) was added magnesium chloride (7.3 mg, 0.076 mmol), sodium hexafluoroantimonate (29.5 mg, 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 \((S)-4\text{-}\text{benzyl}-3\text{-}((2R,3S)-3\text{-}\text{hydroxy}-2\text{-}\text{methyl}-4\text{-}\text{methylene}d\text{ecanoyl})\text{-}5,5\text{-}\text{dimethyl}\text{oxazolidin}2\text{-}\text{one}, 146\) (101.9 mg, 0.253 mmol, 67\% as a colourless oil.

\([\alpha]_D^{24} = -42.1 \ (c = 1.2 \ \text{in CHCl}_3); \ \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3) \ \delta 7.15\text{-}7.31 \ (5H, Ph), 5.03 \ (1H, \text{app. s, } CH_cisH_{trans}=C), 4.91 \ (1H, m, CH_{cis}H_{trans}=C), 4.47 \ (1H, dd, J = 9.8 \text{ and } 3.4 \text{ Hz, CHN}), 4.14 \ (2H, m, CHOCH and CHCO), 3.15 \ (1H, dd, J = 14.7 \text{ and } 3.4 \text{ Hz CH}_A\text{H}_B\text{Ph}), 2.83 \ (1H, dd, J = 14.7 \text{ and } 9.8 \text{ Hz, CH}_A\text{H}_B\text{Ph}), 2.77 \ (1H, br. s, OH), 2.10 \ (1H, m, CH_A\text{H}_B\text{Ph}), 2.0 \ (1H, m, CH_A\text{H}_B\text{Ph}), 1.46 \ (2H, m, CH_2\text{CH}_2), 1.33 \ (3H, s, (CH_3)C(CH_3)), 1.31 \ (3H, s, (CH_3)C(CH_3)), 1.28 \ (6H, m, (CH_2)_{11}), 1.13 \ (3H, d, J = 6.4 \text{ Hz, CH}_3\text{CH}), 0.87 \ (3H, t, J = 6.7 \text{ Hz, CH}_3\text{CH}_2); \ \text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3) \ \delta 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; \ \text{IR (ATR)} \ \nu \ (\text{cm}^{-1}): 3499 \ (\text{broad O-H}), 1780 \ (\text{C=O}), 1700 \ (\text{C=O}); \ \text{HRMS (ES): } m/z \ \text{calculated for } C_{25}H_{35}NO_4: \ \text{requires } 402.2639 \ \text{for } [\text{M+H}]^+; \ \text{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.

¹H NMR (300 MHz, CDCl₃) δ 9.49 (1H, s, CHO), 6.18 (1H, s, C=CH₃H₂), 5.90 (1H, s, C=CH₃H₂), 2.69 (1H, d, sept, J = 7.0 Hz and 1.1 Hz, CH(C₃H₇)₂), 1.17-1.27 (6H, d, J = 7.0 Hz, CH(C₂H₅), 1.18 (3H, CH(C₂H₅)); ¹³C NMR (75 MHz, CDCl₃) 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-((2S,3S)-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-((2S,3S)-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 Et₂O and petroleum ether.

mp = 97-99 °C; [α]D²⁷ = +38.9 (c = 0.88 in CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.07 (5H, m, Ph), 5.13 (1H, t, J = 1.1 Hz, CH₃H₄trans=C), 4.98 (1H, t, J = 1.1 Hz, CH₃H₄trans=C), 4.65 (1H, CHN), 4.43 (1H, br. d, J = 2.1 Hz, CHO), 4.22 - 4.07 (2H, m, CH₂O), 3.89 (1H, dq, J = 7.2 and 3.2 Hz, CHCO), 3.20 (1H, dd, J = 13.45 and 3.25 Hz, CH₃H₄Ph), 2.82 (1H, br. s, OH),
2.73 (1H, dd, $J = 13.6$ and 9.5 Hz, CH$_3$H$_2$Ph), 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-([2S,3S,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-([2S,3S,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=CH$_2$), 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.
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-((2S,3S)-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 <br> [\(\alpha\)]D = -7.5 (c = 0.75 in CHCl3); \(^1^H\) NMR (300 MHz, CDCl₃) \(\delta\) 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); \(^1^3^C\) NMR (75MHz, CDCl₃) \(\delta\) 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\(_{\text{ox}}\)), 1698 (C=O); HRMS (ES): m/z calculated for C\(_{23}\)H\(_{31}\)NO\(_4\) requires 386.2326 for [M+H]\(^+\), found 386.2330.

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 \((S)-4\text{-benzyl-3-}\{2S,3R,Z\}-3\text{-hydroxy-2-methyldec-4-enoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 163j}\) (220 mg, 0.56 mmol) as a yellow oil in 95% yield.

\([\alpha]_D^{21} = -28\) \((c = 0.75, \text{CH}_2\text{Cl}_2)\); \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.72-7.12 (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, OH), 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); \(^{13}\text{C}\) NMR (75MHz, CDCl\(_3\)) \(\delta\) 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.

\(6.2.22\) \((S)-4\text{-benzyl-3-}\{2S,3R\}-3\text{-hydroxy-2,5-dimethylhex-4-enoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 163h}\)

9-Borabicyclo[3.3.1]nonyl trifluoromethanesulphonate (8.05 mL, 4.023 mmol) was added to a solution of \((S)-4\text{-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, 142a}\) (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 \((S)-4\text{-benzyl-3-}\{2S,3R\}-3\text{-hydroxy-2,5-dimethylhex-4-enoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 163h}\) (1.278 g, 3.70 mmol, 92%) as a white solid.

\([\alpha]_D^{21} = -27\) \((c = 1.0 \text{ in CHCl}_3)\); \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\text{C}\) NMR (75MHz, CDCl\(_3\)) \(\delta\) 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 C₂₀H₂₇NO₄ requires 346.2013 for [M+H]⁺; found 346.2011.

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

[α]D²¹ = -14 (c = 0.84 in CHCl₃) ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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=Oₓ), 1696 (C=O); HRMS (ES): m/z calculated for C₁₉H₂₂NO₄: requires 332.1856 for [M+H]⁺; found: 332.1855.

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-[(2S,3R,E)-3-hydroxy-2-methylhex-4-enoyl]-5,5-dimethyloxazolidin-2-one, 163f (701.2 mg, 2.11 mmol, 91%) as a clear oil.
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-((2S,3R)-3-hydroxy-2,4-dimethylpentanoyl)-5,5-dimethyloxazolidin-2-one, 198 (1033.5 mg, 3.10 mmol, 81%) as a clear oil.

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 (3S,4S,5S)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-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.

\[ \text{Rf (7:3 DCM/EtOAc) = 0.32; } [\alpha]_D^{25} = -44.4 \text{ (c = 0.14 in CHCl}_3) \text{; mp = 76-77 °C; } \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 3.91 (1H, d, } J = 12.3 \text{ Hz, CHOH), 3.88 (1H, d, } J = 8.4 \text{ Hz, CH}_3\text{CH}_2\text{OH), 3.79 (1H, d, } J = 12.3 \text{ Hz, CH}_3\text{H}_2\text{OH), 2.79 (1H, dq, } J = 8.7 \text{ and 7.2 Hz, CH}_3\text{CH}_2\text{CH}_3, 1.76-1.53 (2H, m, CH}_3\text{CH}_2\text{OH), CHCH}_3, 1.26 (3H, d, } J = 7.2, \text{ CHCH}_3, 0.90 (3H, t, } J = 7.6, \text{ CH}_2\text{CH}_3); \]

\[ ^13\text{C NMR (75 MHz, CDCl}_3) \delta 177.5, 88.0, 80.9, 65.3, 44.9, 28.8, 14.4, 7.7; \]

IR (ATR) \( \nu \text{ (cm}^{-1}) \): 3286.5 (O-H), 1740.4 (C=O).

HRMS (ES): \( m/z \) calculated for C\(_8\)H\(_{14}\)O\(_4\) requires 192.1230 for [M+NH\(_4\)]\(^+\), found 192.1233.

6.2.26 (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3H)-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, 1.157 mmol) according to General Procedure 5 to afford the crude product as a green oil. Purification via column chromatography afforded (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3H)-one, 181b (128.1 mg, 0.800 mmol, 76%) as a white solid.

Lit for (\textit{ent})-181b \([\alpha]_D^{25} = +26.8 \text{ (c = 0.91 in CHCl}_3)\] \( ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 3.78 (1H, d, } J = 10.5 \text{ Hz, CHOH), 3.77 (1H, d, } J = 12.1 \text{ Hz, CH}_3\text{CH}_2\text{OH), 3.62 (1H, d, } J = 12.1 \text{ Hz, CH}_3\text{CH}_2\text{OH), 2.83 (1H, dq, } J = 9.3, \text{ and 7.1 Hz, CHCO), 1.29 (3H, s, CH}_3, 1.22 (3H, d, } J = 7.3 \text{ Hz, CHCH}_3); \]

\[ ^13\text{C NMR (75 MHz, CDCl}_3) \delta 178.4, 86.2, 82.1, 65.5, 44.0, 22.4, 14.1; \]

IR (ATR) \( \nu \text{ (cm}^{-1}) \): 3340.8 (O-H), 1735.5 (C=O); HRMS (ES): \( m/z \) calculated for C\(_7\)H\(_{12}\)O\(_4\) requires 178.1074 for [M+NH\(_4\)]\(^+\), found 178.1074.
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 \((3S,4S,5S)-5\text{-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-one}\), 181e (48.8 mg, 0.212 mmol, 83%) as a clear oil.

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

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 \((3S,4S,5S)-4\text{-hydroxy-5-(hydroxymethyl)-5-isopropyl-3-methyl-dihydrofuran-2(3H)-one}\), 181d (93.7 mg, 0.498 mmol, 74%) as a pale oil.
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 (3R,4S,5S)-5-hexyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-one, 205 (58.3 mg, 0.253 mmol, 74%) as a clear oil.

Rf (7:3 DCM/EtOAc) = 0.53; [α]D25 = +4.65 (c = 0.43 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 4.23 (1H, d, J = 7.0 Hz, CHO), 3.91 (1H, d, J = 12.0 Hz, CH3CHOH), 3.85 (1H, d, J = 12.0 Hz, CH3CHOH), 2.86 (1H, m, CHCH3), 1.65-1.47 (2H, m, CH2CH2), 1.36-1.11 (8H, m, C4H8), 0.81 (3H, t, J = 6.5 Hz, CH3CH3); 13C NMR (75 MHz, CDCl3) 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 C12H22O4 requires 253.1416 for [M+Na]+, found 253.1394.
6.2.30 (3S,4S,5S)-4-hydroxy-5-((S)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3H)-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 (3S,4S,5S)-4-hydroxy-5-((S)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3H)-one, 181i (174.1 mg, 0.925 mmol, 74%) as a pale oil.

Lit for (ent)-181i [α]D25 = +25.4 (c = 0.66 in EtOH).

Rf (7:3 DCM/EtOAc) = 0.53; [α]D25 = +10.0 (c = 0.54 in CHCl₃); ¹H NMR (300 MHz, MeOD) δ 3.82 (1H, d, J = 9.0 Hz, CHO), 3.62 (1H, dd, J = 10.2 and 2.6 Hz, CH₂CHOH), 2.74 (1H, dq, J = 9.0 and 7.5 Hz, CH₂CH₃), 1.64-1.38 (2H, m, CH₂CH₃), 1.30 (3H, s, CH₃), 1.15 (3H, d, J = 7.2 Hz, CHCH₃), 0.91 (3H, t, J = 7.5 Hz, CH₂CH₃); ¹³C 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) v (cm⁻¹): 3394.8 (O-H), 1747.5 (C=O); HRMS (ES): m/z calculated for C₉H₁₆O₄ requires 211.0941 for [M+Na]⁺, found 211.0940.

6.2.31 (3S,4S,5R)-4-hydroxy-5-((S)-1-hydroxyhexyl)-3-methyl-dihydrofuran-2(3H)-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 (3S,4S,5R)-4-hydroxy-5-((S)-1-hydroxyhexyl)-3-methyl-dihydrofuran-2(3H)-one, 181j (232.7 mg, 1.076 mmol, 84%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.41; [α]D25 = +32.8 (c = 0.34 in CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.07 (1H, br. t, J = 8.8 Hz, CHO), 3.98 (1H, dd, J = 7.9 and 3.2 Hz, OCH), 3.69 (1H, br. s,
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 (3S,4S,5S)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one, 181h (66.37 mg, 0.381 mmol, 78%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.24; [α]D25 = +23.5 (c = 0.17 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 4.11 (1H, ddd, J = 8.7, 6.8 and 4.6 Hz, CHOH), 3.88 (1H, d, J = 7.6 Hz, OCH), 2.61 (1H, dq, J = 8.4 and 6.5 Hz, CHCH3), 2.32 (1H, br. d, J = 4.88 Hz, CHO), 1.72 (1H, br. s, OH), 1.29-1.20 (9H, m, CHCH3, C(CH3)2); 13C NMR (75 MHz, CDCl3) 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 C8H14O4 requires 197.0789 for [M+Na]+, found 197.0774.

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 (3S,4S,5S)-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 \((3S,4S,5R)-4\text{-hydroxy-5-((R)-1\text{-hydroxyethyl})-3\text{-methylidihydrofuran-2(3H)}\text{-one, 181fb}}, (21.2 \text{ mg, 0.132 mmol, 22\%}).\)

### 6.2.33.1 \((3S,4S,5S)-4\text{-hydroxy-5-((S)-1\text{-hydroxyethyl})-3\text{-methylidihydrofuran-2(3H)}\text{-one, 181fa}}\)

\[
\text{Rf (7:3 DCM/EtOAc)} = 0.17; [\alpha]_D^{25} = -35.5 (c = 0.23 \text{ in CHCl}_3); \text{^1}H \text{ NMR (300 MHz, CDCl}_3) \delta 4.10 (1H, app. t., \text{J} = 8.4 \text{ Hz, CHOH}), 3.98 (1H, app. pent., \text{J} = 6.2 \text{ Hz, CHOCH}_3), 3.87 (1H, dd, \text{J} = 7.2 \text{ and 5.7 Hz, OCH}), 2.61 (1H, dq, \text{J} = 8.4 \text{ and 6.5 Hz, CHCH}_3), 2.55 (1H, br. s, OH), 1.98 (1H, br. s, OH), 1.29 (3H, d, \text{J} = 6.2 \text{ Hz, CHOCH}_3), 1.27 (3H, d, \text{J} = 7.1 \text{ Hz, CHCH}_3); \text{^13}C \text{ NMR (75 MHz, CDCl}_3) \delta 176.6, 88.6, 76.1, 68.6, 43.9, 19.9, 12.9; \text{ IR (ATR) } \nu (\text{cm}^{-1}): 3391.2 (\text{O-H}), 1753.4 (\text{C=O}); \text{ HRMS (ESI): m/z calculated for C}_{7}H_{12}O_{4} \text{ requires 183.0633 for [M+Na]}^+, \text{ found } 183.0616.\]

### 6.2.33.2 \((3S,4S,5R)-4\text{-hydroxy-5-((R)-1\text{-hydroxyethyl})-3\text{-methylidihydrofuran-2(3H)}\text{-one, 181fb}}\)

\[
\begin{align*}
\text{Rf (7:3 DCM/EtOAc)} & = 0.21; [\alpha]_D^{25} = -36.4 (c = 0.71 \text{ in CHCl}_3); \text{^1}H \text{ NMR (300 MHz, CDCl}_3) \delta 4.31 (1H, dd, \text{J} = 4.4 \text{ and 2.9 Hz, CHOH}), 4.20 (1H, app. pent., \text{J} = 6.3 \text{ Hz, CHOCH}_3), 4.1 (1H, dd, \text{J} = 6.3 \text{ and 4.4 Hz, OCH}), 2.64 (1H, dq, \text{J} = 7.7 \text{ and 3.0 Hz, CHCH}_3), 1.35 (3H, d, \text{J} = 6.2 \text{ Hz, CHOCH}_3), 1.23 (3H, d, \text{J} = 7.7 \text{ Hz, CHCH}_3); \text{^13}C \text{ NMR (75 MHz, CDCl}_3) \delta 179.1, 83.1, 75.6, 67.1, 44.9, 20.1, 13.8; \text{ IR (ATR) } \nu (\text{cm}^{-1}): 3308.6 (\text{O-H}), 1751.8 (\text{C=O}); \text{ HRMS (ESI): m/z calculated for C}_{7}H_{12}O_{4} \text{ requires 183.0633 for [M+Na]}^+, \text{ found } 183.0624.\]

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

\(N\text{-Propionyl-oxazolidin-2-one resin 222} \) (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 \textit{via} cannula and fresh pre-chilled dichloromethane (10 mL) added to resuspend the resin. \(N,N\text{-diisopropylethylamine (0.391 mL, 2.25 mmol)}\) 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 (2R,3S)-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, 0.15 mmol) in water (0.2 mL), that was then agitated on an orbital shaker for 4 hours. Polymer 221 was then filtered off and washed thoroughly with dichloromethane (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 (2R,3S)-2-methyl-4-methylenehexane-1,3-diol 228 (16.1 mg, 0.112 mmol, 62%) as a colourless oil.

[α]D25 -26 (c = 0.8, CHCl3); 1H NMR (300 MHz, CDCl3) δ 5.05 (1H, br. s, CHA=CH=C), 4.92 (1H, br. s, CHA=CH=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); 13C NMR (75 MHz, CDCl3) δ 152.4, 108.5, 76.4, 67.0, 37.7, 25.6, 12.6, 9.9; IR (thin film): 3380 (broad OH); MS (Cl+, NH4+) m/z (%) 162 (100) [M+NH4]+, 144 (23) [M+H]+, 52 (23); HRMS (ES+): m/z calculated for C8H16O2 requires 162.1489 for [M+NH4]+; found 162.1491.

6.2.35 Solid phase epoxidation/lactonisation reaction for formation of lactone (35,45,55)-181c

Vanadyl acetyl acetonate (24 mg, 0.09 mmol) was added to (syn)-aldol-resin 227 (200 mg, 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 CH2Cl2/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 (3S,4S,5S)-γ-butyrolactone **181c** (17 mg, 0.097 mmol) ([α]_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-[(2S,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl]-5,5-dimethyl-oxazolidin-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; [α]_D^{23} = +6.0 (c = 0.89 in CHCl_3); mp = 147 – 149 °C (Et_2O); ^1H 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 =CHPh), 6.12 (1H, dd, J = 16.0 Hz and 6.0 Hz, CH=CHPh), 4.54 (1H, m, CHOH), 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, CHA H B Ph), 2.84 (1H, dd, J = 14.0 and 9.0 Hz, CHA CH B Ph), 2.74 (1H, broad s, OH), 1.32 (3H, s, (C H_3)C(CH_3)), 1.30 (3H, s, (CH_3)C(CH_3)), 1.13 (3H, s, J = 7.0 Hz, CH(CH_3)); ^13C NMR (75 MHz, CDCl_3) δ 177.1, 152.6, 137.7, 134.1, 129.3, 129.2, 129.1, 127.6, 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); HRMS (ES): m/z calculated for C_{24}H_{27}NO_4: requires 416.1838 for [M+Na]^+; found: 416.1821.
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.

\[
\begin{align*}
\text{[}\alpha\text{]}_D^{25} & = -40.0 \quad (c = 1.0, \text{CHCl}_3); \\
R_f (\text{CH}_2\text{Cl}_2) & = 0.22; \\
^{1}H \text{ NMR (300 MHz, CDCl}_3) & \delta 7.40-7.11 \\
& (5\text{H, m, Ph}), 4.96 \quad (1\text{H, app. d, } J = 1.0 \text{ Hz, } \text{CH}_\text{cis}H_\text{trans}=\text{C}), 4.81 \quad (1\text{H, app. t, } J = 1.5 \text{ Hz, } \text{CH}_\text{cis}H_\text{trans}=\text{C}), 4.53 \quad (1\text{H, dd, } J = 9.0 \text{ Hz and 4.5 Hz, CHN}), 4.46 \quad (1\text{H, dd, } J = 10.0 \text{ Hz and 3.5 Hz, } \text{CHOH}), 4.38 \quad (1\text{H, d, } J = 8.5 \text{ Hz, } \text{CHCH}), 3.08 \quad (1\text{H, dd, } J = 14.5 \text{ Hz and 4.5 Hz, } \text{CH}_\text{A}H_\text{B}Ph), 2.78 \quad (1\text{H, dd, } J = 14.5 \text{ Hz and 10.0 Hz, } \text{CH}_2H_\text{B}Ph), 2.23 \quad (1\text{H, m, } CH(CH_3)_2) 1.90 \quad (1\text{H, broad s, OH}), 1.71 \quad (3\text{H, s, } C=\text{CH}_3), 1.23 \quad (6\text{H, app. d, } J = 5.5 \text{ Hz, } (CH_2)C(CH_3)), 0.97 \quad (6\text{H, t, } J = 7.0 \text{ Hz, } CH(CH_3)_2); \\
^{13}C \text{ NMR (75 MHz, CDCl}_3) & \delta 174.1, 153.0, 146.2, 137.3, 129.4, 129.07, 127.2, 113.5, 82.2, 64.1, 51.0, 35.9, 28.6, 28.4, 22.7, 21.2, 19.1, 18.6; IR (thin film / cm$^{-1}$) 3499 (broad O-H), 1768 (C=O$_\alpha$), 1685 (C=O); HRMS (EI+) $m/z$ calculated for C$_2$H$_{29}$NO$_4$: requires 360.2174 for [M+H]$^+$; found: 360.2165; requires 382.1994 for [M+Na]$^+$; found: 382.1984.
\end{align*}
\]
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.

$[\alpha]_D^{25} = -89.9 \ (c = 1.0, \ \text{CHCl}_3)$; $R_f \ (\text{CH}_2\text{Cl}_2) = 0.35$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42-7.20 (5H, m, Ph), 7.14-6.98 (5H, m, Ph), 5.27 (1H, d, $J = 7.0$ Hz, PhCH) 4.92 (1H, m, CH$_\text{cis}$H$_\text{trans}$=C), 4.85 (1H, br. app. pent., $J = 1.5$ Hz, CH$_\text{cis}$H$_\text{trans}$=C), 4.69 (1H, d, $J = 8.0$ Hz, CHO), 4.43 (1H, dd, $J = 9.0$ Hz and 4.0 Hz, CHN), 4.40 (1H, m, CHO), 2.82 (1H, dd $J = 14.0$ Hz and 4.0 Hz, CH$_A$H$_B$Ph), 2.63 (1H, dd, $J = 14.0$ Hz and 9.0 Hz, CH$_A$H$_B$Ph), 2.05 (1H, br. s, OH), 1.74 (3H, s, CH$_2$=CCH$_3$), 1.27 (3H, s, (CH$_3$)$_2$C(CH$_3$)$_2$), 1.24 (3H, s, (CH$_3$)$_2$C(CH$_3$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 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) $\nu$ (cm$^{-1}$): 3489.6 (O-H), 1768.2 (C=O), 1717.5 (C=O$_\alpha$); 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.

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 (CH₂Cl₂) = 0.20; [α]₂⁰ = -12 (c = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.47 – 7.05 (5H, m, Ph), 5.92 (1H, ddd, J = 17.2, 10.5, 5.5 Hz, CHCH₂), 5.73 (1H, d, J = 4.5 Hz, CHCl), 5.46 (1H, dd, J = 10.5, 1.3 Hz, CHCH₃CH₃), 4.81 – 4.57 (2H, m, CH(OH) & CH₂), 3.31 (1H, ddd, J = 13.5, 3.3 Hz, CH₂), 2.84 (1H, dd, J = 13.5, 9.4 Hz, CH₃CH₃)

13C NMR (75.5 MHz, CDCl₃): 167.95, 153.03, 135.35, 131.91, 129.77, 129.40, 127.90, 119.06, 72.88, 66.88, 59.57, 55.77, 37.57; IR (ATR) ʋmax (cm⁻¹): 3497 (broad O-H), 1759 (C=O ox), 1711 (C=O); HRMS (ES+); m/z calculated for C₁₅H₁₆ClNO₄: 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-dimethylazolidin-2-one, 275

(S)-4-benzyl-3-[(2S,3R)-3-hydroxy-2-methylpent-4-enoyl]azolidin-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]azolidin-2-one 275 (65 mg, 0.24 mmol, 56%) as a colourless oil.

Rf (CH₂Cl₂) = 0.18; [α]₂⁰ = -5.0 (c = 0.87, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.44 – 7.02 (5H, m, Ph), 5.96 (1H, ddd, J = 17.2, 10.5, 5.4 Hz, CHCH₂), 5.37 (1H, dt, J = 17.2, 1.4 Hz, CHCH₃CH₃), 5.20 (1H, dt, J = 10.5, 1.4 Hz, CHCH₃CH₃), 4.82 – 4.59 (2H, m, CH(OH) & CH₂), 3.30 (1H, dd, J = 13.4, 3.3 Hz, CH₂CH₃CH₃), 3.21 (2H, dd, J = 11.4, 6.1 Hz, CH₂CH(OH)), 2.81 (1H, dd, J = 13.5, 9.4 Hz, CH₂CH₃CH₃); ¹³C NMR (75.5 MHz, CDCl₃): 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) ʋmax (cm⁻¹): 3497 (broad O-H), 1776 (C=O), 1711 (C=O); HRMS (ESI); m/z calculated for C₁₅H₁₇NO₄: requires 298.1055 for [M+H]⁺; found: 298.1044.
6.3.6  (3S,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-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 (3S,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-one, 240c (119.5 mg, 0.61 mmol, 69%) as a pale oil. Rf (7:3 DCM/EtOAc) = 0.21; [α]D24 = -3.4 (c = 0.88 in CHCl3); 1H NMR (500 MHz, MeOD) δ 4.24 (1H, d, J = 9.4 Hz, CHO), 3.74 (1H, d, J = 12.1 Hz, CH₃OH), 3.52 (1H, d, J = 12.16 Hz, CH₃OH), 2.68 (1H, dq, J = 9.4 Hz and 7.1 Hz, CHCO), 1.81 (1H, dq, J = 15.0 Hz and 7.5 Hz, CH₃OH), 1.71 (1H, dq, J = 15.0 Hz and 7.5 Hz, CH₃OH), 1.28 (1H, d, J = 7.5 Hz, CH₃), 1.01 (1H, t, J = 7.5 Hz, CH₂CH₃); 13C 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 C₈H₁₄O₄: requires 175.0970 for [M+H]+; found: 175.957; requires 197.0789 for [M+Na]+; found: 197.0777.

6.3.7  (3S,4S)-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3H)-one, 240a1 and (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-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-methylhydrofuran-2(3H)-one, 240a1

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3) & : \delta \ 4.22 - 4.17 \ (1H, \text{ m, CHCH}_2\text{OH}), \ 4.17 - 4.11 \ (1H, \text{ m, CHOH}), \ 3.98 \ (1H, \text{ dd, } J = 12.7 \text{ and } 3.0 \text{ Hz, CH}_3\text{OH}), \ 3.83 \ (1H, \text{ dd, } J = 12.7 \text{ and } 3.2 \text{ Hz, CH}_3\text{CH}_2\text{OH}), \ 2.68 \ (1H, \text{ dq, } J = 8.9 \text{ and } 7.1, \text{ CHCH}_3), \ 1.32 \ (3H, \text{ d, } J = 7.1 \text{ Hz, CH}_3) ; \text{ } ^{13}\text{C NMR (75.5 MHz, CDCl}_3) : \delta \ 177.04, \ 83.59, \ 74.42, \ 60.85, \ 43.95, \ 12.70; \text{ IR (ATR) } \nu_{\text{max}} \ (\text{cm}^{-1}) : \ 3377 \ (\text{broad O-H}), \ 2934 \ (\text{broad O-H}), \ 1763 \ (\text{C}=\text{O}); \text{ HRMS (ESI); } m/z \text{ calculated for C}_6\text{H}_{10}\text{O}_4: \text{ requires } 147.0657 \text{ for } [\text{M}+\text{H}]^+; \text{ found: } 147.0650; \text{ requires } 169.0477 \text{ for } [\text{M}+\text{Na}]^+; \text{ found: } 169.0466.
\end{align*}
\]

6.3.7.2 (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-3-methylhydrofuran-2(3H)-one, 140a2

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3) & : \delta \ 4.55 \ (1H, \text{ dt, } J = 6.9 \text{ and } 3.6 \text{ Hz, CHCH}_2\text{OH}), \ 4.35 \ (1H, \text{ d, } J = 6.0 \text{ Hz, CHOH}), \ 4.06 \ (2H, \text{ d, } J = 3.5 \text{ Hz, CH}_3\text{CH}_2\text{OH}), \ 2.74 \ (1H, \text{ dt, } J = 13.6 \text{ and } 7.5 \text{ Hz, CHCH}_3), \ 1.32 \ (3H, \text{ d, } J = 7.5 \text{ Hz, CH}_3); \text{ } ^{13}\text{C NMR (75.5 MHz, CDCl}_3) : \delta \ 178.42, \ 80.04, \ 76.08, \ 61.52, \ 44.18, \ 30.03, \ 13.89; \text{ IR and HRMS were the same as the other diastereomer.}
\end{align*}
\]

6.3.8 (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-3,5-dimethyl-hydrofuran-2(3H)-one, 240b

\[
\begin{align*}
\text{Osmium tetroxide (9.1 mg, 0.036 mmol) was added to a solution of aldol 163b (120 mg, 0.36 mmol) in acetone/water (8:1, 3 mL) followed by addition of N-methylmorpholine-N-oxide (60% by weight in water, 0.08 mL, 0.40 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification via column chromatography afforded (3S,4S,5R)-4-}
\end{align*}
\]
hydroxy-5-(hydroxymethyl)-3,5-dimethyl-dihydrofuran-2(3H)-one, 240b (43.2 mg, 0.27 mmol, 75%) as a white solid.

Rf (7:3 DCM/EtOAc) = 0.19; [α]_D^{23} = +5.3 (c = 1.78 in MeOH); 1H NMR (500 MHz, MeOD) δ 4.10 (1H, d, J = 9.7 Hz, CHO), 3.65 (1H, d, J = 12.4 Hz, CH₅H₆OH), 3.54 (1H, d, J = 12.2 Hz, CH₅H₇OH), 2.70 (1H, qd, J = 9.7 Hz and 7.0 Hz, CHCO), 1.28 (1H, d, J = 7.2 Hz, CHCH₃), 1.28 (3H, s, CH₃); 13C 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 C₇H₁₂O₄: requires 161.0814 for [M+H]+; found: 161.0810; requires 183.0633 for [M+Na]+; found: 183.0621.

6.3.9 (3S,4S,5R)-4-hydroxy-5-((R)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3H)-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 (3S,4S,5R)-4-hydroxy-5-((R)-1-hydroxypropyl)-3,5-dimethyl-dihydrofuran-2(3H)-one, 240i (89.4 mg, 0.48 mmol, 82%, >95% de) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.22; [α]_D^{23} = -5.4 (c = 1.3 in CHCl₃); 1H NMR (300 MHz, CDCl₃) δ 4.12 (1H, dd, J = 9.8 Hz and 5.4 Hz, CHO), 3.93 (1H, d, J = 5.39 Hz, OH), 3.57 (1H, d, J = 8.57 Hz, OH), 3.37 (1H, ddd, J = 10.8 Hz, 8.8 Hz and 2.24 Hz, CHOCH₂), 2.62 (1H, dq, J = 9.9 Hz and 7.1 Hz, CHCH₃) 1.67 (1H, dqq, J = 15.1 Hz, 7.46 Hz and 2.42 Hz, CH₅H₆CH₃), 1.45 – 1.28 (1H, m, CH₅H₆CH₃), 1.23 (3H, s, CH₃CH₂), 1.18 (3H, d, J = 7.1 Hz, CHCH₃), 0.97 (3H, t, J = 7.3 Hz, CH₂CH₂); 13C NMR (75 MHz, CDCl₃) 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 C₉H₁₆O₄: requires 189.1127 for [M+H]+; found: 189.1120; requires 211.0946 for [M+Na]+; found: 211.0934.
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 (3S,4S,5S)-4-hydroxy-5-((S)-hydroxy(phenyl)methyl)-3-methyl-dihydrofuran-2(3H)-one, 240g1 (89.9 mg, 0.41 mmol, 81%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.34; [α]D = +44.0 (c = 1.62 in CHCl₃); 1H NMR (500 MHz, CDCl₃) δ 7.41 – 7.25 (5H, m, ArH), 4.76 (1H, d, J = 5.7, CHPh), 4.22 (1H, dd, J = 9.2 Hz and 7.5 Hz), 3.95 (1H, dd, J = 9.2 Hz and 7.5 Hz, CHOH), 2.56 (1H, dq, J = 9.2 Hz and 7.2 Hz, CHCO), 1.19 (3H, d, J = 6.9 Hz, CH₃CH); 13C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₄O₄: requires 223.0970 for [M+H]+; found: 223.0964; requires 245.0790 for [M+Na]+; found: 245.0767.

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 (3S,4S,5R)-4-hydroxy-5-((S)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3H)-one, 240f1 and (3S,4S,5S)-4-hydroxy-5-((R)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3H)-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  **(3S,4S,5R)-4-hydroxy-5-((S)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3H)-one, 240f1**

\[
\begin{align*}
\text{Rf (7:3 DCM/EtOAc) } &= 0.15; ~ ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 4.11 (1H, dd, J = 8.8 Hz and 7.0 Hz, CHOH), 4.04 – 3.95 (2H, m, CHOCHO and CHOHCH_3), 2.68 (1H, dq, J = 9.1 Hz and 7.1 Hz, CHCO), 1.37 (3H, d, J = 6.5 Hz, CH_3CHOH), 1.32 (3H, d, J = 7.1 Hz, CH_3CH); ~ ^13\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 176.8, 86.4, 74.9, 66.6, 44.17, 19.9, 12.8; ~ \text{IR (ATR) } \nu (\text{cm}^{-1}): 3356.6 \text{ (broad O-H), 1754.5 (C=O); HRMS (ES+): } m/\text{z} \text{ calculated for C}_{12}H_{20}O_4 \text{ requires 183.0628 for } [\text{M+Na}^+] \text{; found: 183.0613.}
\end{align*}
\]

6.3.11.2  **(3S,4S,5S)-4-hydroxy-5-((R)-1-hydroxyethyl)-3-methyl-dihydrofuran-2(3H)-one, 240f2**

\[
\begin{align*}
\text{Rf (7:3 DCM/EtOAc) } &= 0.15; ~ ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 4.35 - 4.32 (1H, m, CHOH), 4.32 - 4.27 (2H, m, CHOCHO and CHOCH_3), 2.76 (1H, dq, J = 7.7 Hz and 5.3 Hz, CHCO), 1.39 (3H, d, J = 6.7 Hz, CH_3CHOH), 1.32 (3H, d, J = 7.5 Hz, CH_3CH); ~ ^13\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 177.3, 82.9, 76.3, 67.1, 44.6, 19.8, 14.0; ~ \text{IR and HRMS were the same as 240f1.}
\end{align*}
\]

6.3.12  **(3S,4S)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one**

\[
\begin{align*}
\text{Osmium tetroxide (13.5 mg, 0.053 mmol) was added to a solution of aldol 163h (184.0 mg, 0.53 mmol) in acetone/water (8:1, 3 mL) followed by addition of N-methylmorpholine-N-oxide (60\% by weight in water, 0.10 mL, 0.59 mmol) according to General Procedure 7 to afford the crude product as a black oil. Purification via column chromatography afforded (3S,4S,5R)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one, 240h1 (37.8 mg,}
\end{align*}
\]
0.22 mmol, 41%) as a pale oil. The minor diastereomer was also isolated as a white solid
(3S,4S,5S)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one, 240h2,
(27.7 mg, 0.16 mmol, 30%)

6.3.12.1 (3S,4S,5S)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one, 240h1

![Chemical Structure](image1)

Rf (7:3 DCM/EtOAc) = 0.32; [α]D°23 = -55.6 (c = 0.99 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 
4.94 (1H, d, J = 4.1 Hz, OH), 4.26 (1H, app. dt, J = 3.9 Hz and 1.5 Hz, C4H), 4.09 (1H, d, J 
= 4.1 Hz, CHOCO), 2.96 (1H, br. s, OH), 2.68 (1H, qd, J = 7.8 Hz and 1.5 Hz), 1.38 (3H, s, 
(CH3A)C(CH3B)), 1.36 (3H, s, (CH3A)C(CH3B)), 1.19 (3H, d, J = 7.8 Hz, CH2CH); 13C NMR (75 
MHz, CDCl3) 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 C8H14O4: requires 
175.0970 for [M+H]^+; found: 175.0970; requires 197.0790 for [M+Na]^+, found: 197.0784.

6.3.12.2 (3S,4S,5S)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyl-dihydrofuran-2(3H)-one, 240h2

![Chemical Structure](image2)

Rf (7:3 DCM/EtOAc) = 0.24; [α]D°23 = +25.0 (c = 0.53 in CHCl3); 1H NMR (300 MHz, CDCl3) δ 
4.12 (1H, ddd, J = 9.1 Hz, 7.4 Hz and 4.4 Hz, CHOH), 3.88 (1H, d, J = 7.5 Hz, CHOCO), 
2.61 (1H, dq, J = 9.3 Hz and 7.5 Hz, CHCO), 2.32 (1H, d, J = 4.4 Hz, OH), 1.72 (1H, s, OH), 
1.30 – 1.19 (9H, m, CH3CH and (CH3)2C); 13C NMR (75 MHz, CDCl3) 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 C8H14O4 requires 197.0789 for [M+Na]^+, found 197.0774.
6.3.13  
(3S,4S)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3H)-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 \textit{N}-methylmorpholine-\textit{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 (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3H)-one, \textit{240m1} (46.3 mg, 0.24 mmol, 43\%) as a pale oil. The slightly minor diastereomer was also isolated as a white solid (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3H)-one, \textit{240m2} (34.5 mg, 0.18 mmol, 32\%).

6.3.13.1  
(3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3H)-one, \textit{240m1}

Rf (7:3 DCM/EtOAc) = 0.33; \([\alpha]_D^{23} = +39.1 \text{ (c = 0.69 in CHCl}_3\)); \textit{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 4.05 (1H, app. br. d, \(J = 7.5\) Hz, CH\textsubscript{OH}), 3.87 (1H, d, \(J = 12.6\) Hz, CH\textsubscript{A}CH\textsubscript{B}OH), 3.75 Hz (1H, d, \(J = 12.6\) Hz, CH\textsubscript{A}CH\textsubscript{B}OH), 2.67 (1H, dd, \(J = 8.3\) Hz and 4.9 Hz, CHCO), 2.19 (1H, d sept., \(J = 6.9\) Hz and 4.9 Hz, CH(CH\textsubscript{3})\textsubscript{2}), 1.29 (3H, s, CH\textsubscript{3}), 1.03 (3H, d, \(J = 6.8\) (CH\textsubscript{A}CH\textsubscript{B})), 0.94 (3H, d, \(J = 6.8\) (CH\textsubscript{A}CH\textsubscript{B})); \textit{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 175.6, 85.9, 69.6, 65.9, 52.1, 27.2, 20.1, 19.3, 17.3; IR (ATR) \(\nu\) (cm\textsuperscript{-1}): 3333.6 (broad O-H), 1736.7 (C=O); HRMS (ES+): \textit{m/z} calculated for C\textsubscript{9}H\textsubscript{16}O\textsubscript{4}: requires 189.1127 for [M+H]\textsuperscript{+}; found: 189.1124; requires 211.0946 for [M+Na]\textsuperscript{+}; found: 211.0938
6.3.13.2 (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)-3-isopropyl-5-methyl-dihydrofuran-2(3H)-one, 240m2

Rf (7:3 DCM/EtOAc) = 0.42; [α]_D^23 = -17.0 (c = 0.53 in CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.05 (1H, app. br. d, J = 7.5 Hz, CHOH), 3.87 (1H, d, J = 12.6 Hz, CH₃H₂OH), 3.75 Hz (1H, d, J = 12.6 Hz, CH₃H₂OH), 2.67 (1H, dd, J = 8.3 Hz and 4.9 Hz, CHCO), 2.19 (1H, d.sept., J = 6.9 Hz and 4.9 Hz, CH(CH₃)₂), 1.29 (3H, s, CH₃), 1.03 (3H, d, J = 6.8 (CH₃(CH₃)₂CH(CH₃)₂)), 0.94 (3H, d, J = 6.8 (CH₃(CH₃)₂CH(CH₃)₂)); ¹³C NMR (75 MHz, CDCl₃) 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 C₉H₁₆O₄: requires 189.1127 for [M+H]^+; found: 189.1115: requires 211.0946 for [M+Na]^+; found: 211.0927.

6.3.14 (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-5-methyl-3-phenyl-dihydrofuran-2(3H)-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 (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-5-methyl-3-phenyl-dihydrofuran-2(3H)-one, 240l (42 mg, 0.19 mmol, 75%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.34; [α]_D^25 = -9.1 (c = 0.83 in MeOH); ¹H NMR (300 MHz, CDCl₃) δ 7.29 – 7.23 (3H, m, PhH), 7.18 – 7.13 (2H, m, PhH), 4.62 (1H, d, J = 10.5 Hz, CHOH), 3.80 (1H, d, J = 10.5 Hz, CHCO), 3.70 (1H, d, J = 12.6 Hz, CH₃H₂OH), 3.58 (1H, d, J = 12.6 Hz, CH₃H₂OH), 1.32 (3H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₄O₄: requires 223.0970 for [M+H]^+; found: 223.0961: requires 245.0790 for [M+Na]^+; found: 245.0767.
6.3.15 (3S,4R,5R)-3-chloro-4-hydroxy-5-(hydroxymethyl)-5-methyl-dihydrofuran-2(3H)-one, 
240k

[Chemical structure image]

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 (3S,4R,5R)-3-chloro-4-hydroxy-5-(hydroxymethyl)-5-methyl-dihydrofuran-2(3H)-one, 240k (74.1 mg, 0.41 mmol, 76%) as a pale oil.

Rf (7:3 DCM/EtOAc) = 0.13; [\(\alpha\rceil_0^{23}\] = +12.7 (c = 0.85 in MeOH); \(^1\)H NMR (500 MHz, MeOD) δ 4.82 (1H, d, \(J = 9.6\) Hz, CHCl), 4.50 (1H, d, \(J = 9.6\) Hz, CHO), 3.66 (1H, d, \(J = 13.5\) Hz, CH\(^A\)H\(^B\)OH), 3.55 (1H, d, \(J = 13.5\) Hz, CH\(^A\)H\(^B\)OH), 1.33 (3H, s, CH\(^3\)); \(^13\)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\(^6\)H\(^9\)ClO\(^4\): requires 203.0087 for [M+Na]\(^+\); found: 203.0073.

6.3.16 (4S,5R)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one, 272a

[Chemical structure image]

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 (4S,5R)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-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, CHO), 4.43 – 4.37 (1H, m, CH\(^CH\(^2\)OH)), 3.81 (1H, dd, \(J = 12.4, 3.3\) Hz, CH\(^A\)CH\(^B\)OH), 3.73 (1H, dd, \(J = 12.4, 3.6\) Hz,
CH$_4$CH$_2$OH), 2.94 (1H, dt, $J = 17.6$, 6.2 Hz, CH$_4$CH$_2$C=O), 2.51 – 2.32 (1H, m, CH$_4$CH$_2$C=O); $^{13}$C NMR (75.5 MHz, MeOD): $\delta$ 179.5, 91.1, 70.6, 63.4, 40.1; IR (ATR) $\nu_{\text{max}}$ (cm$^{-1}$): 3329 (broad O-H), 2941 (broad O-H), 1793 (C=O); HRMS (ESI); m/z calculated for C$_5$H$_8$NO$_4$: requires 155.0320 for [M+Na]$^+$; found: 155.0325.

6.3.16.1 (4S,5R)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one, 272b

\[
\begin{array}{c}
\text{O} \\
\text{HO} \\
\text{---OH}
\end{array}
\]

$^1$H NMR (300 MHz, MeOD): $\delta$ 4.62 – 4.50 (1H, m, CHO$_2$ & CHCH$_2$OH), 3.91 (1H, dd, $J = 5.4$, 1.6 Hz, CH$_4$CH$_2$OH), 2.94 (2H, dt, $J = 17.6$, 6.2 Hz, CH$_4$CH$_2$C=O), 2.52 – 2.32 (1H, m, CH$_4$CH$_2$C=O); $^{13}$C NMR (75.5 MHz, MeOD): $\delta$ 179.4, 87.4, 69.9, 62.1, 40.9; IR (ATR) $\nu_{\text{max}}$ (cm$^{-1}$): 3329 (broad O-H), 2941 (broad O-H), 1793 (C=O); HRMS (ESI); m/z calculated for C$_5$H$_8$NO$_4$: requires 155.0320 for [M+Na]$^+$; found: 155.0325.
6.4 Compounds from Chapter 5

6.4.1 (S)-4-benzyl-3-[(2S,3R,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.

\[\text{Rf} = 0.21 \text{ (DCM); } [\alpha]_D^{24} = -20 \text{ (c = 1.20 in CHCl}_3)\]; \(^1\text{H NMR (300 MHz, CDCl}_3) \delta 7.30-7.10 \text{ (5H, m, Ph), 5.80 (1H, ddd, } J = 15.5 \text{ Hz, 6.5 Hz and 1Hz, } CH=CHCH}_3\), 5.66 (1H, d, \(J = 5.5 \text{ Hz, CHCl}_3\)), 5.47 (1H, d, \(J = 15.5 \text{ Hz, 6.5Hz and 1Hz, CH=CHCH}_3\)), 4.51–4.40 (2H, m, CHOH and CHN), 3.09 (1H, dd, \(J = 14.5\text{ Hz and 4.0 Hz, } CH_2H_2\text{Ph})\), 2.85 (1H, dd, \(J = 14.5 \text{ Hz and 9.5 Hz, } CH_2H_2\text{Ph})\) 2.61 (1H, br d, \(J = 4.0 \text{ Hz, OH})\), 1.65 (3H, d, \(J = 6.5 \text{ Hz, CH=CHCH}_3\)), 1.34 (3H, s, C(CH_3)), 1.29 (3H, s, C(CH_3)); \(^{13}\text{C NMR (75 MHz, CDCl}_3) \delta 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\(_{\text{os}}\)); HRMS (ES): \text{m/z} \text{ calculated for } C_{18}H_{22}ClNO_4: \text{requires 374.1135 for } [\text{M+Na}^+]; \text{found 374.1147.}
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\textsubscript{4}Cl (191 mg, 3.60 mmol) and methanol (20 mL). The crude reaction product was purified by chromatography (CH\textsubscript{2}Cl\textsubscript{2}) to afford \((S)-4\text{-benzyl-3-((2S,3R)-3-hydroxy-4-enoyl)-5,5-dimethyloxazolidin-2-one, 296}\) (210 mg, 0.66 mmol) as a colourless oil in 74\% yield.

\([\alpha]_D^{21} = -51.5\) (c = 1.23, CHCl\textsubscript{3}); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.28-7.11\) (5H, m, ArH), 5.68 (1H, dqd, \(J = 15.5, 6.5, 1\)Hz, CH=CHCH\textsubscript{3}), 5.47 (1H, ddq, \(J = 15.5, 6.5, 1\)Hz, CH=CHCH\textsubscript{3}), 4.50–4.39 (2H, m, CH\textsubscript{2}OH and CHN), 3.1–3.0 (3H, m, CH\textsubscript{2}CHOH and CH\textsubscript{2}Ph), 2.8 (1H, dd, \(J = 14.5, 6.5\) Hz, CH\textsubscript{2}H\textsubscript{2}Ph), 1.63 (3H, dt, \(J = 6.5\) Hz, CH=CHCH\textsubscript{3}), 1.32 (3H, s, C(CH\textsubscript{3})), 1.30 (3H, s, C(CH\textsubscript{3})); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 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\textsubscript{ox}); HRMS (ES\textsuperscript{+}): m/z calculated for C\textsubscript{19}H\textsubscript{23}NO\textsubscript{4} requires [M+Na]\textsuperscript{+} for 340.1524; found 374.1514.

6.4.3 \((S)-4\text{-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295f}\)

According to General Procedure 9, (S)-4-benzyl-3-((2S,3R,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\text{-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-
methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295f as a white solid in quantitative yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33-7.20 (5H, m, Ph), 4.53 (1H, dd, $J$ = 9.2, 4.3 Hz, CHO), 3.99 (1H, dq, $J$ = 14.0, 3.7 Hz, COCH), 3.20 (1H, dd, $J$ = 8.4, 3.6 Hz, CHN), 3.08 (1H, dd, $J$ = 14.3, 4.3 Hz, CH$_2$H$_2$Ph), 2.90 (1H, dd, $J$ = 14.3, 9.2 Hz, CH$_3$H$_2$Ph), 2.46 (1H, s, OH), 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$_2$CH$_2$H$_2$Ph), 1.03 (3H, d, $J$ = 6.0 Hz, CH$_2$CH), 0.77-0.63 (2H, m, CHCH$_2$CH(H$_2$)), 0.55-0.49 (1H, m, CHCH$_2$CH$_2$H$_2$Ph), 0.35-0.29 (1H, m, CHCH$_2$CHCH$_3$), 0.35 (1H, m, CHCH$_2$CH$_2$H$_2$Ph); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 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) $\nu$ (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-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295g

According to General Procedure 9, (S)-4-benzyl-3-((2S,3R,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-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295g as a white solid in quantitative yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33-7.04 (10H, m, Ph and CH$_2$Ph), 4.44 (1H, dd, $J$ = 9.2, 4.3 Hz, CHN), 4.04 (1H, dq, $J$ = 7.0, 4.4 Hz, COCH), 3.47 (1H, m, CHO), 3.08 (1H, dd, $J$ = 14.3, 4.2 Hz, CHCH$_3$H$_2$Ph), 2.87 (1H, dd, $J$ = 14.3, 9.3 Hz, CHCH$_3$H$_2$Ph), 1.91 (1H, m, CHCH$_2$CHPh), 1.35 (3H, s, (CH$_3$)C(CH$_3$)), 1.25 (3H, d, $J$ = 7.0 Hz, (CH$_3$CH), 1.16 (3H, s, (CH$_3$)C(CH$_3$)), 1.12-1.05 (1H, m, CHCH$_2$CHPh), 1.03-0.83 (2H, m, CHCH$_2$CHPh); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 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) $\nu$ (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.
According to General Procedure 9, \((S)-4\)-benzyl-3-\(((2S,3R)-3-((S)-2,2\text{-dimethylcyclopropyl})-3\text{-hydroxy}\text{-}2\text{-methylpropanoyl})\text{-}5,5\text{-dimethyloxazolidin-2\text{-one}}, 163h\) (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-\(((2S,3R)-3-((S)-2,2\text{-dimethylcyclopropyl})-3\text{-hydroxy}\text{-}2\text{-methylpropanoyl})\text{-}5,5\text{-dimethyloxazolidin-2\text{-one}}, 295h\) as a white solid in quantitative yield.

\([\alpha]_D^{24} = +12.0 \ (c = 1.00, \text{CHCl}_3)\); \(^1\text{H} \text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta 7.27\text{-}7.10 \ (5\text{H, m, Ph}) \ 4.48 \ (1\text{H, dd, } J = 9.2 \text{ Hz and } 4.5 \text{ Hz, CHN}), 3.91 \ (1\text{H, qd, } J = 7.0 \text{ Hz and } 3.4 \text{ Hz, COCH}), 3.47 \ (1\text{H, dd, } J = 9.5 \text{ Hz and } 3.5 \text{ Hz, CHOH}), 3.03 \ (1\text{H, dd, } J = 14.0 \text{ Hz and } 4.5 \text{ Hz, CH}_3\text{H}_9\text{Ph}), 2.83 \ (1\text{H, dd, } J = 14.0 \text{ and } 9.2 \text{ Hz, CH}_3\text{CH}_9\text{Ph}), 2.69 \ (1\text{H, broad s, OH}), 1.32 \ (3\text{H, s, (CH}_3\text{)C(CH}_3\text{)}), 1.31 \ (3\text{H, s, (CH}_3\text{)C(CH}_3\text{)}), 1.18 \ (3\text{H, d, } J = 7.0 \text{ Hz, CH}_2\text{CH}), 1.01 \ (3\text{H, s, (CH}_3\text{)C(CH}_3\text{)}\text{-cyclopropane}), 0.98 \ (3\text{H, s, (CH}_3\text{)C(CH}_3\text{)}\text{-cyclopropane}), 0.77 \ (1\text{H, app. td, } J = 8.3 \text{ Hz and } 5.6 \text{ Hz, CHCH}_3\text{C}), 0.51 \ (1\text{H, dd, } J = 8.3 \text{ Hz and } 4.2 \text{ Hz, CHCH}_3\text{H}_9\text{C}), 0.25 \ (1\text{H, app. t, } J = 5 \text{ Hz, CH}_3\text{H}_9\text{C}); \(^{13}\text{C} \text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta 177.8, 152.5, 137.1, 129.5, 129.0, 127.3, 82.5, 73.5, 64.2, 43.3, 35.8, 28.8, 28.1, 27.5, 23.1, 22.0, 19.5, 18.6, 11.4; \text{IR (ATR) } v \ (\text{cm}^{-1}) : 3483.7 \ (\text{O-H}), 1776.9 \ (\text{C=O}), 1686.4 \ (\text{C=O})\); \text{HRMS (ES): } m/z \text{ calculated for } C_{21}H_{29}NO_4 \text{ requires } 382.1994 \text{ for } [M+Na]^+; \text{found: } 382.1979.
According to General Procedure 9, (S)-4-benzyl-3-((2S,3R)-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-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2R)-2-pentylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 295j as a white solid in quantitative yield.

\[\text{[}\alpha\text{]}_{D}^{24} = -19.0 \text{ (c = 1.0, CHCl}_{3}\text{); }^1\text{H NMR (300 MHz, CDCl}_{3}\text{) }\delta 7.30-7.15 \text{ (5H, m, Ph), 4.50 (1H, dd, } J = 9.2 \text{ Hz and } 3.0 \text{ Hz, CHN), 3.95 (1H, qd, } J = 7.0 \text{ and } 3.0 \text{ Hz, COCH), 3.55 (1H, app. dt, } J = 9.2 \text{ Hz and } 3.0 \text{ Hz, CHOH), 3.09 (1H, dd, } J = 14.5 \text{ and } 4.3 \text{ Hz, CH}_3\text{CHPh), 2.91 (1H, dd, } J = 14.5 \text{ and } 9.3 \text{ Hz, CH}_3CH_2Ph, 2.65 (1H, d, } J = 2.1 \text{ Hz, OH), 1.65-1.20 (8H, obs. m, (CH}_2)_3\text{q), 1.40 (3H, s, (CH}_3)_2C(CH}_3), 1.37 (3H, s, (CH}_3)_2C(CH}_3), 1.29 (3H, d, } J = 7.0 \text{ Hz, CH}_3\text{CH), 1.07-0.93 (2H, m, CHCH}_2\text{CH), 0.88 (3H, t, } J = 7.0 \text{ Hz, CH}_2\text{CH}_3), 0.86-0.76 (1H, m, CHCH}_2\text{CH); }^{13}\text{C NMR (75 MHz, CDCl}_{3}\text{) }\delta 177.9, 152.7, 137.1, 129.5, 129.1, 127.3, 82.6, 72.4, 63.9, 43.3, 35.8, 32.1, 30.2, 29.3, 28.8, 23.1, 22.6, 19.4, 16.7, 14.5, 11.6, 10.2; IR (ATR) v (cm}^{-1}\text{): 3510.7 (O-H), 1774.4 (C=O), 1694.4 (C=O=O); HRMS (ES): m/z calculated for C_{24}H_{35}NO_4: requires 424.2464 for [M+Na]^+; found: 424.2449.\]

According to General Procedure 9, (S)-4-benzyl-3-((2S,3R,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 \((S)-4\text{-benzyl-3-}((2S,3R)\text{-3-hydroxy-3-}((1S,2S)-2\text{-methylcyclopropyl})\text{-2-phenylpropanoyl})\text{-5,5-dimethyloxazolidin-2-one, 295o}\) as a white solid in quantitative yield.

\([\alpha]_D^{24} = -6.0 \) (c = 1.00, CHCl\(_3\)); \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.49 \text{–} 7.10 \) (10H, m, Ph), 5.17 (1H, br. d, \( J = 5.2 \) Hz, \( CH\text{Ph} \)), 4.56 (1H, dd, \( J = 9.7 \text{–} 3.0 \) Hz, CHN), 3.59 (1H, dd, \( J = 7.4 \text{–} 5.2 \) Hz, \( CH\text{OH} \)), 2.98 (1H, dd, \( J = 14.9 \text{–} 3.7 \) Hz, \( CH\text{H}_2\text{Ph} \)), 2.69 (1H, dd, \( J = 14.9 \text{–} 10.4 \) Hz, \( CH\text{H}_2\text{Ph} \)), 1.36 (3H, s, \( CH\text{H}_2\text{C}(CH\text{H}_2) \)), 1.29 (3H, s, \( CH\text{H}_3\text{C}(CH\text{H}_3) \)), 1.01 (3H, d, \( J = 5.9 \), \( CH\text{CH}_3 \)), 0.80 – 0.64 (1H, m, \( CH\text{CH}_2\text{CHMe} \)), 0.63 – 0.45 (2H, m, \( CH\text{CH}_2\text{CHMe} \)), 0.34 – 0.19 (1H, m, \( CH\text{CH}_2\text{CHMe} \)); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta 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, 51.1, 29.1, 24.1, 22.7, 18.7, 12.0, 11.8; IR (ATR) \( \nu \) (cm\(^{-1}\)): 3511.9 (O-H), 1771.6 (C=O), 1690.3 (C=O\(_\text{a} \)); 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-((2S,3R)-3-hydroxy-3-((1S,2S)-2-methylcyclopropyl)-2-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 295p

According to General Procedure 9, \((S)-4\text{-benzyl-3-}((2S,3R,E)-2\text{-chloro-3-hydroxyhex-4-enoyl})\text{-5,5-dimethyloxazolidin-2-one, 163p}\) (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 \((S)-4\text{-benzyl-3-}((2S,3R)-3\text{-hydroxy-3-}((1S,2S)-2\text{-methylcyclopropyl})\text{-2-phenylpropanoyl})\text{-5,5-dimethyloxazolidin-2-one, 295p}\) as a white solid in quantitative yield.

\([\alpha]_D^{24} = -18.0 \) (c = 1.00, CHCl\(_3\)); \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.30 \text{–} 7.11 \) (5H, m, Ph), 5.72 (1H, d, \( J = 4.1 \) Hz, \( CH\text{Cl} \)), 4.45 (1H, dd, \( J = 9.5 \text{–} 3.5 \) Hz and 3.5 Hz, CHN), 3.39 (1H, dd, \( J = 7.9 \text{–} 4.1 \) Hz, \( CH\text{OH} \)), 3.15 (1H, dd, \( J = 14.5 \text{–} 3.5 \) Hz, \( CH\text{H}_2\text{Ph} \)), 2.84 (1H, dd, \( J = 14.5 \text{–} 9.8 \) Hz, \( CH\text{H}_2\text{Ph} \)), 1.33 (3H, s, \( CH\text{H}_3\text{C}(CH\text{H}_2) \)), 1.29 (3H, s, \( CH\text{H}_3\text{C}(CH\text{H}_3) \)), 0.97 (3H, d, \( J = 5.7 \), \( CH\text{CH}_3 \)), 0.86 – 0.68 (2H, m, \( CH\text{CH}_2\text{CHMe} \)), 0.62 – 0.53 (1H, m, \( CH\text{CH}_2\text{CHMe} \)), 0.37 – 0.27 (1H, m, \( CH\text{CH}_2\text{CHMe} \)); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta 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) \( \nu \) (cm\(^{-1}\)) \( ^1\)): 3509.8 (O-H), 1774.9 (C=O), 1711.8 (C=O\(_\text{a} \)); HRMS (ES): \( m/z \) calculated for \( C_{19}H_{24}ClNO_4 \):
requires 366.1472 for [M+H]\(^+\); found: 366.1472; requires 388.1291 for [M+Na]\(^+\); found: 388.1282.

6.4.9  

\((S)-4\text{-benzyl-3-}\{(S)-2-\{(R)-hydroxy(15,25)\text{-2-methylcyclopropyl)methyl}\}-3\text{-methylbutanoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 295q}\)

According to General Procedure 9, \((S)-4\text{-benzyl-3-}\{(2S,3R,E)\text{-3-hydroxy-2-isopropylhex-4-enoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 163q (810 mg, 2.28 mmol)}\) 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 \((S)-4\text{-benzyl-3-}\{(S)-2-\{(R)-hydroxy(15,25)\text{-2-methylcyclopropyl)methyl\}-3\text{-methylbutanoyl}\}-5,5\text{-dimethyloxazolidin-2-one, 295q}\) as a white solid in quantitative yield.

\([\alpha]_D^{24} = -8.0\ (c = 1.0, \text{CHCl}_3)\); \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta\) 7.47 – 7.15 (5H, m, Ph), 4.63 (1H, dd, \(J = 10.4\) Hz and \(3.2\) Hz, \(CHN\)), 4.24 (1H, dd, \(J = 8.5\) Hz and \(6.4\) Hz, \(CH(CH_3)\)), 3.67 (1H, dd, \(J = 8.9\) Hz and \(6.4\) Hz, \(CHOH\)), 3.24 (1H, dd, \(J = 14.3\) Hz and \(3.2\) Hz, \(CH_2\text{HaPh}\)), 2.87 (1H, dd, \(J = 14.5\) Hz and \(10.0\) Hz, \(CH_2\text{HaPh}\)), 2.29 (1H, m, \(CH(CH_3)\)), 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, \(CH^A\text{H}C(CH_3^b)\)), 0.95 (3H, d, \(J = 6.8\) Hz, \(CH^A\text{H}C(CH_3^b)\)), 0.85 – 0.67 (2H, m, \(CHCH_2\text{CHMe}\)), 0.60 – 0.39 (1H, m, \(CHCH_2\text{CHMe}\)), 0.37 – 0.23 (1H, m, \(CHCH_2\text{CHMe}\)); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta\) 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) v (cm\(^{-1}\)): 3511.1 (broad O-H), 1771.7 (C=O), 1689.4 (C=O\(_\text{o}\)); HRMS (ES): \(m/z\) calculated for \(C_{22}H_{31}NO_4\): requires 396.2150 for [M+Na]\(^+\); found: 396.2154.
6.4.10 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoate, 309f

According to General Procedure 10, (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)-propanoyl)-5,5-dimethylloxazolidin-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 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoate, 309f (42 mg, 55%) as a colourless liquid.

R<sub>f</sub> = 0.24 (1:4, EtOAc:Hexane); [α]<sub>D</sub><sup>24</sup> = -8.0 (c = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.71 (3H, s, OCH<sub>3</sub>), 3.13-3.08 (1H, m, CHOH), 2.70 (1H, dq, J = 14.2 Hz and 5.2 Hz, COCH), 2.19 (1H, s, OH), 1.26 (3H, d, J = 7.1 Hz, CH<sub>3</sub>CH), 1.01 (3H, d, J = 5.7 Hz, CHCH<sub>2</sub>CHCH<sub>3</sub>), 0.71-0.58 (2H, m, CH(CH<sub>2</sub>)CHCH<sub>3</sub>), 0.54-0.49 (1H, m, CH(CH<sub>2</sub>)CHCH<sub>3</sub>), 0.34-0.28 (1H, m, CH(CH<sub>2</sub>)CHCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 175.8, 76.8, 52.0, 45.6, 23.9, 18.3, 12.3, 11.5, 11.3; IR (ATR) ν (cm<sup>-1</sup>) = 3444.07 (O-H), 1718.01 (C=O); HRMS (ES+): m/z calculated for C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>: requires 195.0997 for [M+Na]<sup>+</sup>; found: 195.0995

6.4.11 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate, 309g

According to General Procedure 10, (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)-propanoyl)-5,5-dimethylloxazolidin-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 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate, 309g (86 mg, 89%) as a colourless liquid.

R<sub>f</sub> = 0.49 (3:7, EtOAc:Hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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, OCH<sub>3</sub>), 3.35 (1H, dd, J = 8.0 Hz and 4.7 Hz, CHOH), 2.68 (1H, dq, J = 14.2 and 4.7 Hz, COCH), 2.43 (1H, d, J = 4.7 Hz, CH<sub>2</sub>CH), 1.79-1.72 (1H, m, CH(CH<sub>2</sub>)CHPh), 1.30-1.23 (1H, m, CH<sub>2</sub>CHPh), 1.20 (3H, d, J = 7.2 Hz, CH<sub>3</sub>CH), 1.03-
0.97 (1H, m, CH(CH₃H₂)CHCH₃), 0.93-0.87 (1H, m, CH(CH₂H₆)CHCH₃); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₄H₁₈O₃: requires 257.1153 for [M+Na]⁺; found: 257.1148.

6.4.12 (2S,3R)-methyl 3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate, 309h

![Chemical Structure](image)

According to General Procedure 10, (S)-4-benzyl-3-((2S,3R)-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 (2S,3R)-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; [α]D²³ = -11 (c = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 3.72 (3H, s, OC₃H₃), 3.50 (1H, dd, J = 9.4 Hz and 4.1 Hz CHOH), 2.64 (1H, dq, J = 7.1 Hz and 3.9 Hz, COCH), 1.27 (3H, d, J = 7.5 Hz, CH₂CH), 1.07 (3H, s, CHJ), 1.03 (3H, s, CHJ), 0.83-0.74 (1H, m, CH(CH₃H₂)C), 0.57 (1H, dd, J = 8.4 Hz and 4.3 Hz, CH(CH₂H₆)C), 0.33 (1H, app t, J = 5.1 Hz, CH(CH₂C)); ¹³C NMR (75 MHz, CDCl₃) δ 176.3; 173.5, 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 C₁₀H₁₆O₃: requires 209.1153 for [M+Na]⁺; found: 209.1134.

6.4.13 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2R)-2-pentylcyclopropyl)propanoate, 309j

![Chemical Structure](image)

According to General Procedure 10, (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2R)-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 \((2S,3R)\)-methyl 3-hydroxy-2-methyl-3-\{((1S,2R)-2-pentyicyclopropyl)propanoate, 309j\} (157.0 mg, 81%) as a colourless liquid

Rf (3:1, Petrol:EtOAc); \([\alpha]_D^{23} = +8.0 \text{ (c} = 0.88, \text{ CHCl}_3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.71 (3H, s, OCH\(_3\)), 3.58 (1H, dd, \(J = 9.3\) Hz and 3.2 Hz CHOH), 2.66 (1H, dq, \(J = 7.3\) Hz and 3.2 Hz, COCH), 1.63-1.46 (2H, m, CH\(_2\)-alkyl), 1.46-1.16 (9H, m, (CH\(_3\)$_2$ and CH\(_3\)) CH), 0.88 (3H, t, \(J = 7.0\) Hz, CH\(_2\)CH\(_3\)), 0.80 (1H, m, CH(CH\(_3\)H\(_6\))CH); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 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) \(\nu\) (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\((1S,2S)\)-2-methylcyclopropyl)methyl\}-3-methylbutanoate, 309q

According to General Procedure 10, \((S)\)-4-benzyl-3-\{((S)-2-((R)-hydroxy\((1S,2S)\)-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\((1S,2S)\)-2-methylcyclopropyl)methyl\}-3-methylbutanoate, 309q (375 mg, 75%) as a colourless liquid

Rf (3:1, Petrol:EtOAc) = 0.6; \([\alpha]_D^{24} = -13.0 \text{ (c} = 0.78, \text{ CHCl}_3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.70 (3H, s, OCH\(_3\)), 3.18 (1H, app. t, \(J = 8.2\) Hz, CHOH), 2.53 (1H, dd, \(J = 7.9\) Hz and 6.1 Hz, COCH), 2.21 (1H, m, CH(CH\(_3\))$_2$), 1.00 (3H, app. s, CHCH\(_3\)), 0.98 (3H, d, \(J = 2.77\) Hz, CH\(_3\)CH), 0.97 (3H, d, \(J = 2.7\) Hz, CH\(_3\)CH), 0.80-0.63 (2H, m, CH(CH\(_3\))CHCH\(_3\)), 0.55-0.41 (1H, m, CH(CH\(_3\))CHCH\(_3\)), 0.33-0.21 (1H, m, CH(CH\(_3\))CHCH\(_3\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.1, 75.2, 58.6, 51.4, 27.5, 25.5, 21.8, 19.2, 18.6, 12.8, 11.1; IR (ATR) \(\nu\) (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.
According to General Procedure 10, \((S)-4\text{-}\text{benzyl-3-}((S,E)-\text{3-hydroxyhex-4-enoyl})\)-5,5-dimethyl-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 \((S)-\text{methyl 3-hydroxy-3-}((1S,2S)-2\text{-methylcyclopropyl})\)propanoate, 297 (78 mg, 0.54 mmol, 71%) as a colourless oil.

\[
\alpha_d^{22} = -22.2 \ (c = 0.72 \ \text{in CHCl}_3); \\
^1\text{H NMR (300 MHz, CDCl}_3) \delta 5.70 \ (1\text{H, dqq, } J = 15.0 \ \text{Hz, 6.0 Hz and 1.0 Hz, CH} = \text{CHCH}_3), \ 5.43 \ (1\text{H, ddq, } J = 15.0 \ \text{Hz, 6.0 Hz and 1.0 Hz, CH} = \text{CHCH}_3), \ 4.42 \ (1\text{H, app. q, } J = 6.5 \ \text{Hz, CHOH}), \ 3.62 \ (3\text{H, s, OCH}_3), \ 2.78 \ (1\text{H, br. s, CHOCH}), \ 2.47 \ (2\text{H, m, CH}_2), \ 1.63 \ (3\text{H, t, } J = 6.5 \ \text{Hz, CH} = \text{CHCH}_3); \ ^{13}\text{C NMR (75 MHz, CDCl}_3) \delta 173.1, 132.2, 127.9, 69.3, 52.1, 41.8, 18.0; \ IR (\text{KBr/cm}^{-1}) 3431 \ (\text{broad O-H}), \ 1734 \ (\text{C}=\text{O}); \ HRMS (ES\text{+}): m/z \ \text{calculated for C}_{7}\text{H}_{12}\text{O}_3 \text{requires 167.0684 for [M+Na]}^+; \ \text{found 167.0683.}
\]

According to General Procedure 9, diethylzinc (1.9 mL) and diiodomethane (510 mg, 1.9 mmol) were added to \((S)-\text{methyl 3-hydroxy-3-}((1S,2S)-2\text{-methylcyclopropyl})\)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 \((S)-\text{methyl 3-hydroxy-3-}((1S,2S)-2\text{-methylcyclopropyl})\)propanoate, 298 (258 mg, 0.65 mmol) as a yellow oil in 95% yield.

\[
\alpha_d^{25} = +6.0 \ (c = 0.60 \ \text{in CHCl}_3); \\
^1\text{H NMR (300 MHz, CDCl}_3) \delta 3.65 \ (3\text{H, s, OCH}_3), \ 3.25 \ (1\text{H, m, CHOH}), \ 2.56 \ (1\text{H, m, CH}_3\text{CH}_2\text{H}), \ 2.54 \ (1\text{H, d, m, CH}_3\text{CH}_2\text{H}), \ 0.96 \ (3\text{H, d, } J = 5.5 \ \text{Hz, CH}_3), \ 0.57 \ (2\text{H, m, CH-cyclopropyl}), \ 0.49 \ (1\text{H, m, cyclopropyl-CH}_3\text{CH}_2\text{H}), \ 0.25 \ (1\text{H, m, cyclopropyl-CH}_3\text{CH}_2\text{H}); \ ^{13}\text{C NMR (75 MHz, CDCl}_3) \delta 171.9, 71.2, 50.7, 40.5, 24.6, 17.2, 10.5, 9.6; \ IR (\text{KBr/cm}^{-1}) 3435 \ (\text{broad O-H}), \ 1739 \ (\text{C}=\text{O}); \ HRMS (ES\text{+}): m/z \ \text{calculated for C}_{8}\text{H}_{14}\text{O}_3 \text{requires 181.0840 for [M+Na]}^+; \ \text{found 181.0834.}
\]
Mercury trifluoroacetate (371 mg, 0.87 mmol) was added in one portion to a stirring solution of (2S,3R) -methyl 3-hydroxy-2-methyl-3-((1S,2S)-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 MgSO₄ 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 (((2S,3R,4S,5S)-4-hydroxy-2,5-dimethyl-6-oxotetrahydro-2H-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; 1H NMR (500 MHz, CDCl₃) δ 4.06 (1H, dq, J = 9.9 Hz and 6.3 Hz, OCHCH₃), 3.39 (1H, br. d, J = 5.6 Hz, OH), 3.30 (1H, app. dt, J = 10.1 Hz and 5.1 Hz, CHOH), 2.48 (1H, dq, J = 9.8 Hz and 7.1 Hz, CHCH₃), 2.09 – 1.98 (2H, m, CHCHOH and CH₃Hg), 1.48 (3H, d, J = 6.3 Hz, CH₂CO), 1.43 (3H, d, J = 7.1 Hz, CH₂CH), 1.38 (1H, app. t, J = 9.9 Hz, CH₃Hg), 13C NMR (75 MHz, CDCl₃) δ 173.2, 80.1, 74.8, 47.1, 45.2, 27.1, 20.6, 14.3; ¹⁹⁹Hg NMR (89 MHz, CDCl₃) δ -933.9 ppm; IR (ATR) ν (cm⁻¹): 3335.4 (broad O-H), 1682.1 (C=O); HRMS (ES+): m/z calculated for C₁₈H₁₃ClHgO₃: requires 395.0338 for [M+H]+; found: 395.0338; requires 417.0157 for [M+Na]+; found: 417.0148.

Mercury trifluoroacetate (64 mg, 0.273 mmol) was added in one portion to a stirring solution of (2S,3R)-methyl-3-hydroxy-2-methyl-3-((1S,2S)-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 MgSO₄ and concentrated to afford crude product (((2R,3R,4S,5S)-4-hydroxy-5-methyl-6-oxo-2-phenyltetrahydro-2H-pyran-3-yl)methyl)mercury(II) chloride, 313g. The product was not purified due to its potential toxicity.

1H NMR (300 MHz, CDCl₃) δ 7.42-7.38 (3H, m, Ph), 7.32-7.28 (2H, m, Ph), 4.76 (1H, d, J = 10.5 Hz, OC₃H₂Ph), 3.45-3.39 (1H, m, C₃H₂OH), 3.19 (1H, d, J = 4.5 Hz, O₃H), 2.62 (1H, m, COCH₂HgCl), 2.35 (1H, m, CHCH₂HgCl), 1.49-1.43 (5H, m, CH₃ and CHCH₂HgCl); 13C NMR (75 MHz, CDCl₃) δ 137.2, 129.9, 129.4, 127.7, 85.5, 75.4, 46.7, 45.3, 29.8, 26.9, 14.0.

Mercury trifluoroacetate (585 mg, 1.37 mmol) was added in one portion to a stirring solution of [(S)-methyl-2-((R)-hydroxy(1S,2S)-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 MgSO₄ 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 (((2S,3R,4S,5S)-4-hydroxy-5-isopropyl-2-methyl-6-oxotetrahydro-2H-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; 1H NMR (500 MHz, CDCl₃) δ 4.00 (1H, dq, J = 9.9 Hz and 6.3 Hz, OCH₂CH₃), 3.44 (1H, app. dt, J = 10.2 Hz and 6.6 Hz, CH(OH)), 3.25 (1H, br. d, J = 6.3 Hz, OH), 2.55 (1H, dd, J = 6.9 Hz and 3.9 Hz, CHCOO), 2.41 – 2.31 (2H, m, CH(CH₃)₂), 2.05 (1H, dd, J = 12.0 Hz and 3.9 Hz, CH₃H₂Hg), 1.95 (1H, dq, J = 10.5 Hz and 3.9 Hz, CHCH₂Hg), 1.44 (3H, d, J = 6.0 Hz, CH₂CH), 1.35 (1H, t, J = 11.7 Hz, CH₃H₂Hg), 1.27 (1H, d, J = 6.9 Hz, (CH₃)₂C(CH₃)₂), 1.08 (1H, d, J = 6.9 Hz, (CH₃)₂C(CH₃)₂); 13C NMR (75 MHz, CDCl₃) δ 172.7, 78.6, 72.1, 57.3, 47.1, 30.6, 27.1, 20.8, 20.1, 19.9; 199Hg NMR (89 MHz, CDCl₃) δ -
937.7 ppm; IR (ATR) ν (cm⁻¹): 3334.9 (broad O-H), 1681.8 (C=O); HRMS (ES⁺): m/z calculated for C₁₀H₁₇ClHgO₃: requires 423.0650 for [M+H]⁺; found: 423.0637.

6.4.20 (((2R,3R,4S,5S)-4-hydroxy-5-methyl-6-oxo-2-pentyltetrahydro-2H-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 (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2R)-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 MgSO₄ 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 (((2R,3R,4S,5S)-4-hydroxy-5-methyl-6-oxo-2-pentyltetrahydro-2H-pyran-3-yl)methyl)mercury(II) chloride, 313j (160.5 mg, 0.36 mmol, 55%) as a colourless oil and (((2R,3R)-5-methyl-6-oxo-2-pentyl-3,6-dihydro-2H-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; ¹H NMR (300 MHz, CDCl₃) δ 4.49 (1H, dq, 1H, J = 8.0 Hz and 4.0 Hz, CHO), 3.44 (1H, dd, J = 9.3 Hz and 5.6 Hz, CHO), 2.65 (1H, dq, J = 13.3 Hz and 6.8 Hz), 2.42 – 2.33 (1H, m, CH₂Hg), 1.97 (1H, dd, J = 11.6 Hz and 3.6 Hz, CH₅Hg₂Hg), 1.69 (1H, app. t, 11.6 Hz, CH₅Hg₂Hg), 1.70 – 1.46 (2H m, CH₂CHO), 1.36 (3H, d, J = 6.8 Hz, CH₃CH), 1.36 – 1.27 (6H, m, (CH₃)₂), 0.91 (3H, t, J = 6.4, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 175.1, 79.8, 45.1, 43.3, 31.9, 31.4, 29.1, 26.0, 22.9, 14.4, 13.7; ¹⁹⁹Hg NMR (89 MHz, CDCl₃) δ -958.1 ppm; IR (ATR) ν (cm⁻¹): 3438.4 (broad O-H), 1702.9 (C=O).
6.4.20.1  

\(((2R,3R)-5\text{-}methyl\text{-}6\text{-}oxo\text{-}2\text{-}pentyl\text{-}3,6\text{-}dihydro\text{-}2H\text{-}pyran\text{-}3\text{-}yl)\text{methyl}\text{mercury(II) chloride}, 323

![Chemical structure](image)

Rf (DCM) = 0.4; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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, \(CH\text{O}\)), 2.73 (1H, m, \(CH\text{H}\text{O}\)), 2.02 (1H, dd, \(J = \) 11.6 Hz and 8.9 Hz, \(CH\text{H}\text{A}\text{H}\text{B}\text{Hg}\)), 1.92 (3H, s, \(CH\text{C}=C\)), 1.82 (1H, dd, \(J = \) 11.6 Hz and 8.9 Hz, \(CH\text{A}H\text{Hg}\)); 1.91 – 1.49 (2H, m, \(CH\text{OC}H\text{H}\text{2}\)), 1.43 – 1.20 (6H, m, (\(CH\text{H}\text{2}\))\text{3}); 0.90 (3H, t, \(J = \) 6.8 Hz, \(CH\text{H}\text{3}CH\text{2}\)); 199Hg NMR (89 MHz, CDCl\(_3\)) \(\delta\) -937.6 ppm; IR (ATR) \(\nu\) (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\text{-}trimethyl\text{-}6\text{-}oxo\text{-}3,6\text{-}dihydro\text{-}2H\text{-}pyran\text{-}3\text{-}yl)\text{methyl}\text{mercury(II) chloride}, 324

![Chemical structure](image)

Mercury trifluoroacetate (607.0 mg, 1.42 mmol) was added in one portion to a stirring solution of \((S)\)-methyl-2-((\(R\))-hydroxy((1S,2S)-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\text{-}trimethyl\text{-}6\text{-}oxo\text{-}3,6\text{-}dihydro\text{-}2H\text{-}pyran\text{-}3\text{-}yl)\text{methyl}\text{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\(_3\)) \(\delta\) 6.52 (1H, br. d, \(J = \) 5.1 Hz), 2.14 (1H, dd, \(J = \) 11.3 Hz and 3.9 Hz, \(CH\text{A}H\text{Hg}\)), 1.94 (3H, s, \(CH\text{C}=C\)), 1.91 (1H, dd, \(J = \) 12.5 Hz and 10.2 Hz, \(CH\text{A}H\text{Hg}\)), 1.49 (3H, s, \(CH\text{H}\text{2}C(CH\text{3})\)), 1.44 (3H, s, \(CH\text{H}\text{2}C(CH\text{3})\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 165.2, 144.3, 128.0, 83.2, 42.6, 32.3, 28.2, 24.6, 17.4; IR (ATR) \(\nu\) (cm\(^{-1}\)): 1695.8
Sodium borohydride (1 mL, 0.5M in NaOH(aq)) was added dropwise to a stirring solution of \(((2S,3R,4S,5S)-4-hydroxy-2,5-dimethyl-6-oxotetrahydro-2H-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 \((3S,4R,5R,6S)-4-hydroxy-3,5,6-trimethyltetrahydro-2H-pyran-2-one, 326\) in quantitative yield.

\[
\alpha_d^{25} = -27.1 (c = 0.48 \text{ in CHCl}_3); \ \text{H NMR} (300 MHz, CDCl_3) 4.01 (1H, dq, J = 10.5 Hz and 7.1 Hz, CHOCH_3), 3.31 (1H, app. t, J = 9.9 Hz, CHO), 2.41 (1H, dq, J = 10.49 Hz and 7.06 Hz, CHCO), 1.71-1.60 (1H, m, CHCHOH), 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), 13C NMR (75 MHz, CDCl_3) δ 173.5, 79.0, 75.6, 44.9, 43.4, 20.2, 14.2, 13.6; IR (ATR) v (cm\(^{-1}\)): 3423.6 (broad O-H), 1711.8 (C=O); HRMS (ES): m/z calculated for C\(_9\)H\(_{13}\)HgClO\(_2\): requires 391.0389 for [M+H]\(^+\); found: 391.0387; requires 413.0208 for [M+H]\(^+\); found: 413.0190.

**6.4.22 (3S,4R,5R,6S)-4-hydroxy-3,5,6-trimethyltetrahydro-2H-pyran-2-one, 326**

Sodium borohydride (0.63 mL, 0.325 mmol, 0.5M in NaOH(aq)) was added dropwise to a stirring solution of \(((2S,3R,4S,5S)-4-hydroxy-5-isopropyl-2-methyl-6-oxotetrahydro-2H-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 \((3S,4R,5R,6S)-4-hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2H-pyran-2-one, 327\) in quantitative yield.

\[
\alpha_d^{25} = -32.1 (c = 0.48 \text{ in CHCl}_3); \ \text{H NMR} (300 MHz, CDCl_3) 4.01 (1H, dq, J = 10.5 Hz and 7.1 Hz, CHOCH_3), 3.31 (1H, app. t, J = 9.9 Hz, CHO), 2.41 (1H, dq, J = 10.49 Hz and 7.06 Hz, CHCO), 1.71-1.60 (1H, m, CHCHOH), 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), 13C NMR (75 MHz, CDCl_3) δ 173.5, 79.0, 75.6, 44.9, 43.4, 20.2, 14.2, 13.6; IR (ATR) v (cm\(^{-1}\)): 3423.6 (broad O-H), 1711.8 (C=O); HRMS (ES): m/z calculated for C\(_9\)H\(_{14}\)O\(_3\): requires 159.1021 for [M+H]\(^+\); found: 159.1026; requires 181.0841 for [M+Na]\(^+\); found: 181.0834.

**6.4.23 (3S,4R,5R,6S)-4-hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2H-pyran-2-one, 327**
sulphate and concentrated under reduced pressure to yield \((3S,4R,5S,6S)-4\text{-}\text{hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2H-pyran-2-one}, \text{327}\) in quantitative yield.

\(\alpha_d^{25} = -30.1 \ (c = 0.76 \ \text{in CHCl}_3)\); \(^1\text{H NMR} \ (300 \ \text{MHz, CDCl}_3)\) \(\delta 3.96 \ (1\text{H, dq, } J = 9.6 \ \text{Hz and 5.7 Hz, } CHOCH_3), 3.49 \ (1\text{H, dd, } J = 9.6 \ \text{Hz and 7.4 Hz, } CHOH), 2.47 \ (1\text{H, dd, } J = 7.9 \ \text{Hz and 3.9 Hz, } CHCO), 2.44\text{-}2.33 \ (1\text{H, m, } CH(CH_3)_2), 1.66\text{-}1.54 \ (1\text{H, m, } CHCHOH), 1.38 \ (3\text{H, d, } J = 6.2, \ CH_2CHCO), 1.12 \ (3\text{H, d, } J = 6.8 \ \text{Hz, } (CH_3)CH(CH_3)), 1.09 \ (3\text{H, d, } J = 6.8 \ \text{Hz, } (CH_3)CH(CH_3)), 1.07 \ (3\text{H, d, } J = 7.4 \ \text{Hz, } CHCH_3); ^{13}\text{C NMR} \ (75 \ \text{MHz, CDCl}_3)\) \(\delta 172.8, 77.8, 72.38, 56.6, 43.2, 30.1, 20.8, 20.0, 19.9, 13.6; \ IR \ (ATR) \ \nu \ (\text{cm}^{-1})\): 3434.4 \ (\text{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.
References

(2) Noyori, R. Chemical Society Reviews 1989, 18, 187.


(166) Green, R., University of Bath, 2006.


(225) Crystal structure confirmation was elucidated from that reported in Matt Cheeseman's thesis entitled "Temporary stereocentres for the asymmetric synthesis of chiral aldehydes" 2005
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.

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<tr>
<td>Index ranges</td>
<td>-6&lt;=h&lt;=7; -18&lt;=k&lt;=18; -7&lt;=l&lt;=7</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>8674</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2025 [R(int) = 0.0559]</td>
</tr>
<tr>
<td>Reflections observed (&gt;2σ)</td>
<td>1779</td>
</tr>
<tr>
<td>Data Completeness</td>
<td>0.989</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2025 / 1 / 116</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.149</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>R¹ = 0.0554; wR₂ = 0.0926</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R¹ = 0.0679; wR₂ = 0.0959</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.3(13)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.191 and -0.154 eÅ⁻³</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>D-H</th>
<th>d(D-H)</th>
<th>d(H..A)</th>
<th>&lt;DHA</th>
<th>d(D..A)</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>O3-H3</td>
<td>0.840</td>
<td>1.897</td>
<td>169.72</td>
<td>2.728</td>
<td>O4 [ x, y, z+1 ]</td>
</tr>
<tr>
<td>O4-H4A</td>
<td>0.840</td>
<td>1.924</td>
<td>167.70</td>
<td>2.750</td>
<td>O2 [ x-1, y, z ]</td>
</tr>
<tr>
<td>O4-H4A</td>
<td>0.840</td>
<td>2.621</td>
<td>134.98</td>
<td>3.269</td>
<td>O1 [ x-1, y, z ]</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 1. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>8345(3)</td>
<td>8800(1)</td>
<td>9406(2)</td>
<td>31(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>9941(3)</td>
<td>7395(1)</td>
<td>8907(3)</td>
<td>37(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>3756(3)</td>
<td>8476(2)</td>
<td>12861(2)</td>
<td>41(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>3461(3)</td>
<td>8491(1)</td>
<td>7400(2)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>6453(4)</td>
<td>9224(2)</td>
<td>10561(4)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>8566(4)</td>
<td>7873(2)</td>
<td>9808(3)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>6985(4)</td>
<td>7555(2)</td>
<td>11478(4)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>6210(4)</td>
<td>8485(2)</td>
<td>12435(3)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>8376(5)</td>
<td>6859(2)</td>
<td>13253(4)</td>
<td>45(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>4074(5)</td>
<td>9335(2)</td>
<td>8710(4)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>7494(5)</td>
<td>10172(2)</td>
<td>11493(4)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>5845(5)</td>
<td>10676(2)</td>
<td>12916(5)</td>
<td>47(1)</td>
</tr>
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</table>

Table 3. Bond lengths [Å] and angles [°] for 1.

<table>
<thead>
<tr>
<th></th>
<th>Bond lengths</th>
<th>Bond angles</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(2)</td>
<td>1.335(3)</td>
<td></td>
</tr>
<tr>
<td>O(2)-C(2)</td>
<td>1.210(3)</td>
<td></td>
</tr>
<tr>
<td>O(4)-C(6)</td>
<td>1.427(3)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.525(3)</td>
<td></td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.506(3)</td>
<td></td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.527(3)</td>
<td></td>
</tr>
<tr>
<td>C(2)-O(1)-C(1)</td>
<td>111.29(17)</td>
<td>O(1)-C(1)-C(7)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(6)</td>
<td>106.11(16)</td>
<td>C(7)-C(1)-C(6)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(4)</td>
<td>103.15(18)</td>
<td>C(7)-C(1)-C(4)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(4)</td>
<td>113.71(19)</td>
<td>O(2)-C(2)-O(1)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>127.5(2)</td>
<td>O(1)-C(2)-C(3)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(5)</td>
<td>112.2(2)</td>
<td>C(2)-C(3)-C(4)</td>
</tr>
<tr>
<td>C(5)-C(3)-C(4)</td>
<td>115.90(18)</td>
<td>O(3)-C(4)-C(3)</td>
</tr>
<tr>
<td>O(3)-C(4)-C(1)</td>
<td>110.93(18)</td>
<td>C(3)-C(4)-C(1)</td>
</tr>
<tr>
<td>O(4)-C(6)-C(1)</td>
<td>112.0(2)</td>
<td>C(1)-C(7)-C(8)</td>
</tr>
</tbody>
</table>
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]

<table>
<thead>
<tr>
<th>Atom</th>
<th>U11</th>
<th>U22</th>
<th>U33</th>
<th>U23</th>
<th>U13</th>
<th>U12</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>28(1)</td>
<td>40(1)</td>
<td>28(1)</td>
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<td>-5(1)</td>
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<tr>
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<td>-3(1)</td>
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<tr>
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<td>34(1)</td>
<td>71(1)</td>
<td>19(1)</td>
<td>-2(1)</td>
<td>9(1)</td>
<td>-13(1)</td>
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<td>C(1)</td>
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<td>22(1)</td>
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<td>44(1)</td>
<td>19(1)</td>
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<td>-7(1)</td>
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<tr>
<td>C(5)</td>
<td>59(2)</td>
<td>43(2)</td>
<td>31(1)</td>
<td>5(1)</td>
<td>5(1)</td>
<td>-5(1)</td>
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<tr>
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<td>34(1)</td>
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<td>26(1)</td>
<td>5(1)</td>
<td>13(1)</td>
<td>-3(1)</td>
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<tr>
<td>C(7)</td>
<td>38(1)</td>
<td>44(2)</td>
<td>42(1)</td>
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<td>14(1)</td>
<td>-8(1)</td>
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<tr>
<td>C(8)</td>
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<td>39(1)</td>
<td>-6(1)</td>
<td>17(1)</td>
<td>-6(1)</td>
</tr>
</tbody>
</table>

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 1.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(3)</td>
<td>3822</td>
<td>8436</td>
<td>14286</td>
<td>60(8)</td>
</tr>
<tr>
<td>H(4A)</td>
<td>2238</td>
<td>8224</td>
<td>7801</td>
<td>41(7)</td>
</tr>
<tr>
<td>H(3A)</td>
<td>5445</td>
<td>7238</td>
<td>10591</td>
<td>39</td>
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<tr>
<td>H(4)</td>
<td>7423</td>
<td>8644</td>
<td>13891</td>
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<td>H(5A)</td>
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<tr>
<td>H(5B)</td>
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<td>14248</td>
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<td>H(8C)</td>
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<td>13450</td>
<td>71</td>
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</tbody>
</table>
Appendix 2

Publications