Unsaturated Aldols as Useful Substrates in Natural Product Synthesis

Jennifer Peed

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

January 2013

COPYRIGHT

Attention is drawn to the fact that copyright of this thesis rests with its author. A copy of this thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with the author and they must not copy or use it or use material from it except as permitted by law or with the consent of the author.

This thesis may be made available for consultation within the University Library and maybe photocopied or lent to other libraries for the purpose of consultation.

[Signature]  [Date]
Abstract

This thesis focuses on the use of unsaturated aldols as useful substrates in natural product synthesis. Two methodologies have been investigated for the asymmetric synthesis of highly substituted lactones containing multiple contiguous stereocentres from unsaturated aldol precursors. These lactones have potential application as building blocks for natural product synthesis. Firstly, synthetic applications of the retro aldol reaction are reviewed.

The second chapter describes a novel methodology for the asymmetric synthesis of highly substituted δ-lactones from syn-aldol cyclopropanes. Mercury mediated cyclopropane ring-opening of the methyl ester cyclopropanes followed by concomitant cyclisation produced organomercurial δ-lactones, which subsequently undergo reductive demercuration in basic sodium borohydride to afford the highly substituted δ-lactones in good yield and excellent diastereoselectivity. The scope of this method was investigated with variation of the R and R groups. The synthetic utility of this process was also demonstrated with the synthesis of a series of (+)-Prelactone natural products.

Scheme i Novel methodology for the synthesis of highly substituted δ-lactones containing multiple contiguous stereocentres

11 examples
51-94% yield
>95% de
The third chapter describes a method of preparing hydroxy-γ-butyrolactones (viii-x) containing multiple contiguous stereocentres in high yield with good diastereoselectivity. Upjohn dihydroxylation conditions using catalytic osmium tetroxide were employed to β-alkenyl-β-hydroxy-N-acyloxazolidin-2-ones vii with different alkene substitution patterns. This resulted in the formation of triols that underwent spontaneous intramolecular 5-exo-trig cyclisation reactions to afford hydroxy-γ-butyrolactones viii, ix or x depending on the substitution pattern of the alkene precursor.

![Scheme](attachment:image.png)

**Scheme ii** Dihydroxylation/lactonisation method for the asymmetric synthesis of highly substituted hydroxy-γ-butyrolactones

The configurations of the hydroxy-γ-butyrolactones (viii-x) were established using $^1$H NOE spectroscopic analysis and X-ray crystallography. It was found that 1-substituted, 1,1-disubstituted, (E)-1,2-disubstituted, (Z)-1,2-disubstituted, and 1,1,2-trisubstituted alkenes undergo dihydroxylation with anti-diastereoselectivity with respect to their γ-hydroxyl groups, whereas a 1,2,2-trisubstituted alkene gave the syn-diastereoisomer. The poor levels of diastereoselectivity observed for the Upjohn dihydroxylation/lactonisation of 1,2-cis-disubstituted systems was improved using Sharpless asymmetric dihydroxylation conditions. The synthetic utility of this directed dihydroxylation/lactonisation methodology was also demonstrated for the synthesis of 2-Deoxy-γ-ribonolactone.
Contents

1 Literature Review – Synthetic Applications of the Retro Aldol Reaction 1
  1.1 Introduction 1
     1.1.1 Retro Aldol Reactions in Nature 2
     1.1.2 Retro Aldol Reactions for Natural Product Degradation 4
  1.2 Epimerisation 6
  1.3 Reversible Aldol Reactions 10
  1.4 Synthetically Useful Retro Aldol Reactions of Acyclic Aldol Substrates 16
  1.5 Retro Aldol Reactions for the Ring-Opening Monocyclic Systems 22
  1.6 Retro Aldol Reactions for the Ring-Opening of Bicyclic Systems 28
  1.7 Retro Aldol Reactions in Tricyclic Systems 38
  1.8 Aldol-Tishchenko Reactions 46
  1.9 De Mayo Reactions 49
  1.10 Aldolase Enzymes 55
  1.11 Aldolase Antibodies 58
  1.12 Conclusion 64

2 Results and Discussion - Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres 65
  2.1 Introduction 65
  2.2 Synthesis of δ-Lactones with Multiple Contiguous Stereocentres 67
  2.3 Literature Precedent and Previous Work 70
  2.4 The Asymmetric Aldol Reactions 74
     2.4.1 Stereoselectivity in the Aldol Reaction 74
     2.4.2 Asymmetric Synthesis of Unsaturated syn-Aldol Products 78
  2.5 Non-Evans’anti-Aldol 83
  2.6 Directed Cyclopropanation 85
     2.6.1 Stereoselectivity in the Directed Cyclopropanation Reaction 85
     2.6.2 Synthesis of syn-Cyclopropane Products 87
2.7 Removal of the Auxiliary
2.8 Lactonisation via Mercury(II) Mediated Cyclopropane Ring-Opening
2.8.1 Oxymercuration of Methyl Ester Products
2.8.2 Reductive Demercuration of Organomercurial δ-Lactones
2.8.3 Confirmation of Stereochemistry
2.9 Synthesis of Highly Substituted δ-Lactones with a Synthetic Handle
2.10 Synthesis of N-Protected (S,S)-2-Aminomethyl-1-Cyclopropanecarboxylic Acid
2.11 Total Synthesis of (+)-Prelactone B, E and V
2.12 Conclusion

3 Results and Discussion – Dihydroxylation Based Approach for the
Asymmetric Synthesis of Highly Substituted Hydroxy-γ-Butyrolactones
3.1 Introduction
3.2 Dihydroxylation Approaches for the Asymmetric Synthesis of Highly Substituted
Hydroxy-γ-Butyrolactones
3.3 Previous Work and Initial Results
3.4 Asymmetric Synthesis of Unsaturated syn-Aldol Products
3.5 Upjohn Dihydroxylation
3.5.1 Mechanism of Upjohn Dihydroxylation
3.5.2 Synthesis of Highly Substituted Hydroxy-γ-Butyrolactones
3.6 Assignment of Stereochemistry of Hydroxy-γ-Butyrolactones
3.6.1 Literature Examples
3.6.2 Stereochemical Models
3.6.3 $^1$H NOE Spectroscopic Analysis
3.7 Reassignment of Literature Published by Dias and Co-workers
3.8 Improving the Diastereoselectivity – Sharpless Asymmetric Dihydroxylation
3.8.1 Sharpless Asymmetric Dihydroxylation – AD Mix
3.8.2 Sharpless Asymmetric Dihydroxylation – Predicting the Diastereoselectivity
3.8.3 Sharpless Asymmetric Dihydroxylation of 1,2-cis-Disubstituted Aldol 536
3.9 Total Synthesis of 2-Deoxy-D-Ribonolactone
4 Experimental

4.1 Compounds from Chapter 2

4.1.1 Synthesis of N-Acylated-Oxazolidin-2-ones 95, 471-473, 515

4.1.2 Synthesis of syn-Aldol Products 474-481, 517

4.1.3 Synthesis of anti-Aldol Product 483

4.1.4 Synthesis of syn-Cyclopropyl Aldols 493-501, 518

4.1.5 Synthesis of Methyl Esters 506-514

4.1.6 Synthesis of Highly Substituted δ-Lactones 526-532

4.1.7 Synthesis of Compounds for Highly Substituted δ-Lactones with a Synthetic Handle 534-542, 544

4.1.8 Synthesis of Compounds for N-Protected (S,S)-2-Aminomethyl-1-Cyclopropanecarboxylic Acid 545-549

4.1.9 Synthesis of Compounds for (+)-Prelactone B, E and V 550, 554-568

4.2 Compounds from Chapter 3

4.2.1 Synthesis of Non-Commercially Available Aldehydes

4.2.2 Synthesis of syn-Aldol Products 613, 614, 615

4.2.3 Upjohn Dihydroxylation for the Synthesis of Hydroxy-γ-Butyrolactones 632-637

4.2.4 Synthesis of Compounds for 2-Deoxy-D-Ribonolactone 660-663

5 References

6 Appendix

X-Ray Crystal Structure Data for δ-Lactone 527

X-Ray Crystal Structure Data for γ-Lactone 633
Acknowledgements

I would like to thank Dr Steven Bull for giving me the opportunity to work with him over the past four years. I am so grateful for his constant support, guidance, encouragement and humour throughout. I would like to thank him for the freedom to pursue the projects that captured my imagination and for providing me with opportunities to develop other skills outside the lab, and also for all the international conferences I was given the opportunity to attend. Thank you for believing in me and sorry for occasionally being General Peed!

Thanks to Dr John Lowe for all the NMR support, Dr Gabriele Kociok-Köhn for the X-ray crystal structures, Dr Anneke Lubben for mass spectrometry support, Sarah Elkins for giving us solvents with a smile and Dave Elkins for endlessly fixing things in our lab.

Thank you to all Bull and Williams group members past and present who have made the lab such a fun place; Dr Tracy Nixon, Dr Iwan Davies, Dr James Taylor, Dr Paul Fordred, Dr Caroline Evans, Dr Rob Archer, Lucy Peacock, Sarah Abou-Shehada, Rich Blackburn, Ruth Lawrence and Luke Williams. Thanks for making the bad days bearable and the good days exceptional. I have so many good memories of Alphabeat music videos, copious tea drinking, cake clubs, 2 for 1 cocktails and Come Dine with Me’s. Also, thanks to the students who worked so hard on the projects I supervised; Victor Forgerit, Antony Burton, Andrea Schreiner and Amy Groome. I’m sure you will all be extremely successful!

I would particularly like to thank Dr James Taylor and Dr Iwan Davies (Team Borromean Rings!) for supervising me when I was a naïve MChem student. Thanks to Iwan for all his work on the first half of these projects. Thanks to James and Caroline for being my partners in crime and an exceptional sounding board for ideas. And thank you to James for proof reading this beast!

Lastly, thank you to my family (Mum, Dad and Tom) for all of their support and for providing me with an environment in which to pursue any ambition. Thank you to my boyfriend Rob for constantly building my confidence and for all of his encouragement. I’m extremely grateful for this support network and I love you.
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2-DMP</td>
<td>2,2-Dimethoxypropane</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclononane</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>Acetylacetone</td>
</tr>
<tr>
<td>AD</td>
<td>Asymmetric dihydroxylation</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>atm</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1’-Bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethyl ether</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Equiv</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-Propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-red</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyldisilazane</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mol</td>
<td>Mole</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl ether</td>
</tr>
<tr>
<td>MS</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesylate</td>
</tr>
<tr>
<td>MTBD</td>
<td>7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>NCS</td>
<td>N-Chlorosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<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>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>PBS</td>
<td>Sodium perborate</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-Toluene sulphonlic acid</td>
</tr>
<tr>
<td>rac</td>
<td>Racemic</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>$S_{n}2$</td>
<td>Bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>‘Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</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>TMEDA</td>
<td>Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>$\chi_p$</td>
<td>SuperQuat auxiliary</td>
</tr>
</tbody>
</table>
1 Literature Review

Synthetic Applications of the Retro Aldol Reaction

The retro aldol reaction is often viewed as an undesirable pathway, particularly during the asymmetric synthesis of aldol products, and many reports focus on its minimisation.\textsuperscript{1-3} However, there are a number of reported examples demonstrating its synthetic utility. For example, many authors have demonstrated using retro aldol reactions as an impressive technique for constructing complex carbon frameworks found in natural products, through intricate rearrangement reactions. The retro aldol/aldol equilibrium can also be exploited to epimerise stereocentres of aldol products into the thermodynamically favourable product. Catalytic antibodies can make use of retro aldol reactions for the kinetic resolution of racemic mixtures of β-hydroxyketones, and this technique has been applied to the preparation of synthons for several natural product syntheses. There is also great scope for use of the retro aldol reaction in unmasking useful aldehyde and enolate functionality, which can be trapped \textit{in situ} in Wittig reactions and aldol-Tishchenko reactions to afford useful building blocks. This review focuses on the use of the retro aldol reaction as a powerful tool in a diverse range of synthetic applications.

1.1 Introduction

The aldol reaction is an extremely powerful carbon-carbon bond forming process, often generating two new stereocentres with good levels of stereocontrol, and has been used for numerous synthetic applications. Therefore, it may seem unusual to view its reverse process, the retro aldol reaction, as synthetically useful. The position of the aldol/retro aldol equilibrium is dependent on the stability of the enolate as well as the nature of the substituents of the reactants and products. Generally, the more stable the resultant enolate and aldehyde fragmentation products then the more readily the retro aldol reaction proceeds. The retro aldol reaction can be catalysed by acid or base, sometimes using Lewis acidic metal catalysts, or with an enamine/imine mechanism, and can also been thermally initiated (Scheme 1). However, thermal retro aldol reactions often lead to competing formation of the corresponding dehydration product, which limits their usefulness.\textsuperscript{4}
Synthetic Applications of the Retro Aldol Reaction

1.1.1 Retro Aldol Reaction in Nature

The β-hydroxycarbonyl motif is ubiquitous throughout Nature and the retro aldol reaction is found as a key transformation in many biosynthetic pathways. For example, fructose 1,6-bisphosphate is broken down into glyceraldehyde 3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) by an aldolase enzyme during glycolysis. Alternatively, a stereochemically promiscuous aldolase from Sulfolobus solfataricus has been shown to catalyse the retro aldol reaction of both D-2-keto-3-deoxygluconate and D-2-keto-3-deoxy-galactonate to afford pyruvate and D-glyceraldehyde. It is also an important reaction in producing flavours in food, where many desirable flavours are created as thermal retro aldol products of sugars in Maillard reactions and associated degradation reactions. For example, a key component of ginger flavour is formed during a thermal retro aldol reaction of gingerol 1 to produce zingerone 2 during cooking.
Retro aldol reactions of sugars in biomass conversion have also been demonstrated as a potential renewable energy source. For example, Sasaki and co-workers reported in 2002 the use of supercritical water for the retro aldol decomposition of glucose to glyceraldehyde, which has use as a raw material in many industrial processes. The retro aldol decomposition of sugars also has potential in providing useful chiral building blocks from enantiopure d-sugars that are readily available from Nature.

Scheme 2 Thermal retro aldol reaction that occurs during cooking of ginger

Scheme 3 Retro aldol degradation of glucose to afford d-glycolaldehyde, glyceraldehyde and 1,3-dihydroxyacetone
### 1.1.2 Retro Aldol Reactions for Natural Product Degradation

The aldol motif is found in many natural products and therefore the retro aldol reaction has featured heavily in degradation studies of these compounds. Bafilomycins are 16-membered macrolides, which are potent inhibitors of H⁺-ATPases that have potential uses in the treatment of osteoporosis. However, native bafilomycins show acute toxicity in animals. Consequently, Granberg and co-workers used a thermal retro aldol reaction to obtain intermediate 11, which was used as a useful building block for the construction of new biologically active bafilomycin derivatives.

![Scheme 4 Thermal retro aldol cleavage of Bafilomycin C₁ 10 for the synthesis of intermediate 11 that is useful for the synthesis of new bafilomycin analogues](image)

There has also been considerable interest in employing the retro aldol reaction for the degradation of the immunosuppressive antibiotic Rapamycin 12 to prepare fragmentation products for synthetic and biological studies. It has been found that Rapamycin 12 is particularly susceptible to base catalysed retro aldolisation of the aldol fragment identified in Figure 1. Caufield and co-workers were able to isolate some of the degradation products formed from β-elimination and retro aldol reactions of Rapamycin 12 when it was treated with methanolic sodium hydroxide. Danishefsky also treated derivatives of Rapamycin 12 with lithium diisopropylamide to obtain advanced synthetic intermediates via a retro aldol pathway. It was found by Luengo and co-workers that retro aldolisation could be promoted exclusively using the Lewis acid ZnCl₂. In 1999, Holt and co-workers found that a Lewis acidic titanium catalyst could selectively epimerise the stereocentres of the aldol fragment of Rapamycin 12 via action of a reversible retro aldol/aldol equilibration reaction.
Figure 1 Lewis acid or base catalysed retro aldol cleavage of Rapamycin

Ley and co-workers prepared highly functionalised decalin precursor 16 via base catalysed retro aldol reaction of Azadirachtin derivative 13 using sodium methoxide. This intermediate was used for the preparation of further derivatives of this antifeedant and growth disruptor for biological evaluation and as a relay to facilitate its eventual total synthesis in 2007.20-22

Scheme 5 Retro aldol cleavage of a derivative of Azadirachtin

Reagents and conditions: (i) MeI, Ag₂O; (ii) H₂ (1 atm), Pd/C, MeOH, 20 min; (iii) PCC, 4Å MS, CH₂Cl₂, rt, 48 h; (iv) NaOMe, MeOH, rt, 24 h.
Kam and co-workers showed in 1999 that the likely origin of the novel pentacyclic indole alkaloid Danuphylline 22 is via a pathway involving a retro aldol reaction of precursor 17 found in the same leaf extract. It was proposed that the ring-opened alkaloid arises from the methylchanofruticosinate precursor 17 that provides the iminium ion 18, which is hydrolysed to give an unstable carbinolamine 19 that then undergoes a retro aldol type reaction (20) to provide the natural product. A biomimetic semi-synthesis was carried out by extracting the abundant precursor 17 from the leaf, followed by an electrochemical oxidation. The mixture was then subjected to silica gel chromatography, whose acidic nature facilitated the retro aldol reaction of the intermediate compound 19.23

![Scheme 6 Biomimetic synthesis of Danuphylline via retro aldol reaction of an aminol intermediate derived from methylchanofruticosinate 17](image)

1.2 Epimerisation

Retro aldol reactions are often associated with the epimerisation of one or more stereocentres of β-hydroxy-carbonyl fragments in natural products. For example, Appendino and co-workers utilised a retro aldol epimerisation reaction that is typical of the 7-hydroxy group of Baccatin III 23 to reductively trap out the aldehyde group of a key intermediate 25 to afford 28, which was subsequently elaborated into a novel series of Taxol analogues (Scheme 7).24
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) CeCl₃, NaBH₄, MeOH, rt.

Scheme 7 Retro aldol epimerisation of Baccatin III derivatives

Studies by Deprés, Greene and co-workers into the first comprehensive total synthesis of the Bakkane family of natural products serendipitously revealed a crucial retro aldol/aldol epimerisation reaction of the spiro-fused γ-butyrolactone motif in favour of the natural configuration (Scheme 8). Upon exposure of 29 to TBAF, a C-7,C-9 retro aldol/aldol epimerisation reaction took place, transforming the unnatural C-7 configuration into the desired configuration for the natural product (−)-Bakkenolide III 30 in 82% yield. The authors employed this discovery for the synthesis of other spiro-fused γ-butyrolactones of the Bakkane family and postulated that this epimerisation might also occur during the biosynthesis of these natural products in Nature.25
In 2008, Moloney and co-workers showed that bicyclic hydroxypyroglutamate 31 underwent epimerisation via a reversible retro aldol reaction. Under mild basic conditions, 31 epimerised to give the thermodynamically preferred stereochemistry via a sequence of retro aldol/aldol reactions to afford 33 in 80% yield. Alternatively, treatment with Mel/CaCO₃ did not lead to the expected aldehyde product 36, but instead afforded the ring expansion product 35. This is thought to have been formed via hydrolysis of the thioacetal and a retro aldol reaction to afford the ester enolate of α-ketoaldehyde intermediate 34, which ring closes onto the aldehyde group to afford the [4.3.0]-bicyclic ring 35 in 95% yield.

Reagents and conditions: (i) Mel/CaCO₃, CH₃CN-H₂O (5:1), 70 °C, overnight; (ii) NEt₃/THF, 0 °C, 1 h.

Scheme 9 Retro aldol equilibration of hydroxypyroglutamates
In 2006, Kalesse and co-workers developed novel methodology to access four diastereomeric bicyclic [4.3.0] derivatives by a retro aldol reaction and subsequent epimerisation as potential building blocks for natural product synthesis. Unsaturated ester 37 underwent a tandem intramolecular Michael-aldol reaction to selectively provide either the thermodynamic product 38, or the kinetic product 39, depending on the reaction time and temperature. It was found that short exposure of the kinetic product 39 to TBAF at -30 °C initiated a retro aldol reaction to afford 40 in 80% yield. Further treatment of 40 with TBAF at room temperature led to epimerisation α- to the keto group to afford 41 as a single product. However, treatment of thermodynamic product 38 under the same conditions produced a 2.8:1 diastereomeric mixture of 42 and 43, with this mixture subsequently being epimerised to 43 via treatment with TBAF at room temperature.27

Reagents and conditions: (i) TMSCl, HMDS, rt, 6 h, ClCH₂CH₂Cl; (ii) TMSCl, HMDS, -30 °C, 3 h, ClCH₂CH₂Cl; (iii) TBAF (1 equiv), -30 °C, 3 min; (iv) TBAF (3 equiv), 3 h, rt.

Scheme 10 Synthesis of four diastereomeric bicyclic [4.3.0] derivatives via retro aldol reaction
As mentioned previously, epimerisation into the thermodynamically favoured isomer via retro aldol/aldol reaction pathways is sometimes an unexpected and problematic issue associated with natural product synthesis. For example, Hsung and co-workers discovered during their total synthesis of Arisugacin A that an intermediate was undergoing an unexpected retro aldol/aldol epimerisation to afford the undesired stereochemistry. Treatment of 44 under \( \text{K}_2\text{CO}_3/\text{MeOH} \) deacetylation conditions, followed by PCC oxidation led to the undesired retro aldol/aldol epimerisation product 45 in 73\% yield. Using molecular modelling calculations (AM1-Spartan\textsuperscript{TM}) it was found that the cis-fused decalin 45 was in fact more stable than the desired trans-fused decalin 46, presumably due to steric interactions between the axial methyl groups. Therefore, attempts to re-equilibrate the material failed, and the authors had to abandon this synthetic route.\textsuperscript{28-29}

\[
\begin{align*}
\text{44} & \xrightarrow{(i), \ (ii)} \text{45} \\
\text{46}
\end{align*}
\]

Reagents and conditions: (i) \( \text{K}_2\text{CO}_3, \text{MeOH} \); (ii) PCC.

**Scheme 11** Unexpected epimerisation of 44 leading to the undesired stereochemistry of 45

### 1.3 Reversible Aldol Reactions

Carlier and co-workers demonstrated the first example of an enantioselective aldol reaction using lithium ephedrinate as a nucleophile that operates via a retro aldol/aldol pathway to afford enantiomerically enriched products (Scheme 12). Treatment of arylacetonitrile 47 and pivalaldehyde with lithium ephedrinate was shown to afford pure anti-48 in 40\% and 77\% ee. The authors determined that the aldol reaction was reversible by exposing racemic samples of aldol product to the reaction conditions, which resulted in deracemisation. It was proposed that asymmetric induction was induced by the lithium alkoxide of 48 forming mixed aggregate complexes with ephedrine that are diastereomeric and lower in energy than the corresponding mixed aggregate formed from alkoxide complexes of ent-48 with ephedrine.\textsuperscript{30}
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) (-)-Ephedrine (1.1 equiv), \( \text{\textsuperscript{\textdagger}}\text{BuLi} \) (2.2 equiv), 78 °C, 30 min, \( \text{t-BuCHO} \) (1 equiv), 78 °C, 24 h.

Scheme 12 Stereoselective aldol/retro aldol reaction using lithium ephedrinate to induce enantioselectivity

They subsequently demonstrated that thermally controlled HMPA-facilitated aldol/retro aldol reaction could be employed to give syn-selective aldol products 50 from reaction of the lithium enolate of arylacetonitriles 49 with aromatic aldehydes under thermodynamic control, which is opposite to the anti-diastereoselectivity normally observed for aldol products of arylacetonitriles.\(^{31}\)

Reagents and conditions: (i) LDA, -78 °C, THF, HMPA (6 equiv) then ArCHO.

Scheme 13 HMPA promoted aldol/retro aldol reactions to achieve thermodynamic syn-aldol 50

Bolm and co-workers have demonstrated enantioenrichment of an aldol product that crystallises as a homochiral conglomerate, using a combination of crystal growth and iterative retro aldol/aldol reactions to induce enantioselectivity. Solid anti-53 aldol product in an 85:15 enantiomeric ratio was ground with \( \text{ZrO}_2 \) beads in the presence of an achiral or racemic catalyst such as pyrrolidine, piperidine or rac-proline. Samples of the slurry were taken out and
analysed over time, showing that the enantiomeric ratio of the solid 53 changed significantly over time, to a ratio of 96:4 over one day and 98:2 after eleven days. The authors demonstrated that a reversible retro aldol reaction was operating to racemise 53 by introducing cyclohexanone as a co-reactant, which gave 43% of anti-54 after six days.\textsuperscript{32}

\textbf{Scheme 14} Enantioenrichment of conglomerate crystalline aldol product 53

In 2010, Luo, Cheng and co-workers reported the first asymmetric retro aldol reaction catalysed by a simple primary amine as an aldolase antibody mimic of imine/enamine catalysis. This method enables the kinetic resolution of racemic aldol products to access enantiomerically enriched aldols that are difficult to prepare by other methods. The best catalyst was found to be the cyclohexyl diamine 56 in CDCl\textsubscript{3}, with the conversion and enantiomeric excess of the kinetic resolution of \textit{rac}-55 being monitored by NMR and HPLC analysis over time. This revealed that the conversion reached a plateau after 50% and that the retro aldol cleavage reaction barely proceeded after an enantioselectivity of >95% ee was reached, in a nearly ideal resolution process.
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) 56 (20 mol%), CDCl$_3$.

Scheme 15 Kinetic resolution of 55 using a simple chiral primary amine 56

The authors also reported a novel transfer aldol reaction, in which excess acetone 61 was used to trap out the aryl aldehyde 59 generated by the initial retro aldol reaction via a forward aldol reaction, whereby the chiral catalyst 56 also mediates formation of a new enantiomerically pure aldol product 60 with an opposite sense of chiral induction. Use of this trapping approach enabled high enantioselectivities to be achieved for sluggish retro aldol reactions, by preventing the forward aldol reaction of cyclohexanone with an arylaldehyde proceeding, which could potentially lead to a decrease in the overall enantiomeric excess of 57. 33
In 2009, Shibasaki and co-workers developed a dynamic kinetic asymmetric transformation (DYKAT) process for the asymmetric synthesis of α-alkylidene-β-hydroxy esters 66. An (S)-barium-BINOL complex generates dienolate 63 in situ, which can undergo either α- or γ-addition to an aldehyde to afford either α-adduct 65, or the undesired γ-adduct 64. The α-adduct undergoes a highly enantioselective alkene isomerisation reaction to afford the thermodynamically stable α,β-unsaturated aldol 66 in up to 99% ee. A barium promoted retro aldol reaction was shown to be operating to enhance the enantioselectivity of the reaction, resulting in the α-adduct 66 being formed with up to 20:1 selectivity.\textsuperscript{34}
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) Ba(O\textit{i})\textsubscript{2} (10 mol%), (S)-\textit{BINOL} (10 mol%), DME, 0 °C.

Scheme 17 (S)-Ba-BINOL catalysed dynamic kinetic asymmetric transformation involving a retro aldol reaction

Shibasaki and co-workers have also developed a catalytic asymmetric multi-component reaction for the synthesis of highly functionalised δ-lactones containing quaternary chiral centres. The three component system consists of an allenic ester 67, ketone 69 and dialkylzinc 70 in the presence of copper acetate and (R)-DIFLUORPHOS. Initially, conjugate addition of an alkyl group of the chiral copper catalyst to allenic ester 67 forms a highly reactive copper enolate 68, which can undergo either α-addition to the ketone to form the undesired α-adduct 71, or γ-addition to form the target γ-adduct 72. The γ-adduct then undergoes further irreversible cyclisation to afford thermodynamically stable lactone 73. The α-pathway was suppressed by addition of a Lewis base (\textit{Ph}_2\textit{S}=\textit{O}, DMSO or HMPA) and 4Å MS, to facilitate retro aldol reaction of the α-adduct, thus ensuring that this undesired pathway was reversed in a 'proof reading effect', which increased the yields of the target α,β-unsaturated lactones 73.\textsuperscript{35}
1.4 **Synthetically Useful Retro Aldol Reactions of Acyclic Aldol Substrates**

Retro aldol reactions of acyclic aldol systems are not normally that synthetically useful since they result in cleavage into a mixture of structurally less complex enolate and aldehyde products. Retro aldol reactions of stable aldol substrates can be used to generate reactive carbonyl components *in situ*, which can then be incorporated into multi-step pathways. For example, Jha and co-workers have demonstrated a one pot synthesis of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1H-naphtho[2,1-b]pyrans 80 from 2,2-disubstituted-3-hydroxypropanals 74, 2-naphthol 77 and secondary cyclic amines 76. The mechanism of this reaction is thought to involve retro aldol reaction of β-hydroxy-aldehyde 74 to form isobutyraldehyde 81 and formaldehyde 75. A Mannich reaction between the formaldehyde 75, 2-naphthol 77 and a secondary amine 76 then occurs to afford 78, which subsequently deaminates to afford a transient α,β-unsaturated ketone 79 that undergoes a Diels-Alder reaction with enamine 85 (formed from the imine of isobutyraldehyde) to afford naphthopyran 80.36
Another less well explored approach is to generate an aldol product via nucleophilic addition of an oxygen nucleophile to a Michael acceptor, whose retro aldol cleavage is then employed to trigger a cyclisation event. For example, Razdan and co-workers have described a one pot synthesis of 2,4,6-triarylpyridines 90 from benzylideneacetophenones 86 using Bi(III) nitrate-Al₂O₃. Formally, Michael addition of a catalytic metal alkoxide species to benzylideneacetophenone 86 results in an enolate species that undergoes conjugate addition to another equivalent of 86. Intermolecular imine formation with urea 87 then affords 88, which undergoes a retro aldol cleavage-cyclisation event to afford 89 that subsequently aromatises to afford pyridine 90.³⁷
A potentially useful application of the retro aldol reaction is to employ a metal alkoxide of an aldol product that fragments to afford a metal enolate that is difficult to prepare via traditional metalation of the parent carbonyl compound. Yorimitsu and co-workers have reported the rhodium catalysed retro aldol reaction of tertiary \( \beta \)-hydroxyketones \( 91 \) to generate rhodium enolates \( 93 \), which could be used in situ for regioselective aldol reactions with an aldehyde to afford \( 92 \) in high yield. Unfortunately, the diastereoselectivity of the resultant aldol reactions of these rhodium enolates with aldehydes were poor, although these were not reported.\(^{35}\)

---

Reagents and conditions: (i) \( \text{Bi(NO}_3\text{)}_3 \cdot \text{Al}_2\text{O}_3 \) (5\% \( \text{w/w} \)), 125-135 \degree C.

Scheme 20 A retro aldol reaction facilitates the solid supported catalytic synthesis of 2,4,6-triarylpyridines \( 90 \)
Bull and co-workers have developed ‘temporary stereocentre’ methodology for the asymmetric synthesis of chiral aldehydes using the SuperQuat oxazolidin-2-one to relay stereocontrol. For example, a novel three step aldol/cyclopropanation/retro aldol sequence was developed to produce enantiopure chiral cyclopropyl-carboxaldehydes in >95% ee. The asymmetric boron aldol reaction of N-acyl-oxazolidin-2-one 95 with α,β-unsaturated aldehyde 96 proceeds with excellent diastereoselectively producing β-vinyl-syn-aldol products 97. A subsequent asymmetric syn-cyclopropanation reaction, directed by the β-hydroxyl group of the aldol product, furnishes cyclopropyl-aldols 98 in >95% dr. Subsequent treatment of cyclopropyl-aldol 98 then with LiHMDS at 0 °C initiates a retro aldol reaction, to afford enantiopure carboxaldehydes 99 in excellent yield and diastereoselectivity. This methodology has been used to prepare chiral cyclopropyl-carboxaldehydes of use as synthons for natural product synthesis, such as in the synthesis of Cascarillic acid.39-42
This ‘temporary stereocentre’ methodology has also been utilised for the stereodivergent synthesis of either enantiomer of \( \alpha \)-methyloctanal using an asymmetric hydrogenation procedure. Aldol products 101 and 105 were synthesised using the Evans’ antii-aldol protocol from reaction of \( N \)-acyl-oxazolidin-2-one 95 with 2-methyleneoctanal 100 and (\( E \))-2-methyloct-2-enal 104 respectively. The best conditions for the substrate directed asymmetric hydrogenation were found to be the use of Wilkinson’s catalyst for aldol 101, which produced saturated aldol \( (4S)\)-102 in 96% de. Aldol 102 underwent asymmetric hydrogenation using Brown’s catalyst to afford saturated aldol \( (4R)\)-102 in a slightly lower 85% de, which was purified to >95% de. Retro aldol reactions of aldols \( (4S)\)-102 and \( (4R)\)-102 with LiHMDS in toluene afforded \( (S)\)-\( \alpha \)-methyloctanal \( (S)\)-103 and \( (R)\)-\( \alpha \)-methyloctanal \( (R)\)-103 respectively in >95% ee. Unfortunately, purification of these aldehydes on silica caused racemisation, decreasing the enantiomeric excess to 85%. Therefore, it was shown that \( \alpha \)-methyloctanal 103 could be derivatised \textit{in situ} to afford dithiane and Wittig products as well as reduction to \( \alpha \)-methyloctanol with no racemisation, which function as useful chiral building blocks.\(^{41}\)
Synthetic Applications of the Retro Aldol Reaction

Scheme 23 Temporary stereocentre approach for the synthesis of both enantiomers of α-methyloctanal (S)-103 and (R)-103

Reagents and conditions: (i) MgCl₂, NEt₃, TMSCl, EtOAc, rt, 24 h then TFA, MeOH; (ii) Wilkinson's catalyst (17.5 mol%), H₂ (5 bar), CH₂Cl₂; (iii) Brown's catalyst (17.5 mol%), H₂ (5 bar), CH₂Cl₂; (iv) LiHMDS, toluene, 0 °C.
1.5 Retro Aldol Reactions for the Ring-Opening Monocyclic Systems

In 2009, Taylor and co-workers described a number of novel cascade sequences initiated by a retro aldol reaction to afford a range of novel functionalised cyclopentanes. Treatment of 2,2-di(carboethoxy)cyclopentanol 106 with MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) in the presence of Wittig or aza-Wittig reagents resulted in one pot retro aldol/Wittig/intramolecular Michael addition reactions to afford cyclopentanes 109 in good yield. Therefore, retro aldol reaction of 106 affords 107, followed by Wittig trapping of the resulting aldehyde, to afford intermediate 108 that undergoes an intramolecular nucleophilic addition reaction to afford the final cyclopentane product 109.43

Hayashi and co-workers have developed a high yielding synthesis of the antiviral (-)-Oseltamivir 119 (Tamiflu) using two ‘one pot’ reaction sequences. The first of the reaction sequences involved the organocatalysed Michael reaction of 110 with 111 to afford an intermediate 112 that underwent reaction with the Horner-Wadsworth-Emmons reagent 113 in situ to afford a mixture of cyclohexyl products 114, 115 and 116. It was found that addition of the more polar solvent ethanol resulted in retro Michael reaction of 115, and tandem retro aldol/Horner-Wadsworth-Emmons reaction of 114 to afford a better yield for the desired cyclohexene 117. A second one pot reaction on 118 was then carried out involving six reactions to afford (-)-Oseltamivir 119 as a single diastereomer in 74% yield.44

Reagents and conditions: (i) Ph3P=X, MTBD, MeCN, heat, 16-22 h.

Scheme 24 Retro aldol/Wittig/intramolecular Michael addition cascade reaction to afford 109
Reagents and conditions: (i) (R)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine, ClCH$_2$CO$_2$H (20 mol%), toluene, rt, 6 h; (ii) 113, toluene, 0 °C to rt, 4 h; (iii) EtOH, rt, 10 min; (iv) TolSH, -15 °C, 36 h.

Scheme 25 Domino retro aldol/Horner-Wadsworth-Emmons reaction for a one pot synthesis of (-)-Oseltamivir 119

Funk and co-workers have employed a retro aldol cleavage reaction to remove the chiral auxiliary fragment of cyclopentenone 122 for the asymmetric synthesis of cycloalkanones 123.
The (-)-menthone auxiliary was first treated with alkenyllithium reagent 121, followed by hydrolysis of the acetonide fragment, to afford C-1 substituted menthol derivative 122. These substrates then underwent stereoselective conjugate addition reactions with cuprate reagents, which upon quenching with methanol resulted in the chiral auxiliary fragment undergoing facile retro aldol cleavage to afford \( \beta \)-alkylcycloalkanones 123 in high yield and good ee.\(^{45}\)

\[
\text{Scheme 26} \quad \text{Retro aldol reaction removes the } (-) \text{-menthone auxiliary fragment of cyclopentenone 122}
\]

Takai and co-workers have developed a transition metal-catalysed synthesis of multisubstituted aromatic compounds that features a key retro aldol cleavage as part of its mechanism. Rhenium catalysed reaction between \( \beta \)-keto ester 124 and alkyne 125 results in formation of 2-pyranone 126, which can undergo Diels-Alder reaction with another alkyne 125 followed by loss of carbon dioxide, resulting in aromatisation to afford multi-substituted aromatic compounds 127 in high yield and regioselectivity.

\[
\text{Reagents and conditions: (i) } [\text{ReBr(CO)}_3(\text{THF})_2]_2 (2.5 \text{ mol\%}), 4\text{Å MS}, (200 \text{ wt. } \% \text{-Re cat.}), \text{toluene, } 180°C, 24 \text{ h}; (ii) \text{Alkyne 125, } 150°C, 24 \text{ h.}
\]

\[
\text{Scheme 27} \quad \text{Reaction conditions for the formation of multi-substituted aromatics}
\]
In the first step reaction, rhenium activated alkyne 125 undergoes a cycloaddition with enol 128 to afford rhenium pentacycle 129. Retro aldol cleavage of this intermediate occurs to cleave the ring system and produce the vinyl rhenium species 130, which then undergoes reductive elimination to form the α,β-unsaturated carbonyl functionality of 131 followed by ring closure to give 2-pyranone 126.\textsuperscript{46}

![Diagram of the reaction mechanism]

Scheme 28 Proposed mechanism for the synthesis of pyranone intermediate 126

Reiser and co-workers have demonstrated a tin catalysed retro aldol reaction of cyclopropane 136 as part of their total synthesis of (-)-Roccellaric acid 137. Furan 132 underwent asymmetric cyclopropanation to afford 133, which was subsequently subjected to ozonolysis and nucleophilic allylation to afford 134. The crude allyl product 134 was treated \textit{in situ} with a tin(IV) catalyst, promoting a key retro aldol reaction (135) and subsequent lactonisation to furnish lactone 136 in 72% yield with a 95:5 \textit{anti/syn} ratio. This intermediate was then used as a precursor to synthesise (-)-Roccellaric acid 137 in a further five steps.\textsuperscript{47}
Reagents and conditions: (i) Ethyl diazoacetate, Cu(OTf)$_2$ (2 mol%), (−)-(S,S)- bis(4-tert-butyloxazoline), PhNHNH$_2$, CH$_2$Cl$_2$; (ii) O$_3$, CH$_2$Cl$_2$, −78 °C then Me$_2$S; (iii) BF$_3$·OEt$_2$, −78 °C then allyltrimethylsilane; (iv) [Sn$_3$(Bu)$_4$(NCS)$_2$O]$_2$ (0.05 mol%), 1,2-ethyleneglycol, benzene, reflux.

Scheme 29 Key retro aldol reaction used in the total synthesis of (−)-Roccellaric acid 137

Reiser and co-workers also developed a diastereoselective method for the synthesis of highly substituted γ-butyrolactones 141 using aryl titanium reagents. Cyclopropanecarboxaldehyde 138 was treated with various aryl titanium reagents to generate intermediate 139, which was treated in situ with a tin catalyst 142-144 to initiate a one pot retro aldol-acetalisation-lactonisation sequence to afford cis- or trans- γ-aryl lactone acetals 141.
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) $\text{BF}_3\cdot\text{OEt}_2$, THF, $-78\, ^\circ\text{C}$, 16 h; (ii) Catalyst $142-144$ (10 mol%), MeOH, reflux, 12 h.

Scheme 30 Synthesis of $\gamma$-butyrolactones via tin mediated retro aldol reaction of 139

In 1991, Kuwajima and co-workers reported a tin(IV) chloride mediated retro aldol reaction of 2-alkoxycyclopropyl carbonyl compounds $145$ to generate a three carbon 1,3-zwitterion $147$, which underwent formal [3+2]-cycloaddition reactions with enol silyl ethers $148$ to afford highly functionalised cyclopentanes $150$ in good yield, but with relatively poor diastereoselectivity. $^{49}$
1.6 Retro Aldol Reactions for the Ring Opening of Bicyclic Systems

Bicyclic ring systems that undergo ring-strain promoted retro aldol rearrangements offer an attractive route into chiral building blocks for natural product synthesis that are difficult to access using more conventional methodology. Ogasawara and co-workers have employed a bicyclo[3.2.1]octane chiral building block 152 that undergoes an acid catalysed retro aldol reaction to afford hexahydrophenanthrene frameworks. These structures comprise the backbone of many alkaloid and diterpenoid natural products, and the synthetic utility of this methodology has been demonstrated for the total synthesis of (+)-Ferruginol 160. In this case, chiral building block 152 was first prepared from norbornane-2,5-dione 151 via an enzymatic resolution procedure. Treatment of bicyclo[3.2.1]octane 152 with catalytic p-TSA and ethylene glycol in toluene at reflux initiated an acid catalysed retro aldol reaction, in which the MOM group was deprotected followed by hemi-ketalisation with ethylene glycol to afford active intermediate 154. This intermediate 154 then undergoes a retro aldol reaction to produce intermediate 155, followed by an intramolecular tandem Friedel-Crafts alkylation of 156 and elimination/rearomatisation to afford hexahydrophenanthrene 159 in quantitative yield and high enantioselectivity.50
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) (CH₂OH)_₂, p-TSA (cat), toluene, reflux.

Scheme 32 Synthesis of hexahydrophenanthrene 159 via retro aldol reaction of bicyclo[3.2.1]octenone 152.
Yamada and co-workers have developed a fragmentation method employing a bicyclo[2.2.1]heptane derivative 163, which undergoes a retro aldol reaction to afford a tetrasubstituted cyclopentane derivative 165. Initially, bicyclo[2.2.1]heptane 163 was prepared from cyclopentanone 161 and chiral ester 162 via a double Michael addition in 5.3:1 dr and 82% yield. This intermediate underwent several protecting and functional group manipulations to afford bicyclic β-hydroxyketone 164. Treatment of 164 with sodium hydride and 15-crown-5 in toluene at room temperature resulted in retro aldol cleavage to furnish the desired tetrasubstituted cyclopentane derivative 165, which was subsequently used as a synthon for the total synthesis of dollabellane marine diterpenoids Claenone 166, Palominol 167 and Dolabellatrienone 168.\textsuperscript{51-52}

![Scheme 33 Retro aldol cleavage of bicyclic β-hydroxyketone 164](image_url)

*Reagents and conditions: (i) LDA, THF, -78 °C then 162; (ii) NaH, 15-crown-5, toluene, rt.*
Yamada and co-workers have also used this type of fragmentation chemistry for the total synthesis of the marine diterpenoid Stolonidiol 175. Bicyclic β-hydroxyketone 173 was treated with K₂CO₃ in methanol at 40 °C, which initiated the retro aldol rearrangement as well as epimerising the C-12 stereocentre to afford tetrasubstituted cyclopentane 174 in 92% yield.⁵³

$$\begin{array}{c}
\text{169} + \text{170} \xrightarrow{(i)} \text{171} + \text{172} \\
1:7.5 \text{171:172}
\end{array}$$

Reagents and conditions: (i) LDA, THF, -78 °C then 170 to rt; (ii) K₂CO₃, MeOH, 40 °C.

Scheme 34 Retro aldol reaction of bicyclic β-hydroxyketone 173 in the total synthesis of Stolonidiol 175

In 2009, Rueping and co-workers demonstrated a novel tandem retro aldol/cyclisation reaction to afford a tetrahydrochromenone product 182 in 96% ee and 68% yield. An asymmetric organocatalytic domino Michael/aldol reaction of diketone 176 and enone 177 was employed to afford bicyclo[3.2.1]octane-6-carbaldehyde 179 in 96% ee. Treatment of this β-hydroxyketone 179 with base led to the diketone 181, which cyclised in situ to afford hemiacetal 182 in 96% ee, dr 6:1 and 68% yield.⁵⁴
Reagents and conditions: (i) 178 (10 mol%), EtOH, rt, 7-24 h; (ii) K$_2$CO$_3$, MeOH.

Scheme 35 Novel retro aldol reaction to form tetrahydrochromenones 182

Tam and co-workers have reported molybdenum-mediated cleavage of bicyclic isoxazoline rings to afford substituted cyclopentane ring systems (189, 192, 195). The isoxazole rings (186, 188, 193) were prepared by 1,3-dipolar cycloaddition of nitrile oxide 184 and norbornadiene 185. It was proposed that the nitrogen atom of the isoxazoline ring (188 and 193) coordinates to the molybdenum 190, facilitating N-O bond cleavage. This forms a molybdenum complex (191 and 194) that undergoes retro aldol cleavage, which upon hydrolysis provided the final cyclic products (189, 192, 195) in moderate to good yield with varying levels of stereoselectivity.
Scheme 36 Formation of ring attached systems via two cleavage reactions

Reagents and conditions: (i) (Boc)$_2$O, DMAP, toluene, 25 °C; (ii) Mo(CO)$_6$, MeCN/H$_2$O, 80 °C.
Gelmi and co-workers have developed a new synthetic approach to diastereomeric cyclopentene derivatives 203 and 204 arising from retro aldol reaction of functionalised spirocyclic norbornene derivatives exo-198. Spiro oxazolone exo-198 was treated with the Lewis acid bis-(dibutylchlorotin)oxide in ethanol at reflux to afford ethyl ester exo-199 in 85% yield. Under mild basic conditions, ethyl ester exo-199 undergoes alcoholysis and retro aldol-like cleavage (200) to give enolate 201, which was protonated to provide 202 as a 1:1 mixture of diastereomers. This mixture then undergoes double bond isomerisation to afford the more thermodynamically stable cyclopentene diastereomers 203 and 204 in a 1:1 ratio and 82% yield. Interestingly, the cyclopentene derivatives 203 and 204 could be accessed directly from spiro oxazolone exo-199 via reflux in methanol with sodium carbonate.56

\[ \text{Reagents and conditions: (i) Mg(ClO}_4\text{)}_2, \text{CH}_2\text{Cl}_2, 25 \, ^{\circ}\text{C; (ii) EtOH, (Bu}_2\text{ClSn})_2\text{O, reflux; (iii) EtOH, Na}_2\text{CO}_3, \text{reflux; (iv) MeOH, Na}_2\text{CO}_3, \text{reflux.}} \]

**Scheme 37** Retro aldol reaction to form cyclopentenes
Robina and co-workers have developed methodology that employs the ring strain of bicyclic systems to trigger retro aldol-like reactions of bridgehead substituted bicyclo[2.2.1]-azaheptanes. Racemic and enantiomerically pure N-Boc-3-tosyl-7-azabicyclo[2.2.1]hept-5-en-2-ols 205, 208 and 210 were treated with base to afford pyrrolidine 207, 209 and 211 in excellent yields. However, attempts to repeat this retro aldol reaction using O- and CH₂-analogues at the N-Boc position were unsuccessful, which was proposed to be due to insufficient ring strain being present in these bicyclic derivatives.\(^{57}\)

\[
\begin{align*}
\text{205} & \xrightarrow{(i)} \text{206} & \text{rac-207, (+)-207 and (-)-207} \\
\text{205} & \xrightarrow{(ii)} \text{208} & 82\% \text{ yield} \\
\text{205} & \xrightarrow{(iii)} \text{210} & 76\% \text{ yield} \\
\end{align*}
\]

Reagents and conditions: (i) NaOMe (cat), MeOH, rt; (ii) H₂, Pd/C, MeOH; (iii) 1. OsO₄ (cat), NMO, acetone-H₂O (9:1); 2. 2,2-DMP, p-TSA, acetone.

Scheme 38 Retro aldol cleavage of N-Boc-3-tosyl-7-azabicyclo[2.2.1]hept-5-en-2-ols 205, 208 and 210

Totah and co-workers demonstrated a tandem retro aldol-epoxide ring opening-cyclisation sequence for the formation of the tricyclic core 215 of Phomactin A 216 in 95% yield. In this
case, O-TBS deprotection of 212 triggers a retro aldol reaction that eliminates acetaldehyde to afford unstable epoxide 213 that is ring opened to generate the hemiacetal functionality of 215. This methodology was highly stereoselective, resulting in an impressive installation of three out of the five possible stereocentres required.58

Reagents and conditions: (i) TBAF.

Scheme 39 Synthesis of a tricyclic core 215 found in Phomactin A 216

Helquist and co-workers reported the formation of γ-substituted conjugated hydrazulenones 221 via rearrangement reaction of cyclopropylcarbinol 217 to afford the unstable β-hydroxyketone 218, which then undergoes a spontaneous retro aldol cleavage reaction to afford 220 followed by an aldol condensation reaction to afford 221. The authors found that retro aldol reaction of 218 only proceeds when R is larger than Me, presumably due to steric effects triggering the retro aldol fragmentation reaction.59
Jung and co-workers reported formation of a bridged bicyclic furan 227 by rearrangement of tetrahydroxydecalinone 222 under mild acidic or basic conditions in 95% yield. Therefore, anionic retro aldol fragmentation of the aldol fragment of 223 occurs to give enolate 224, which eliminates a β-hydroxyl group to give the α,β-unsaturated ketone group of 225. Subsequent hemi-acetal formation followed by dehydration/aromatisation then affords the furan ring of 227, as part of the total synthesis of Arisugacin A. It is thought that the key retro aldol fragmentation reaction of 223 is promoted due to relief of steric hindrance caused by its three axial methyl groups. \(^6\)

---

**Scheme 40** Rearrangement of 217 followed by retro aldol/aldol to afford 221

**Scheme 41** Unexpected formation of bridged bicyclic furan 227 from rearrangement of tetrahydroxydecalinone
1.7 Retro Aldol Reactions in Tricyclic Systems

Ogasawara and co-workers have applied Yamada’s retro aldol Friedel Crafts alkylation/dehydration/aromatisation methodology for the total synthesis of (-)-Morphine\textsuperscript{61} as well as other natural products\textsuperscript{62-65} containing hexahydrophenanthrene frameworks containing quaternary or tertiary benzylic stereocentres.

\[ \text{Reagents and conditions: (i) } (\text{CH}_3\text{OH})_2, \text{ p-TSA (cat), benzene, reflux.} \]

\textbf{Scheme 42} A retro aldol cleavage reaction employed as a key transformation for the synthesis of Morphine 236.
This type of skeletal rearrangement protocol has also been used by Yamada and co-workers for the synthesis of the bicyclo[4.2.1]nonane fragment of the marine natural products Mediterraneols such as 244. In this case, the tricyclic intermediate 242 was treated with DBU in benzene to afford the desired bicyclo[4.2.1]nonane fragment 243 in 53% yield.66

Reagents and conditions: (i) LDA, THF, -78 °C then 238; (ii) DBU, benzene, rt.

Scheme 43 Retro aldol cleavage of the cyclic ring system of 242 for the synthesis of bicyclo[4.2.1]nonane fragment of Mediterraneols such as 243

Yamada and co-workers also used this rearrangement chemistry for the synthesis of bicyclo[4.3.0]nonane derivative 249 as a synthon for preparing the CD ring moiety of a series of 12-oxygenated steroids, the Aragusterols. The authors found that the key retro aldol reaction of 248 could be triggered using a mixture of ZnCl₂, NEt₃ and TMSCl, or NaH and
crown-5-ether, to afford 249 and 250 after hydrolysis as a 2:1 ratio of β:α epimers at the C-8 centre.\(^{67}\)

Scheme 44 Retro aldol cleavage of tricyclic ring 248 for the synthesis of bicyclo[4.3.0]nonane ring system of Aragusterols

Reagents and conditions: (i) LDA then 246; (ii) TMSCI, ZnCl\(_2\), NEt\(_3\), 110 \(^\circ\)C; (iii) AcOH-THF-H\(_2\)O (2:1:1).

Ranu and co-workers demonstrated that acid catalysed rearrangements of α-hydroxycyclobutane derivatives 253 give transient cyclic β-hydroxyaldehydes 258 that undergo retro aldol cleavage to afford [5.3.0] ring systems 254 followed by subsequent Jones’ oxidation to afford 255 in 77% yield. Several six and seven membered ring systems were synthesised in this manner as potential cyclic synthons for the synthesis of a range of natural product skeletons, such as Grayanotoxin I 259 and Dolatriol 260.\(^{68-69}\)
Reagents and conditions: (i) 1,3-dithiane, n-BuLi, THF; (ii) HgO (red), HBF₄, THF; (iii) Jones’ reagent.

Scheme 45 Retro aldol reaction for the synthesis of functionalised six and seven membered bicyclic ring systems

In 2000, da Silva and co-workers demonstrated the synthesis of bicyclo[6.2.1]undecane 264 from retro aldol reaction of the tricyclic intermediate 261, which is the bicyclic core found in the furanoheliangolide class of sesquiterpene natural products such as Goyazensolide 265. In this case, a retro aldol reaction was used to cleave the trans-annular bond to give the desired [6.2.1] ring system.⁷⁰
Synthetic Applications of the Retro Aldol Reaction

In 2010, Danishefsky and co-workers reported an elegant total synthesis of the steroidal natural product Aplykurodinone-1 271, involving a tandem hydrolysis/retro aldol/iodo-lactonisation sequence. They described this approach as a ‘traceless stereochemical guide’ that was used to secure the correct configurational relationship between the C-3 and C-7 stereocentres of 271. Treatment of 268 with base resulted in lactone hydrolysis to afford a β-hydroxyketone fragment that underwent retro aldol elimination of formaldehyde to afford acid 269 that then underwent an intramolecular iodo-lactonisation reaction to afford tricyclic lactone 270 in 75% yield.71

Reagents and conditions: (i) NaH, toluene, reflux.

Scheme 46 Formation of the bicyclic core 264 of furanoheliangolide sesquiterpenes via retro aldol reaction of 261
Wang and co-workers have developed a gold-catalysed cascade reaction of propargylic esters tethered to cyclohexadienones. Mechanistically, the propargylic ester 272 undergoes a cascade of multiple bond rearrangement reactions to afford tricyclic ketone 273 in good yield. However, in the presence of water, oxy-Michael addition of water is followed by retro aldol-like reaction of 276, to afford ring-opened products 277 in high yield, which are common structural motifs of many natural products.\textsuperscript{72}
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) [PPh₃AuCl]/AgOTf (0.04 equiv/0.04 equiv), DCE, air, rt, 8-12 h.

Scheme 48 Gold catalysed cascade reaction of propargylic esters 272 with retro aldol collapse of 276

In 2012, Porco Jr. and co-workers completed the first total synthesis of 7-epi-nemorosone, which involved use of a key cerium mediated retro aldol/vinyl Grignard reaction on triketone 280 for construction of the densely functionalised skeleton of the natural product to afford orthogonally protected 284 in 45% yield over three steps.⁷³
Reagents and conditions: (i) LiHMDS (2 equiv), THF, 0 °C to rt then conc. HCl (8 equiv), THF, 0 °C to rt; (ii) CeCl₃ (2.5 equiv), vinylmagnesium bromide (2.5 equiv), THF, -78 °C to -30 °C; (iii) Piv₂O/pyridine, DMAP (0.03 equiv), 0 °C to rt; (iv) DMAP, Ac₂O, NEt₃, CH₂Cl₂, 0 °C.

**Scheme 49** Tandem retro aldol/vinyl Grignard addition reaction for the synthesis of bridged-[3.3.1] ring system of 285
1.8 Aldol-Tishchenko Reactions

In 2000, Nevalainen reported the first catalytic aldol-transfer reaction using aluminium enolates generated from the retro aldol reaction of diacetone alcohol 286, with the resultant aluminium enolate 291 reacting in situ with an aldehyde 287 to afford β-hydroxyketone 288 in moderate yield. 74

[Chemical structures and reaction scheme]

Reagents and conditions: (i) Al(III) catalyst (5-10 mol%), CH₂Cl₂, rt.

Scheme 50 Retro aldol/aldol transfer mechanism via aluminium enolates

In 2001, Schneider and co-workers developed a zirconium alkoxide catalysed aldol-Tishchenko reaction using ketone aldols as an enolate equivalent to furnish 1,3-anti-diol monoesters 296. This methodology was also independently established by Nevalainen in 2001 using trimethylaluminium alkoxides 75 and was developed further in 2003 using alternative aluminium catalysts. 76 The thermodynamically less stable ketol 294 undergoes a rapid and facile retro aldol reaction to afford zirconium enolates 299 in situ. These enolates can then undergo an aldol-Tishchenko reaction with aldehyde 295 to afford 1,3-anti-diol monoesters 296 in high yield. The best conditions were found to be the use of zirconium catalyst 298 in
Synthetic Applications of the Retro Aldol Reaction

dichloromethane at 0 °C, which resulted in suppression of formation of any undesired acyl migration product 297.

Reagents and conditions: (i) 298 (10 mol%), CH₂Cl₂, 0 °C, 3 h.

Scheme 51 Generation of zirconium enolates 299 through retro aldol reaction of 294 mediates aldol-Tishchenko reaction

Mahrwald and co-workers also observed a retro aldol/aldol equilibrium during their investigations on a titanium catalysed aldol-Tishchenko reaction with enolizable aldehydes. They found that their reactions gave diol 304 regardless of whether the syn-aldol 300 or anti-aldol 301 diastereomers were used as a substrate. Treatment of syn- or anti-β-hydroxyketone 300-301 or 302-303 with (R)-BINOL(Ti(OTBu)₂)/cinchonine in the presence of isobutyraldehyde followed by base hydrolysis afforded syn-anti-product 304 or 305 in high enantioselectivity in each case. The reactions were monitored to reveal that the Tishchenko reaction of anti-301 was complete within three to four days, with almost no detection of any retro aldol/aldol equilibration having occurred. However, when syn-300 was employed, after 24 hours the Tishchenko reaction had not proceeded, with only retro aldol/aldol equilibration to the anti-301 being observed. Only after six to seven days was the Tishchenko reaction complete, with comparable yields and enantioselectivities of 304 with those using anti-301. The authors explained these differences in reactivity using transition state models 308 and 311. When R =
Et, iPr, the 1,3-diaxial interactions between R² and R³ are large enough (308) for the Tishchenko reaction of syn-306 to be unfavourable, making this process slow. A fast, reversible retro aldol/aldol reaction interconverts syn-306 to anti-309, whose transition state 311 does not have these unfavourable 1,3-diaxial interactions, and the Tishchenko reaction therefore proceeds rapidly and irreversibly. The authors also found that when R = Me, the 1,3-diaxial interactions were not as severe, and the Tishchenko reaction of the syn-aldol proceeded, without the need for retro aldol/aldol equilibration to occur.⁸⁰

Reagents and conditions: (i) iPr-CHO, (R)-BINOLTi(OᵗBu)₂/cinchonine then OH.

Scheme 52 Retro aldol equilibrium for titanium catalysed asymmetric aldol-Tishchenko reaction
1.9 De Mayo Reactions

The de Mayo reaction was first demonstrated in 1971 by Paul de Mayo, involving photochemical [2+2] cycloaddition between an enol 313 and an alkene 314, to afford a cyclobutanol 315 which is often then followed by spontaneous retro aldol collapse to generate a 1,5-diketone 316.

![Scheme 53 General de Mayo photocycloaddition followed by spontaneous retro aldol reaction](image)

The de Mayo reaction has recently been reviewed by Yong-Jin Wu in 2010, where numerous examples can be found that detail its synthetic utility. Winkler and co-workers have also reviewed applications of the de Mayo reaction for the synthesis of natural products for the period prior to 1995. Therefore, only selected highlights of this methodology with respect to retro aldol fragmentation are reviewed in this section.

In 1967, Wiesner and co-workers used a modified de Mayo procedure in their total synthesis of 12-epi-lycopodine. Precursor 317 underwent intramolecular photocycloaddition to afford 318 in 70% yield. The ketone group was acetal protected, followed by epoxidation of the exocyclic alkene and subsequent reduction to afford tertiary alcohol 319 in 96% yield. Acid mediated deprotection of ketal 319 led to a retro aldol reaction (320) to afford 321 in 47% yield. This intermediate subsequently underwent an intramolecular aldol reaction to afford a new aldol product 322 that was then converted in four steps to furnish 12-epi-lycopodine 323.
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) hν, THF, -70 °C; (ii) 1. (CH$_2$OH)$_2$, p-TSA (cat), benzene, reflux; 2. mCPBA (1.5 equiv), NaHCO$_3$ (1.5 equiv), CHCl$_3$; 3. LiBH$_4$, THF, reflux; (iii) HCl THF-H$_2$O, 45 min; (iv) NaOH (0.6% in H$_2$O), MeOH, 36 h.

Scheme 54 Total synthesis of 12-epi-Lycopodine 323 via a modified de Mayo photocycloaddition-retro aldol sequence

In 1978, Oppolzer and co-workers demonstrated a total synthesis of Longifolene 329 using a de Mayo fragmentation strategy. 1,3-Diketone 324 was converted into a benzyloxy carbonyl derivative 325, which was then irradiated to trigger an intramolecular de Mayo reaction to afford 326 as a 2:3 mixture of stereoisomers. Hydrogenolysis of the benzyl protecting group initiated a clean retro aldol cleavage reaction (327) to afford 1,5-diketone 328 in 83% yield, which was converted in four more steps into Longifolene 329. This methodology was also employed in the total synthesis of Sativene 330.
Reagents and conditions: (i) Benzoyloxychloroformate (2.7 equiv), pyridine, 5 °C, 8 h; (ii) hv, cyclohexane, pyrex, 15-30 °C; (iii) H₂ (3atm) Pd/C (10 mol%), HOAc, 25 °C.

Scheme 55 Retro aldol reaction resulting in ring expansion product for the total synthesis of Longifolene

In 1983, Pattenden and co-workers reported a total synthesis of Δ^8(9)-Capnellene 334 using a de Mayo reaction. The precursor 331 was irradiated to afford a tricyclic adduct, which was then bis-alkylated via treatment with LiHMDS and methyl iodide to afford geminal dimethyl adduct 332. This intermediate then underwent retro aldol fragmentation under basic conditions to furnish the ring expanded product 333 in 36% yield, which was then elaborated further to afford Δ^8(9)-Capnellene 334.

Reagents and conditions: (i) hv, hexane, 6 h, rt; (ii) LiHMDS, Mel, THF, -70 °C, 3.5 h; (iii) KOH, DMSO-H₂O.

Scheme 56 Total synthesis of Δ^8(9)-Capnellene 334 using de Mayo strategy
In 1992, Wickberg and co-workers utilised a de Mayo strategy in their total synthesis of (+)-Aphanamol I 341. Photocaddition of alkene 335 to α,β-unsaturated ketone 336 produced a mixture of regioisomers 337 and 338 in 20% and 23% yield respectively. Treatment of 338 with dimethyloxosulfonium methylide furnished endo-epoxide 339 in 50% yield. Hydrolysis of the acetyl with lithium methoxide initiated a retro aldol-like reaction (340) with concomitant epoxide ring opening to afford (+)-Aphanamol 341 in 70% yield. This type of ring expansion methodology has also been demonstrated by Weedon and co-workers in their total synthesis of Hirsutene.90

\[ \text{Reagents and conditions: (i) } \hν, \text{MeCN, 12 h; (ii) } \text{Me}_2\text{S(O)=CH}_2, \text{THF, 3.5 h; (iii) LiOMe, MeOH, reflux, 1 h.} \]

\[ \text{Scheme 57 de Mayo strategy for the total synthesis of (+)-Aphanamol I 341} \]

Hiemstra and co-workers have developed a new route to functionalised cyclobutanes via retro aldol reaction of photocycloaddition products. The de Mayo sequence was initiated via irradiation of precursors 342-347 to afford cycloaddition products 343 and 348, which occurred with complete regioselectivity. Base induced retro aldol reaction then afforded spiro[3.4]octanes 345, spiro[3.5]nonanes 346 and novel substituted cyclobutanes 350-351 in good yield as a mixture of epimers.91
Reagents and conditions: (i) hν, MeCN/acetone; (ii) KOH, dioxane/H$_2$O; CH$_2$N$_2$, MeOH.

**Scheme 58** Synthesis of highly functionalised cyclobutanes 345-346 and 350-351 via retro aldol cleavage of photocycloaddition products 343 and 348.

In 2003, Minter and co-workers demonstrated a de Mayo approach for the synthesis of the Galanthan ring system 356, which is a tetracyclic skeleton found in a number of alkaloids. Enol 353 was initially synthesised from isoquinolin-1(2H)-one 352 in 63% overall yield, and then irradiated to initiate a de Mayo reaction to produce photocycloaddition intermediate 354,
which underwent a subsequent retro aldol sequence to afford 355 as a single product in 70% yield. Treatment of 355 with piperidine then initiated a base catalysed aldol reaction to afford the desired tetracycle skeleton of 356 in 78% yield.\(^92\)

![Diagram of the synthesis process](image)

*Reagents and conditions: (i) hν, MeCN, 1.5 h; (ii) Piperidine, benzene, reflux.*

**Scheme 59** de Mayo approach to the synthesis of tetracyclic Galanthan ring system 356 found in several alkaloids

In 2002, Winkler and co-workers described the first total synthesis of (±)-Ingenol 362 using a modified intramolecular de Mayo photocycloaddition/retro aldol fragmentation sequence. A particular challenge of this synthesis was establishment of the highly unusual C-8/C-10 ‘inside-outside’ configuration, or trans intrabridgehead configuration of the bicyclic ring system. Irradiation of 357 gave a 2:5 mixture of 358 and 359 isomers in 60% yield, which was separated via flash column chromatography. Isomer 359 was treated with methanolic K\(_2\)CO\(_3\) to give 360, with the correct trans intrabridgehead stereochemistry for (±)-Ingenol 362.\(^93\)-\(^94\) A similar methodology has also been applied by Winkler and co-workers for other natural product syntheses such as the tricyclic skeleton of Taxol diterpene analogues.\(^95\)
Reagents and conditions: (i) hv (pyrex); (ii) \( \text{K}_2\text{CO}_3, \text{MeOH} \).

Scheme 60 Retro aldol fragmentation of a de Mayo photocycloaddition product 359 used for the total synthesis of (±)-ingenol 362

1.10 Aldolase Enzymes

Aldolase enzymes are capable of catalysing both the aldol reaction and its reverse process with good substrate specificity and in high stereoselectivity.\(^{96}\) Aldolase enzymes are divided into two main classes according to the mechanism by which they operate. Class I aldolases utilise lysine residues to covalently link with the substrate, forming enamine/imine intermediates that activates the substrate towards stereoselective deprotonation. Class II aldolases employ active site bound transition metal ions such as Zn(II) as Lewis acids, which coordinate with the substrate to assist enolate formation.\(^{97-98}\) In 1993, Herbert and co-workers discovered a novel aldolase enzyme from Streptomyces amakusaensis that catalysed the retro aldol reaction of threo-β-hydroxy-α-amino acids 363 into their corresponding aldehydes 364 and glycine 365. The enzyme was highly selective for the (2S,3R) configuration of threo-(4-hydroxyphenyl)serine. The substrate scope was limited to aromatic and hetero-aromatic compounds, but showed broad structural tolerance within this limitation.\(^{99}\) It was later
discovered that the enzyme is dependent on PLP (pyridoxal-5'-phosphate) as a cofactor that acts to generate a Schiff base of the amino group of the substrate. The novel aldolase was employed for the preparation of a range of (2S,3R)-aromatic amino acids including (2R,3R)-3-(2-furyl)serine and (2R,3R)-3-(2-thienyl)serine, in good yield and above 95% ee.\textsuperscript{100}

![Scheme 61 Enzymatic resolution of rac-arylserine catalysed by Streptomyces aldolase](image)

Hilvert and co-workers have shown that the activity of a PLP dependant racemase enzyme can be changed to an aldolase by a single active site mutation. Alanine racemase from \textit{Geobacillus stearothermophilus} was mutated by substitution of Tyr265 in the active site with an alanine residue to afford a mutant aldolase that catalysed the retro aldol reaction of \(\alpha\)-substituted \(\beta\)-phenylserine \textsuperscript{370} via a Class I like enamine/iminium catalysis (Scheme 62). It was initially thought that this would allow the imidazole of an adjacent histidine residue to act as a general base in a retro aldol reaction.\textsuperscript{101} However, it was subsequently discovered by computational calculations that the histidine residue is too far away from the alcohol nucleophile in the active site, and therefore the base is likely to be the PLP cofactor. The engineered aldolase displayed high stereocontrol at the \(\alpha\)-carbon configuration but low selectivity at the \(\beta\)-carbon of \(\alpha\)-substituted \(\beta\)-phenylserine \textsuperscript{370}.\textsuperscript{102}
Barbas III, Tanaka and co-workers have developed small designer aldolase peptides between 24-35 amino acid residues that have been shown to catalyse aldol, retro aldol and Michael reactions. A combination of design and reaction based selection was employed to create libraries of aldolase peptides. Randomised amino acids were appended to peptides and 1,3-diketones were employed in selection reactions to trap reactive lysine residues that would act as enamine catalysts for retro aldol reactions. The designer peptides showed good rate acceleration and excellent substrate specificity for retro aldol reactions of substrates such as aromatic aldol 371. 103
1.11  Aldolase Antibodies

Antibodies that catalyse enantioselective retro aldol reactions have received a large amount of attention in recent years. These antibodies are generated by reactive immunisation and generally have a much broader substrate scope than aldolase enzymes.\textsuperscript{104} Mechanistically, the retro aldol reaction proceeds through an enamine mechanism\textsuperscript{105} catalysed by an uncharged $\varepsilon$-amino group of a reactive lysine residue in the active site, similar to the catalytic cycle observed for natural class I aldolases.\textsuperscript{106} One promising application is their use in chemotherapeutic drug activation, where a prodrug undergoes an antibody catalysed retro aldol reaction at the required site, thereby reducing the toxic effects of the parent drug.\textsuperscript{107-109} Another application is their use in organic synthesis as a tool for the kinetic resolution of racemic aldol products. This topic has been extensively reviewed.\textsuperscript{110-112} Therefore, only selected highlights will be included in this section.

Reactive immunisation\textsuperscript{113} is a process whereby mice are exposed to a hapten, a molecule specifically designed to resemble the transition state of a chemical reaction.\textsuperscript{114} In the case of aldolase antibodies, the hapten is usually a 1,3-diketones\textsuperscript{115} or contains a phosphinate residue.\textsuperscript{116} The hapten covalently traps a lysine residue of an antibody forming an enamine intermediate, thus mimicking the intermediates found in the transition state of an aldol reaction, which induces a catalytically active binding site for an aldol/retro aldol reaction to occur.\textsuperscript{106} The antibodies are then isolated from the immunised mice and purified for use in synthetic reactions.\textsuperscript{113} For example, in 1999 Barbas III, Lerner and co-workers designed a $\beta$-diketo sulphone hapten \textbf{376} for the generation of new aldolase antibodies. The tetrahedral geometry of the sulphone unit mimics the transition state \textbf{374} of the carbon-carbon bond formation in the aldol reaction.\textsuperscript{114}
In 1998, Barbas III, Lerner and co-workers employed a catalytic antibody to mediate kinetic resolution of simple \( \beta \)-hydroxyketones using an enantioselective retro aldol reaction, with these reactions reaching \( \sim 50\% \) conversion after four hours, and the unreacted aldol being recovered in high enantiomeric excess.\textsuperscript{117}

Scheme 64 Reactive immunisation with hapten 376 to generate new aldolase antibodies

Scheme 65 Kinetic resolution of \( \beta \)-hydroxyketones using antibody 38C2

Reagents and conditions: (i) Antibody 38C2, PBS.
The authors had previously shown that antibodies could be used to catalyse the corresponding enantioselective aldol reactions, thus enabling a single antibody catalyst to be used to prepare both aldol enantiomers.\textsuperscript{117}

Gouverneur and co-workers have demonstrated an unusual reversal of regioselectivity in aldolase antibody mediated aldol and retro reactions using unsymmetrical methyl ketones as enolate partners. In the uncatalysed aldol addition of methyl ketone with \textit{para}-nitrobenzaldehyde, a branched regioisomer is produced. However, when aldolase antibody 84G3 is employed the linear regioisomer is favoured, with carbon-carbon bond formation taking place on the least substituted carbon, even when \(\alpha\)-heteroatoms were present, thus showing that the antibody could differentiate between the reactive sites of an unsymmetrical methyl ketone. Both aldol enantiomers could be selectively accessed by carrying out either aldol or retro aldol reactions with antibody 84G3 in good conversions and excellent enantioselectivity.\textsuperscript{118-119}
Gouverneur and co-workers have also demonstrated kinetic resolution of β-hydroxyenones 384 using aldolase antibodies in a novel approach to the synthesis of formal hetero Diels-Alder adducts. The resolution process led to highly enantiomerically enriched α,β-unsaturated methyl ketones 385 in up to 99% ee, which underwent a ring closing reaction to afford pyranones 386 and 387. However, the antibodies employed did not tolerate long aliphatic R2 substituents, which limited the overall scope of the strategy.120

Scheme 67 Unusual reversal in regioselectivity for the aldol reaction of unsymmetrical methyl ketones catalysed by antibody 84G3

Scheme 68 Kinetic resolution of β-hydroxyenones for the preparation of hetero-Diels Alder adducts
Catalytic antibodies have also been used to prepare aldol products for the total synthesis of Epothilones A-F, which are sixteen membered macrolides that stabilise tubulin formation via a Taxol-like mode of action.121-123

![Epothilone Structures](image)

**Figure 2** Structures of Epothilone A-F

Two key precursors were synthesised via kinetic resolution of racemic β-hydroxy ketones rac-389 and rac-390, using antibodies generated against a β-diketone hapten via reactive immunisation. The best results were obtained for kinetic resolution of rac-thiazole aldol 388 using antibody 84G3 that led to >98% ee at 50% conversion. Attempts to synthesise 389 via the corresponding antibody catalysed aldol reaction were less successful, as enantiomeric purity eroded over time due to the retro aldol reaction being more favoured. Aldol rac-389 also underwent a kinetic resolution with antibody 38C2 to afford a recovered aldol product in 98% ee at 60% conversion in 36% yield.121-123
Synthetic Applications of the Retro Aldol Reaction

Reagents and conditions: (i) Antibody 84G3, PBS, pH 7.4; (ii) Antibody 38C2, PBS, pH 7.4.

Scheme 69 Kinetic resolution of thiazole aldol 388 and aldol 389

Barbas III, Lerner and co-workers also reported kinetic resolution of tertiary β-hydroxy ketones rac-390 with catalytic antibodies, providing a route to ketol products containing hydroxyl substituted quaternary β-stereocentres. These kinetic resolutions did not proceed past 50% conversion, suggesting that they are highly enantioselective, with the majority of aldol products being obtained in excellent enantioselectivities.124

Reagents and conditions: (i) Antibody 38C2, PBS.

Scheme 70 Kinetic resolution of tertiary alcohols by antibody 38C2
The synthetic utility of this antibody catalysed methodology has been employed for the total synthesis of (+)-Frontalin 393, a sex pheromone found in beetles and for the total synthesis of a series of Brevicomin natural products with a related bicyclic skeleton to (+)-Frontalin 393.

\[
\begin{align*}
\text{rac-391} & \xrightarrow{(i)} \text{391} \xrightarrow{(ii)} \text{393} \\
& \text{(+)-Frontalin}
\end{align*}
\]

Reagents and conditions: (i) Antibody 38C2, PBS; (ii) Diethyl (2-oxopropyl)phosphonate, LiOH, THF; (iii) H$_2$/Pd(OH)$_2$/C.

Scheme 71 Total synthesis of (+)-Frontalin using an antibody catalysed kinetic resolution of aldol 391

1.12 Conclusion

In summary, it is hoped that this review has demonstrated that the retro aldol reaction can be extremely useful for many synthetic applications. This reversible process can potentially be utilised to unmask useful aldehyde and enolate functionality, which can then be elaborated further to afford synthetically useful building blocks. Retro aldol reactions have also been used to initiate fragmentations reaction of complex cyclic frameworks, which is useful for the synthesis and structure elucidation of natural products. Its reversible nature can also be exploited for accessing thermodynamically stable epimers, as well as for the kinetic resolution of racemic mixtures of aldol substrates. It has also been utilised in the removal of chiral auxiliaries in the synthesis of enantiomerically pure building blocks that are of use in natural product synthesis. It is believed that there is still a great deal of potential for the retro aldol reaction to be used in many more applications for organic synthesis.
2 Results and Discussion

Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

2.1 Introduction

Substituted δ-lactones are exceptionally widespread in Nature and have a broad range of applications. The δ-lactone motif is found in many natural products isolated from fungi and marine organisms, where they often form parts of attractants and pheromones. δ-Lactones are also shunt metabolites of prematurely terminated polyketide syntheses. δ-Lactones display a broad range of potent pharmacological activities including antitumour, antimicrobial, and immunosuppressive activity. For example, the polyketide (+)-Discodermolide 394 is an inhibitor of tumour cell growth, (-)-Goniofupyrone 395 is cytotoxic against human tumours and the macrocycle Lankacidin C 396 is an antibiotic and antitumour agent. The δ-lactone subunit is also present in pharmaceutical compounds such as the statin Zocor (Simvastatin) 397, a synthetic derivative of a natural product isolated from Aspergillus terreus.

![Figure 3 Examples of biologically active δ-lactones found in natural products](image-url)
δ-Lactones are also important in the flavour and fragrance industry. The δ-lactone motif is present in compounds found in dairy products and is important in the flavour of fruit. For example, decalactone \(398\) has been identified in the \((R)\)-configuration in apricots, peaches and strawberries but in the \((S)\)-configuration in raspberries.\(^{136}\) Glucono δ-lactone \(399\) is a naturally occurring food additive found in honey, fruit juice and wine.

![Figure 4 δ-Lactone natural products found in food](image)

δ-Lactones are also useful precursors to medicinally interesting compounds such as l-Callipeltose \(406\), the deoxyamino sugar of l-Callipeltoside A, a potential antitumour agent.\(^{137-138}\) The total synthesis by Evans and co-workers began with well-established protecting group procedures of the amino acid \(\text{D-threonine} 400\) to afford \(N\)-Cbz-\(\text{D-threonine methyl ester} 401\). Stereoselective aldol addition of the lithium enolate of 1,4-dioxaspiro[4.5]decan-2-one \(402\), provided aldol \(403\) with high diastereoselecivity, which was deprotected and methylated to furnish δ-lactone \(404\) in 71% yield. A Rychnovsky’s one-pot lactone reduction-acylation procedure, using diisobutylaluminium hydride followed by acetic anhydride, was employed to afford lactol \(405\), which underwent reduction of the Cbz group to furnish the cyclic carbamate unit. Further elaboration completed the total synthesis of l-Callipeltose \(406\) in an overall 13% yield across ten steps.\(^{138}\)
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) LDA, then 402; (ii) AcOH, H₂O; (iii) Me₃O.BF₃, 2,6-di-tert-butyl-4-methylpyridine; (iv) DIBAL then Ac₂O, pyridine, DMAP; (v) NaH, THF; (vi) DBU, Cl₃CCN; (vii) MeOH, TMS-OTf, CH₂Cl₂.

Scheme 72 Intermediate δ-lactone for the synthesis of L-Callipeltose 406

2.2 Synthesis of δ-Lactones with Multiple Contiguous Stereocentres

The diverse range of pharmacological activity displayed by natural products containing a δ-lactone unit, as well as the versatility of substituted δ-lactone fragments in synthetic strategies, has resulted in the development of a wide variety of methodology for their asymmetric synthesis. Furthermore, highly substituted δ-lactones can perform as useful building blocks in the synthesis of polyketide natural products containing stereotetrads. Many strategies have been developed for the synthesis of precursors containing four or more contiguous stereocentres for natural product synthesis.

One of the most popular approaches for the asymmetric synthesis of highly substituted δ-lactones is the use of chiral auxiliaries to direct aldol reactions, since it allows reliable incorporation of multiple contiguous stereocentres into an aldol product. The advantage of this strategy is that the methodology can be altered to access many stereochemical
arrangements. There are two general strategies when using Evans’ type auxiliaries in the synthesis of δ-lactones containing multiple contiguous stereocentres; whereby pre-existing stereocentres originate in either the enolate (using β-keto-N-acyl-oxazolidin-2-ones),\textsuperscript{147-149} or the electrophile (using enantiopure aldehydes).\textsuperscript{128,140,150-152}

For example, Lee and co-workers employed β-keto-N-acyl-oxazolidin-2-one 407 in a tin promoted Evans’ aldol reaction with aldehyde 408 to afford aldol 409 in 82% yield. This subsequently underwent a reduction-lactonisation sequence to afford highly substituted δ-lactone 410, which was used as a chiron for the total synthesis of Kendomycin 412.\textsuperscript{148}

Reagents and conditions: (i) Sn(OTf)\textsubscript{2}, NEt\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C; (ii) NaBH(OAc)\textsubscript{3}, AcOH, 5 °C; (iii) DBU, CH\textsubscript{2}Cl\textsubscript{2}; (iv) Pd(OAc)\textsubscript{2}, PCy\textsubscript{3}, n-Bu\textsubscript{3}SnH, Hexane-THF; (v) I\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}.

Scheme 73 Chiral auxiliary directed aldol reaction to afford δ-lactone 410 precursor for the total synthesis of Kendomycin 412
Davies and co-workers have demonstrated a strategy for the synthesis of more challenging ‘mismatched’ aldol products 415 and 416, using a N-acylated SuperQuat 413 chiral auxiliary and an enantiopure aldehyde 414 (Scheme 74). These aldol products could then be deprotected and cyclised to produce stereodefined tetrasubstituted δ-lactones 417 and 419. The initial reaction is a double diastereoselective SuperQuat aldol addition of acylated SuperQuat 413 to aldehyde 414. This provided a 57:43 mixture of separable diastereomers 415 and 416, both isolated in >95% de, with the stereochemistry differing only at the β-position.

Treatment of the aldol product 415 with TBAF induced O-deprotection and concomitant lactonisation, providing the tetrasubstituted δ-lactone 417 in an 85% yield. The same procedure was applied to compound 416, but this resulted in a mixture of δ-lactone 419 in a 34% yield and deprotected aldol product 418 in a 45% yield. Subsequent separation of this mixture and heating 418 at reflux in toluene provided δ-lactone 419 in an overall 76% yield.140

Reagents and conditions: (i) Et₂BOTf, N(Pr)₂Et, CH₂Cl₂, -78 °C to 0 °C; (ii) TBAF, AcOH, THF, rt; (iii) Toluene, Δ.

Scheme 74 Synthesis of δ-lactones 417 and 419 from SuperQuat auxiliary
2.3 Literature Precedent and Previous Work

The mercury(II) mediated cyclopropylcarbinol ring opening reaction is well documented and has been previously employed for the synthesis of oxygen heterocycles. For example, Collum and co-workers have reported that disubstituted δ-lactones can be synthesised from cyclopropane 420 in a mercury mediated ring-opening reaction with mercury trifluoroacetate. Subsequent radical demercuration with tributyltin hydride furnished δ-lactone 421 in 12:1 ratio of δ-lactone 421 to γ-lactone 422. Cossy and co-workers have also utilised this highly regio- and stereoselective transformation to produce disubstituted δ-lactone 424 from 423 in 66% yield.

Cossy and co-workers have also applied this methodology to the synthesis of the highly functionalised C-1-C-10 fragment of the polyketide natural product Zincophorin 427. The resulting tetrahydropyran was obtained in excellent yield (85%) and diastereoselectivity (dr > 93:7).

Reagent and conditions (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, rt then saturated KBr; (ii) n-Bu$_3$SnH, cat. AIBN, THF.

Scheme 75 Mercury mediated synthesis of disubstituted δ-lactone 421 and 424

Cossy and co-workers have also applied this methodology to the synthesis of the highly functionalised C-1-C-10 fragment of the polyketide natural product Zincophorin 427. The resulting tetrahydropyran was obtained in excellent yield (85%) and diastereoselectivity (dr > 93:7).
Asymmetric Synthesis of Chiral $\delta$-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, rt then aq. KBr; (ii) n-Bu$_3$SnH, cat. AIBN, THF/toluene, 60 °C.

Scheme 76 Synthesis of the C-1-C-10 fragment 426 of Zincophorin 427

As discussed earlier, the Bull group has previously reported a novel approach for the synthesis of chiral cyclopropane carboxaldehydes using temporary stereocentres, which has been applied to the synthesis of the natural products Grenadamide and Cascarillic acid. The asymmetric aldol reaction was achieved using the SuperQuat chiral auxiliary to afford syn-aldol products 429. A substrate directed cyclopropanation reaction furnished cyclopropanes 430, which underwent a retro-aldol reaction to afford the cyclopropane carboxaldehydes 431 in >95% de. The acylated auxiliary 95 could then be separated from the reaction mixture and recycled.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) 9-BBN-OTf, N(Pr$_2$)Et, CH$_2$Cl$_2$, -78 to 0 °C; (ii) Et$_2$Zn, CH$_2$I$_2$, CH$_2$Cl$_2$, -10 to 0 °C; (iii) LiHMDS (1.1 equiv), toluene.

Scheme 77 Synthesis of cyclopropane carboxaldehydes 431 using temporary stereocentres

The aim of this project was to investigate novel methodology for the asymmetric synthesis of tetrasubstituted δ-lactones via mercury mediated ring-opening of cyclopropanated aldol products. Given the literature precedent, it was initially proposed that this methodology could be applied to our cyclopropanated syn-aldol products to afford highly substituted δ-lactones with high diastereoselectivity.

The proposed asymmetric synthesis of δ-lactones 437 is shown in Scheme 78. It had been previously shown within the Bull group that mercury mediated ring-opening of cyclopropanated aldol products 434 led to α,β-unsaturated δ-lactones 438. Although α,β-unsaturated δ-lactones are useful precursors in natural product synthesis, this strategy is undesirable since two stereocentres are destroyed in the lactonisation process. Using the previously described literature precedent,$^{153}$ the chiral auxiliary was replaced with a methyl ester 435 and it was found that oxymercuration of this product led directly to organomercurial δ-lactone 436 retaining all four contiguous stereocentres. A subsequent reductive demercuration step with basic sodium borohydride furnished the highly substituted δ-lactone 437.
This project aimed to explore the scope and limitations of this novel methodology for the asymmetric synthesis of highly substituted δ-lactones, as well as strategies for their conversion into versatile building blocks for the synthesis of stereoisomeric analogues of polyketide natural products.
2.4 The Asymmetric Aldol Reaction

The aldol reaction is one of the most important carbon-carbon bond forming reactions in organic synthesis. It involves the addition of an enolate 440 to an aldehyde or ketone 441 to produce a β-hydroxyketone 442 with the generation of two new stereocentres. Under certain conditions, the β-hydroxyketone 442 can dehydrate to form an α,β-unsaturated ketone 443.

![Scheme 79 General aldol reaction](image)

2.4.1 Stereoselectivity in the Aldol Reaction

The stereochemical outcome of the aldol reaction can be controlled using chiral auxiliaries. Evans and co-workers first reported the use of a chiral oxazolidinone auxiliary 444 with boron enolates to control the enantioselectivity of the aldol reaction.\[^{159}\] Davies and co-workers subsequently demonstrated that a modified chiral oxazolidinone auxiliary with 5,5-substitution, known as the ‘SuperQuat’ auxiliary 445, often provides greater stereoselectivity compared with Evans’ auxiliary.\[^{160}\]

![Figure 5 Chiral oxazolidinone auxiliaries](image)

The stereoselectivity of the aldol reaction originates from both the enolate geometry and the influence of the auxiliary. Aldol products potentially contain two stereocentres and therefore up to four different stereoisomers can be formed during the aldol reaction. The
diastereoselectivity of the aldol reaction is controlled by the geometry of the enolate, whereas the enantioselectivity is controlled by the auxiliary.

Boron reagents are often employed in directed aldol additions to generate the desired enolate geometry. Bulky boron substituents such as cyclohexyl groups result in \(E\) enolates 448, whereas substituents that are less sterically demanding, such as butyl groups or 9-BBN (9-borabicyclononane), result in the formation of the \(Z\) enolate 447. The desired enolate is produced by treatment of the ketone with the boron triflate reagent in the presence of an amine base. The Lewis acidic boron coordinates to the oxygen of the carbonyl group to aid deprotonation of the ketone by the base. The geometry of the boron enolate is important for the stereochemical outcome of the aldol reaction. The \(Z\) enolate 447 provides the \textit{syn} product 449-450, whereas the \(E\) enolate 448 provides the \textit{anti} product 451-452.

The stereochemical outcome of the aldol reaction is rationalised using a closed six-membered transition state known as the Zimmerman-Traxler model. The boron associated with the enolate binds to the oxygen of the incoming aldehyde to form a chair-like six-membered ring. The \(Z\) enolate 447 must orientate itself with its substituents fixed in the axial position (Scheme 81). However, the incoming aldehyde can orientate itself with its \(R^2\) group in either the axial or equatorial position, leading to two possible transition states 453 and 455. The axial position is disfavoured due to the unfavourable pseudo 1,3-diaxial interaction between the \(R^1\) group of
the enolate and the \( R^2 \) group of the aldehyde (455). Therefore, the reaction proceeds through the transition state in which the \( R^2 \) group is equatorial to minimise steric interactions (453) to afford the \textit{syn} product 454. Therefore, enolate geometry controls the overall diastereoselectivity, but not the enantioselectivity so a racemic mixture is obtained.\(^{161-162}\)

The absolute stereochemistry of the aldol reaction can be controlled using chiral auxiliaries such as the SuperQuat auxiliary 445. The chiral auxiliary is used to control which \textit{syn} enantiomer is produced when a \( Z \) boron enolate is used in the aldol reaction.\(^{163}\) The Lewis acidic boron coordinates both oxygen atoms of the enolate and chiral auxiliary in the \( Z \) enolate (457). However, the incoming aldehyde 458 forces the boron atom to detach from the oxygen atom of the oxazolidinone and coordinate to the oxygen of the incoming aldehyde instead (459). This causes the conformational lock of the auxiliary to be broken, leaving the carbon-nitrogen bond of the auxiliary free to rotate by 180° from its original position into a lower energy conformation (460).\(^{159,164-165}\)
This new conformation minimises the adverse dipole-dipole interactions between the two carbon-oxygen bonds, which are parallel to each other in the boron enolate. The incoming aldehyde approaches from the \textit{Re} face where the dipole is minimised resulting in \textit{syn} enantiomer 462.\textsuperscript{159,164-165}

\begin{center}
\includegraphics[width=\textwidth]{scheme82.png}
\end{center}

\textbf{Scheme 82} Minimisation of adverse dipole-dipole interactions in the aldol reaction favours formation of \textit{syn}-aldol 462

The absolute stereochemical outcome can also be explained using Zimmerman-Traxler transition states.\textsuperscript{159} The boron coordinates to the incoming aldehyde creating four possible transition states (465-468). The R group of the aldehyde must adopt a pseudo equatorial position to minimise the 1,3-diaxial interactions. The most favourable transition state 465 minimises the dipole-dipole interactions by positioning the carbon-oxygen bonds of the auxiliary and the aldehyde antiparallel, as well as minimising steric interactions induced by the directing benzyl group of the SuperQuat. This leads solely to the \textit{syn} product 463.\textsuperscript{163}
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Scheme 83 Zimmerman-Traxler transition states using SuperQuat auxiliary to control facial selectivity of syn-aldol reaction

2.4.2 Asymmetric Synthesis of Unsaturated syn-Aldol Products

Our novel strategy for the synthesis of highly substituted δ-lactones 437 allows for variation at two of the substituents, R¹ and R² (Scheme 84). Structural variation at R¹ could be introduced by employment of different acid chlorides 469 in the auxiliary N-acylation step. The R² substituent would then be varied by using different aldehydes 470 in the asymmetric aldol reaction.

Scheme 84 Variation of substituents R¹ and R² on δ-lactone 437 framework
Asymmetric Synthesis of Chiral 6-Lactones Containing Multiple Contiguous Stereocentres

A range of N-acylated oxazolidin-2-ones were synthesised to investigate the scope of this methodology. SuperQuat auxiliary 445 in THF was treated with n-butyl lithium (2.5 M in hexane) at -78 °C followed by the addition of the appropriate acid chloride 469. The resulting solution was allowed to warm to room temperature over two hours before quenching with saturated ammonium chloride. The crude product was purified by either flash silica chromatography or recrystallisation.

\[
\text{Scheme 85 Synthesis of N-acylated SuperQuat auxiliary products 432}
\]

The following acylated SuperQuat auxiliary products were synthesised in high yield using the methodology described (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chloride</th>
<th>Acylated Auxiliary (\chi_p)</th>
<th>Product</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl (\text{CH}_2)</td>
<td>(\chi_p) (\text{CH}_2)</td>
<td>95</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>Cl (\text{CH}_2)</td>
<td>(\chi_p) (\text{CH}_2)</td>
<td>471</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>Cl (\text{C}_6\text{H}_5)</td>
<td>(\chi_p) (\text{C}_6\text{H}_5)</td>
<td>472</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>Cl (\text{C}_6\text{H}_5\text{OMe})</td>
<td>(\chi_p) (\text{C}_6\text{H}_5\text{OMe})</td>
<td>473</td>
<td>78%</td>
</tr>
</tbody>
</table>

\(\chi_p\) refers to SuperQuat auxiliary; \(^b\)isolated yield after column chromatography

Table 1 \(\text{N-}^{\text{Acylated oxazolidin-2-one products}}\) 432
The N-acylated auxiliary products in Table 1 were then used to synthesise the unsaturated syn-aldol products 433. The acylated auxiliary 432 was treated with dibutylboron triflate (1.1 equiv) followed by diisopropylethylamine (1.3 equiv) in dichloromethane at 0 °C. After 30 minutes, the solution was cooled to -78 °C and the appropriate aldehyde 470 (1.3 equiv) added before the solution was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution, methanol and hydrogen peroxide, and was stirred for a further two hours. The crude product were then purified using flash silica chromatography to afford the unsaturated syn-aldol product 433.

Reagents and conditions: (i) Bu₂BOTf, N(Pr)₂Et, CH₂Cl₂, 0 °C then aldehyde 470, -78 °C.

Scheme 86 Synthesis of unsaturated syn-aldol products 433

This asymmetric syn-aldol methodology was applied to (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one (R¹ = Me) using different aldehydes 470 as substrates to introduce variation at the R² position. The following syn-aldol products were synthesised in high yield and de (Table 2).
Asymmetric Synthesis of Chiral $\delta$-Lactones Containing Multiple Contiguous Stereocentres

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Aldol Product$^a$</th>
<th>Product</th>
<th>Yield$^b$, de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Aldehyde" /></td>
<td><img src="image2.png" alt="Aldol Product" /></td>
<td>474</td>
<td>95%, &gt;95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Aldehyde" /></td>
<td><img src="image4.png" alt="Aldol Product" /></td>
<td>475</td>
<td>86%, &gt;95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Aldehyde" /></td>
<td><img src="image6.png" alt="Aldol Product" /></td>
<td>476</td>
<td>81%, &gt;95%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Aldehyde" /></td>
<td><img src="image8.png" alt="Aldol Product" /></td>
<td>477</td>
<td>66%, &gt;95%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Aldehyde" /></td>
<td><img src="image10.png" alt="Aldol Product" /></td>
<td>478</td>
<td>66%, &gt;95%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Aldehyde" /></td>
<td><img src="image12.png" alt="Aldol Product" /></td>
<td>479</td>
<td>56%, &gt;95%</td>
</tr>
</tbody>
</table>

$a\chi_p$ refers to SuperQuat auxiliary; $^b$isolated yield after column chromatography

**Table 2** Unsaturated syn-aldol products produced from different $\alpha,\beta$-unsaturated aldehydes

The following syn-aldol products were then synthesised via reaction of different $N$-acylated oxazolidin-2-ones with crotonaldehyde in high yield and high de (Table 3).
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylated Auxiliary&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Aldol Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \chi_p )</td>
<td>( \chi_p ) OH</td>
<td>480</td>
<td>82% &gt;95%</td>
</tr>
<tr>
<td>2</td>
<td>( \chi_p ) OMe</td>
<td>( \chi_p ) OH</td>
<td>481</td>
<td>72% &gt;95%</td>
</tr>
</tbody>
</table>

<sup>a</sup>\( \chi_p \) refers to SuperQuat auxiliary; <sup>b</sup>isolated yield after column chromatography.

Table 3 Unsaturated syn-aldol products prepared using different N-acylated auxiliaries

An asymmetric aldol reaction was attempted using N-acylated oxazolidin-2-one 472 where \( R^1 = \text{Ph} \). However, this aldol product showed a high propensity to undergo a retro-aldol reaction during purification by flash silica chromatography, possibly due to the acidic nature of the silica. This problem persisted with the pure material in subsequent reactions. Therefore, it was decided to use the para-methoxyphenyl derivative 473 instead to illustrate aromatic diversity at the \( R^1 \) position. This aldol product 481 showed much less of a tendency to retro-aldol, so the synthesis could be continued using this product.

The syn-configuration of the aldol product was confirmed from the value of the \( J_{2,3} \) coupling constant of >6 Hz in each case. The configuration of the alkene in the unsaturated syn-aldol products 474-475 and 477-479 was confirmed using the \(^1\)H NMR spectra. The characteristic alkene protons were present between 5.40-5.90 ppm when \( R^2 = \text{aliphatic} \) and 6.9-6.2 ppm when \( R^2 = \text{aromatic} \), with a coupling constant of between 15-16 Hz indicating \( E \) alkene geometry.
2.5 Non-Evans’ anti-aldol

A non-Evans’ anti-aldol product 483 was prepared to investigate the effect of using substrates with an alternative stereochemistry at the α-position. According to a literature procedure, (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 was dissolved in dry ethyl acetate along with a catalytic amount of magnesium chloride and sodium hexafluoroantimonate. Triethylamine was added dropwise followed by cinnamaldehyde 482 and freshly distilled chlorotrimethylsilane. The crude product underwent desilylation on work up, followed by purification via flash silica chromatography to afford the anti-aldol product 483 in 82% yield and in >95% de. The 1H and 13C NMR spectra were similar to that of syn-aldol product 483, although the most noticeable difference in chemical shift was that of the CH$_A$H$_B$Ph proton of the auxiliary, which had shifted from 2.91 ppm to 2.67 ppm due to the different orientation of the α-methyl group.

Reagents and conditions: (i) MgCl$_2$ (0.1 equiv), NaSbF$_6$ (0.3 equiv), NEt$_3$, TMSCl, dry EtOAc, rt, 24 h.

Scheme 87 Synthesis of non-Evans anti-aldol product 483

Mechanistically, it is thought that the magnesium coordinates to the N-acyl auxiliary 95 to generate a metal enolate 485, which reacts with the aldehyde to afford intermediate 487. This aldol reaction is reversible, but is trapped by silylation with TMSCl aiding the release of the magnesium ion to proceed further in the catalytic cycle. It has been proposed that boat transition state 489 leads to the anti-aldol product, which is different to the Zimmerman-Traxler transition state observed in the Evans’ syn-aldol reaction.
Attempts were made to synthesise other anti-aldol products using different aldehydes. However, these failed possibly owing to the non-general nature of this procedure, which is most successful when non-enolisable electrophiles such as aromatic and unsaturated aldehydes are employed for reaction. The syn-aldol products 474-479 were then taken along with anti-aldol product 483 onto the next stage of the synthesis.
2.6 Directed Cyclopropanation

The next step in the synthesis was a directed cyclopropanation reaction of the allylic alcohol functionality of aldol products 474-479 using diethylzinc and diiodomethane to afford a series of syn-cyclopropane products. The use of a directed cyclopropanation reaction on these types of α,β-unsaturated aldol product is an efficient strategy for the construction of two new stereocentres in one step. The Bull group has previously demonstrated the utility of the directed cyclopropanation reaction on α,β-unsaturated aldol products to afford syn-cyclopropanes in high yield and excellent diastereoselectivity.40 This methodology utilises Furukawa’s cyclopropanation conditions that have previously been applied to the synthesis of Grenadamide within the Bull group.158

2.6.1 Stereoselectivity in the Directed Cyclopropanation Reaction

Simmons and Smith first reported the use of diiodomethane and zinc-copper couple to convert alkenes into cyclopropanes.168-169 The reaction has been shown to proceed through a three membered ‘butterfly-type’ transition state 490170-171 in which IZnCH2I is the active cyclopropanating agent.172 The reaction is stereospecific with respect to the alkene geometry and is influenced by both electronic and steric factors.173-174

![Scheme 89 Simmons-Smith 'butterfly-type' transition state](image_url)

Many variations of this method were reported shortly after this seminal publication, including a report by Wittig who described that treatment of zinc iodide with diazomethane afforded an alternative method for the preparation of active cyclopropanating species.175 In 1966, Furukawa found that diethylzinc could be substituted for the Zn-Cu couple to prepare the reactive species.176-177
Winston and co-workers reported the first application of a Simmons-Smith reaction to an allylic alcohol 491. The oxygen atom coordinates to the zinc to direct the methylene group to the neighbouring alkene to afford the syn product 492 as a single stereoisomer in 75% yield.\(^{178}\) It has also been found that the overall rate of reaction with allylic alcohols is much faster than with simple alkenes (\(>1000\) fold), with the cyclopropane group forming on the same side as the hydroxyl group in most cases.\(^{179,180}\) There have been many reports of directed cyclopropanations of allylic alcohols to afford syn products since the reaction was first discovered.\(^{158,169,181-182}\)

![Scheme 90: Hydroxyl-directed Simmons-Smith cyclopropanation reaction](image)

The stereoselectivity of the cycloropanation reaction with acyclic allylic alcohols can be explained using the allylic strain model. The ‘staggered’ model proposed by Houk considers the possible allylic conformation for the transition states in the addition of the cyclopropane carbon to the double bond.\(^{183-184}\) Coordination of the active species EtZnCH\(_2\)I with the alcohol directs formation of the cyclopropyl group syn with respect to the hydroxyl group. Therefore, the modified conditions of the Simmons-Smith reaction developed by Furukawa are syn-selective due to minimisation of \(A^{1,3}\) strain in the transition state.\(^{181}\)
2.6.2 Synthesis of syn-Cyclopropane Products

A series of syn-cyclopropane products were prepared from the α,β-unsaturated aldol products 474-479. Each syn-aldol substrate was treated with diethylzinc (5 equiv) and diiodomethane (5 equiv) in dry dichloromethane at 0 °C under nitrogen, and the solution was stirred for two hours in the absence of light. The reaction was quenched with saturated sodium sulfite and the resulting white precipitate dissolved in 1 M HCl. After extraction, the crude product was purified via flash column chromatography or recrystallisation.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) $\text{Et}_2\text{Zn}$ (5 equiv), $\text{CH}_2\text{I}_2$ (5 equiv), $\text{CH}_2\text{Cl}_2$, 0 °C, 2 h.

Scheme 92 Synthesis of syn-aldol cyclopropane products 434

The $^1\text{H}$ NMR spectra confirmed that the cyclopropanation reactions had been successful, with the absence of the alkene peaks between 5-7 ppm indicating that all the starting material had been consumed. The characteristic shielded cyclopropane proton multiplets between 0 and 1 ppm indicated that the cyclopropane had been formed in high diastereoselectivity. This methodology was applied to the $\alpha,\beta$-unsaturated aldol products 474-479, 480-481 and 483 to afford the syn-aldol cyclopropane products 493-501 in high yield and high de (Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cyclopropane Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; De</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Aldol Product" /></td>
<td><img src="image2" alt="Cyclopropane Product" /></td>
<td>493</td>
<td>84% &gt;95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Aldol Product" /></td>
<td><img src="image4" alt="Cyclopropane Product" /></td>
<td>494</td>
<td>98% &gt;95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Aldol Product" /></td>
<td><img src="image6" alt="Cyclopropane Product" /></td>
<td>495</td>
<td>98% &gt;95%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Aldol Product" /></td>
<td><img src="image8" alt="Cyclopropane Product" /></td>
<td>496</td>
<td>98% &gt;95%</td>
</tr>
</tbody>
</table>
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

<table>
<thead>
<tr>
<th></th>
<th><img src="image" alt="Structure 5" /></th>
<th><img src="image" alt="Structure 6" /></th>
<th>497</th>
<th>97% &gt;95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 7" /></td>
<td><img src="image" alt="Structure 8" /></td>
<td>498</td>
<td>98% &gt;95%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 9" /></td>
<td><img src="image" alt="Structure 10" /></td>
<td>499</td>
<td>72% &gt;95%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 11" /></td>
<td><img src="image" alt="Structure 12" /></td>
<td>500</td>
<td>68% &gt;95%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 13" /></td>
<td><img src="image" alt="Structure 14" /></td>
<td>501</td>
<td>99% &gt;95%</td>
</tr>
</tbody>
</table>

*a*χ*ᵣ* refers to SuperQuat auxiliary; *b*isolated yield after column chromatography

Table 4 Cyclopropanated syn-aldol products

2.7 Removal of the Auxiliary

It had been observed previously in the Bull group that direct mercury mediated ring-opening of the syn-aldol cyclopropane products 434 led to the α,β-unsaturated δ-lactone product 438 with cleavage of the auxiliary 445. This reaction is undesirable since two of the contiguous stereocentres are destroyed. Furthermore, separation of the SuperQuat auxiliary from the δ-lactone during purification presents a further unnecessary challenge.
Mechanistically, it is thought that the mercury ion coordinates to the cyclopropane ring facilitating regioselective ring-opening via nucleophilic attack by the endocyclic carbonyl group (502), resulting in iminium species 503. This species then undergoes rapid E1cB elimination to afford intermediate 505, which upon hydrolysis produces α,β-unsaturated lactone 438 along with the parent oxazolidin-2-one 445.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Scheme 94 Proposed mechanism for the formation of α,β-unsaturated lactone 438

It was found that removal of the auxiliary 445 using sodium methoxide to afford the methyl ester 435 prior to oxymercuration led to the desired highly substituted δ-lactone product 437 upon oxymercuration. This method also provides a simpler purification for removing the auxiliary by flash silica chromatography. Therefore, syn-aldol cyclopropane products 434 were treated with sodium methoxide (1 equiv, 0.5 M in methanol) at room temperature and the resulting solution was stirred for five minutes before being quenched with brine. The crude mixture was purified using flash silica chromatography to separate the methyl ester product 435 from the auxiliary 445. This methodology was applied to syn-aldol cyclopropane products 493-501 to afford methyl ester products 506-514 (Table 5).
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) NaOMe (1 equiv, 0.5 M in methanol), CH₂Cl₂, rt, 5 min.

Scheme 95 Transesterification of syn-aldol cyclopropane products 434

Methyl ester 510 required a longer reaction time of 24 hours at room temperature. This is possibly due to the steric hindrance of the isopropyl group at the α-position of the syn-aldol cyclopropane product, which slows down the rate of nucleophilic substitution of the auxiliary for the methoxide ion.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropane Product⁴</th>
<th>Methyl Ester Product</th>
<th>Product</th>
<th>Yield⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>506</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>507</td>
<td>94%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>508</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>509</td>
<td>74%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>510</td>
<td>82%</td>
</tr>
</tbody>
</table>
**Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres**

<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>511</td>
<td>76%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>512</td>
<td>62%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Structure" /></td>
<td>513</td>
<td>55%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /></td>
<td>514</td>
<td>78%</td>
</tr>
</tbody>
</table>

*χo refers to SuperQuat auxiliary; †isolated yield after column chromatography*

**Table 5 Synthesis of methyl ester products**

A problem that was encountered with this step in the synthesis was that methyl ester 511 co-eluted with the free SuperQuat auxiliary during flash silica chromatography in all attempted solvent systems. A pure sample of methyl ester 511 could not be isolated and was always contaminated with auxiliary. Therefore, it was decided that SuperQuat auxiliary be substituted for Evans’ auxiliary for this analogue. This synthesis afforded a pure sample of methyl ester 511 in 76% yield.
Reagents and conditions: (i) n-BuLi (1.1 equiv), THF, -78 °C for 30 min, propionyl chloride (1 equiv), -78 °C, 2 h; (ii) Bu$_3$BOTf (1.1 equiv), N/(iPr)$_2$Et (1.3 equiv), CH$_2$Cl$_2$, 0 °C then aldehyde 516, -78 °C to rt; (iii) Et$_2$Zn (5 equiv), CH$_2$I$_2$ (5 equiv), CH$_2$Cl$_2$, 0 °C, 2 h; (iv) NaOMe (1 equiv), CH$_2$Cl$_2$, rt, 5 min.

Scheme 96 Synthesis of methyl ester 511 using Evans’ auxiliary 444

2.8 Lactonisation via Mercury(II) Mediated Cyclopropane Ring-Opening

Mercury mediated ring-opening of cyclopropanes is well documented and occurs with high regio- and stereoselectivity. For example, Cossey and co-workers have reported stereoselective oxymercuration of cyclopropanealkanols 519 to afford 1,3-diols 521 after hydrolysis and reductive demercuration of 520. The mechanism involves a concerted electrophilic ring-opening of the cyclopropanealkanols at the most electron rich carbon-carbon bond with anti nucleophilic attack of the trifluoroacetate ion. This concerted mechanism explains the high level of stereoselectivity observed, and this methodology has been applied by Cossey and co-workers to the synthesis of polypropionate units with up to four contiguous stereocentres.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagent and conditions (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, then aq. NaCl; (ii) LiAlH$_4$, THF.

Scheme 97 Mercury mediated cyclopropane ring-opening reaction to form 1,3-diols 521

2.8.1 Oxymercuration of Methyl Ester Products

Previous investigations in the Bull group into the mercury(II) mediated cyclopropane ring-opening of methyl ester product 507 had resulted in clean conversion into the organomercurial δ-lactone 522 in high yield. However, the crucial step in this synthesis was demercuration of this species to afford highly substituted δ-lactone 527, which could serve as a synthetically useful building block in natural product synthesis. Therefore, methyl ester 507 was treated with mercury trifluoroacetate (2.5 equiv) in dichloromethane and the resulting yellow solution was stirred at room temperature for 48 hours. The mixture was quenched with brine and was stirred for a further hour. The crude product was not analysed or purified due to toxicity issues and was taken through immediately to the demercuration step.

Reagents and conditions: (i) Hg(OCOCF$_3$)$_2$, CH$_2$Cl$_2$, rt, 24h then aq. NaCl.

Scheme 98 Synthesis of organomercurial δ-lactone 527

It is thought that the oxymercuration reaction of methyl ester 435 proceeds via a different mechanism to that for formation of α,β-unsaturated lactone 438, since the methyl ester group in 435 is a poorer anchimeric nucleophile than the N-acyl-oxazolidin-2-one fragment of 434. It is proposed that the mercury ion coordinates to the cyclopropane ring of 435, activating it
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

towards nucleophilic attack by a trifluoroacetate ion in an \( S_N 2 \) fashion, ring-opening the cyclopropane with inversion of stereochemistry and forming a carbon-mercury bond (523). This organomercurial intermediate 524 is then hydrolysed upon quenching with brine, to afford intermediate 525, which undergoes an intramolecular cyclisation reaction to afford organomercurial δ-lactone 438 (Scheme 99).\(^{153,185-186}\)

![Scheme 99](image)

The predicted stereochemistry of organomercurial δ-lactone 522 was confirmed using an \(^1\)H NOE spectrum (interactions shown in Figure 6). Proton G shows a strong interaction with proton D confirming the \( cis \) relationship of these axial protons. Further to this, G is also shown to interact with the adjacent equatorial proton on F. The interaction of proton B with E again confirms the \( cis \) relationship. Furthermore no interaction is observed between protons B and G verifying the predicted \( trans \) geometry for these two stereocentres. From this study, the stereochemistry of δ-lactone 522 can be confirmed as \((2R,3R,4S,5S)\), with its solution phase conformation being consistent with that of a distorted chair conformer.
2.8.2 Reductive Demercuration of Organomercurial δ-Lactones

The final step in the synthesis was demercuration of the organomercurial species to afford highly substituted δ-lactones. An initial attempt to demercurate the organomercurial δ-lactone 522 following methodology demonstrated by Cossy and co-workers employed tributyltin hydride and AIBN in a radical demercuration. However, separation of the product from the tributyltin residues proved unsuccessful and this method was abandoned.

A literature search provided an alternative reductive demercuration method developed by Collum and co-workers. Organomercurial δ-lactone 522 was dissolved in methanol and cooled to 0 °C. Sodium borohydride (3 equiv) was dissolved in 3.5 M NaOH and added to the methanolic solution of organomercurial δ-lactone 522. The solution immediately turned grey and was stirred for two minutes at room temperature before being quenched to pH 2 using 1 M HCl. The crude residues were passed through a silica plug and purified via flash silica chromatography to provide demercurated δ-lactone 527 in 81% yield.

Reagents and conditions: (i) NaBH₄ (3 equiv), NaOH (3.5 M), MeOH, rt, 2 min then 1 M HCl quench.

Scheme 100 Reductive demercuration of organomercurial δ-lactone 522
This methodology was then applied to the organomercurial δ-lactones resulting from methyl esters \(506-514\) to afford highly substituted δ-lactones \(526-532\) in high yield and high \(de\). The methyl ester products underwent mercury(II) mediated cyclisation to afford the crude organomercurial δ-lactone species, which was not purified or analysed and was immediately subjected to the reductive demercuration conditions (\(\text{NaBH}_4/\text{NaOH}/\text{MeOH}\)).

| Entry | Methyl Ester Product | δ-Lactone Product | Product | Yield\(^a\)  \\
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Methyl Ester 1" /></td>
<td><img src="image2.png" alt="δ-Lactone 1" /></td>
<td>526</td>
<td>71% &gt;95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Methyl Ester 2" /></td>
<td><img src="image4.png" alt="δ-Lactone 2" /></td>
<td>527</td>
<td>81% &gt;95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Methyl Ester 3" /></td>
<td><img src="image6.png" alt="δ-Lactone 3" /></td>
<td>528</td>
<td>52% &gt;95%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Methyl Ester 4" /></td>
<td><img src="image8.png" alt="δ-Lactone 4" /></td>
<td>529</td>
<td>66% &gt;95%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Methyl Ester 5" /></td>
<td><img src="image10.png" alt="δ-Lactone 5" /></td>
<td>530</td>
<td>72% &gt;95%</td>
</tr>
</tbody>
</table>
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

<table>
<thead>
<tr>
<th></th>
<th>Structure 531</th>
<th>Structure 532</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 531" /></td>
<td><img src="image" alt="Structure 532" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 531" /></td>
<td><img src="image" alt="Structure 532" /></td>
</tr>
</tbody>
</table>

*Isolated yield after column chromatography

Table 6 Synthesis of δ-lactone products 526-532

The reactions of methyl ester 512 and 513 were unsuccessful. The $^1$H NMR spectra of the crude demercurated product showed the starting material had been completely consumed to afford a complex mixture of products. It was unclear as to whether some of the desired demercurated highly substituted δ-lactone was present and purification was not undertaken on these compounds.

2.8.3 Confirmation of Stereochemistry

The stereochemistry of the demercurated highly substituted δ-lactone 527 was again confirmed using NOE spectroscopy. The $^1$H NOE spectrum revealed strong interactions between both sets of axial protons on either side of the chair conformation. Furthermore, there were no interactions observed between protons with a *trans* relationship on the ring. This confirms the *cis* relationship of the axial protons, thus establishing the stereochemistry as (35,4R,5R,6R).
An X-ray crystal structure of δ-lactone 527 provided unequivocal confirmation of the predicted stereochemistry and indicates that the lactone exists in the solid state as a distorted chair conformation.

2.9 Synthesis of Highly Substituted δ-Lactones with a Synthetic Handle

Highly substituted δ-lactones are potentially versatile building blocks for the synthesis of stereomeric analogues of polyketide natural products. However, the incorporation of building blocks containing stereotetrads is simplified if the fragment is bifunctional and orthogonally addressable. Therefore, it was decided to synthesise a highly substituted δ-lactone with a synthetic handle, using the methodology previously described. A benzyl protected alcohol on the R² substituent of the lactone fragment was chosen as the synthetic handle, since a simple deprotection via hydrogenation would furnish an alcohol group that could be functionalised to afford a synthon for natural product syntheses.
The proposed synthesis began with the synthesis of aldehyde 535 (Scheme 101), which would subsequently be used in an asymmetric aldol reaction. A literature procedure developed by Anderson and co-workers was followed for the synthesis. The starting material was commercially available (Z)-but-2-ene-1,4-diol 533, which underwent a mono-benzyl protection (534) in 73% yield and a Swern oxidation to furnish the cis-aldehyde 535 in 84% yield in a 99:1 cis:trans ratio. The cis-aldehyde was then used immediately in an asymmetric aldol reaction to furnish cis-aldol product 536 in 88% yield.

Reagents and conditions: (i) NaH, DMF then BnBr, -20 °C, 5 h then H₂O; (ii) (COCl)₂, DMSO, CH₂Cl₂, -55 °C, 15 min then NEt₃, 15 min then H₂O; (iii) 95, Bu₂BOTf, NEt₃, CH₂Cl₂, -10 °C, 30 min then -78 °C, aldehyde 535, 45 min, then 0 °C, 3 h.

Scheme 101 Synthesis of cis-aldol product 536

It was also discovered that the trans isomer 537 could be obtained in a 99:1 ratio by stirring cis-aldehyde 535 overnight at room temperature in dichloromethane (1 mL) with a catalytic quantity of para-toluenesulphonic acid. This was subsequently used as a substrate in a syn-aldol reaction using the same conditions to afford trans-aldol product 538 in 89% yield.

Reagents and conditions: (i) (COCl)₂, DMSO, CH₂Cl₂, -55 °C, 15 min then NEt₃, 15 min then H₂O. Stir at room temperature in CH₂Cl₂ with p-TSA (cat.) overnight; (iii) 95, Bu₂BOTf, NEt₃, CH₂Cl₂, -10 °C, 30 min then -78 °C, aldehyde 537, 45 min, then 0 °C, 3 h.

Scheme 102 Synthesis of trans-aldol product 537
Aldol products 536 and 538 underwent cyclopropanation in 89% and 95% yield respectively to afford syn-aldol cyclopropane products 539 and 541, which were then transesterified with sodium methoxide to furnish methyl esters 540 and 542 in high yield.

Reagents and conditions: (i) Et₂Zn, CH₂I₂, CH₂Cl₂, 0 °C, 2 h.; (ii) NaOMe, CH₂Cl₂, rt, 5 min.

Scheme 103 Synthesis of methyl esters 540 and 542

Methyl ester 542 was treated with mercury trifluoroacetate in dichloromethane and was stirred for 72 hours at room temperature. The resulting organomercurial δ-lactone 543 then underwent reductive demercuration with sodium borohydride in 3.5 M sodium hydroxide in methanol for one hour before quenching with 1 M HCl to pH 2. The crude product was purified via flash silica chromatography to afford highly substituted δ-lactone 544 in 82% yield as a single diastereomer. However, repeating this procedure on cis-cyclopropyl-methyl ester 540 led to a complex mixture of products. Unfortunately, it appears that this methodology is not successful for the ring-opening of cyclopropanes derived from cis-alkene functionality.

Reagents and conditions: (i) Hg(OCOCF₃)₂, CH₂Cl₂, rt, 72h; (ii) NaBH₄, NaOH (3.5 M), MeOH, rt, 1 h then 1 M HCl.

Scheme 104 Synthesis of δ-lactone 544 containing a terminal O-benzyl group as a potential synthetic handle
2.10 Synthesis of \(N\)-Protected (S,S)-2-Aminomethyl-1-Cyclopropanecarboxylic Acid

The synthetic utility of the retro aldol reaction has been discussed previously in Chapter 1, including previous work by the Bull group for the synthesis of cyclopropane carboxaldehydes, which can function as chiral building blocks for natural product synthesis (Page 19-21). This retro aldol methodology has now been applied to the synthesis of \(\gamma\)-amino acid 549, which has applications in foldamer science.* Initially, syn-cyclopropyl aldon 541 was treated with LiHMDS in toluene at 0 °C for three hours to afford chiral cyclopropane-carboxaldehyde 545 in 92% yield.

\[
\text{Reagents and conditions: (i) LiHMDS (2.2 equiv), toluene, 0 °C, 3h.}
\]

Scheme 105 Retro aldol reaction to afford chiral cyclopropane-carboxaldehydes

Aldehyde 545 underwent reductive amination with sodium triacetoxyborohydride and dibenzylamine to afford amine 546 in 62% yield. An attempt to debenzylate 546 under transfer hydrogenation conditions led to a 50:50 mixture of 547:548 after Boc protection of the amine. However, it was found that treatment of this mixture with \(\text{Pd(OH)}_2\) in THF under a hydrogen atmosphere produced the desired compound 548 in quantitative yield. Finally, alcohol 548 underwent Jones’ oxidation to afford the desired \(\gamma\)-amino acid 549 in 63% yield.

* Work completed in collaboration with Prof. D.J. Aitken and co-workers.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

Reagents and conditions: (i) NaBH(OAc)$_3$, Bn$_2$NH, 545, DCE, 4Å MS, rt, 4 h; (ii) Pd/C (10%), 546, HCO$_2$H, MeOH, rt, 16 h then Boc$_2$O, NaOH, MeOH, rt, 16 h; (iii) Pd(OH)$_2$/C (20%, 60% wet), THF, H$_2$, rt, 2.5 h; (iv) Jones’ reagent, acetone, 0 °C, 2 h then rt, 2 h.

Scheme 106 Synthesis of N-protected (S,S)-2-aminomethyl-1-cyclopropanecarboxylic acid 549

2.11 Total Synthesis of (+)-Prelactone B, E and V

This novel methodology for the synthesis of δ-lactones was then applied to the synthesis of (+)-Prelactone B, E and V 566-568, a series of highly functionalised lactones isolated from bafilomycin-producing microorganisms such as *Streptomyces griseus*. Their discovery supports the hypothesis that polyketide chains are functionalised in an iterative fashion in the biosynthesis of macrolides, where they are formed as ‘shunt-end’ metabolites via premature cleavage from polyketide synthase. These molecules have been shown to exhibit antibacterial, antifungal and immunosuppressive activities as well as ATPase inhibition. Many total syntheses have been reported.

The first consideration when applying our methodology to the synthesis of this natural product series is that the α-position of the Prelactones 566-568 is unsubstituted and therefore $R^1 = H$. It is well known that α-unsubstituted enolates lead to poor stereocontrol in the Evans’ aldol reaction. Therefore, an α-chloro substituent was employed to increase the stereoselectivity of the asymmetric syn-aldol addition that could be removed at a later stage.
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

The boron enolate of α-chloropropionyl-N-acyl-oxazolidin-2-one was reacted with crotonaldehyde, (E)-pent-2-enal and (E)-4-methylpent-2-enal to afford syn-aldol products 554, 555 and 556 respectively. This reaction had a propensity to undergo retro aldolisation, particularly during purification on silica, possibly due to the stabilising effect of the α-chloro substituent on the resulting enolate, which had an impact on the overall yield of these reactions. These syn-aldol products underwent directed cyclopropanation using the conditions previously described to afford 557-559, followed by dechlorination using zinc dust and ammonium chloride in methanol to produce 560-562 in moderate to good yield. The auxiliary fragments of 560-562 were removed via methanolysis, and the resulting methyl esters 563-565 were treated with Hg(OCOCF₃)₂/NaCl(qaq), followed by reductive demercuration with NaBH₄/NaOH/MeOH, to furnish (+)-Prelactone B, E and V 566-568 in acceptable yields and excellent diastereoselectivity of >95%.

Reagents and conditions: (i) 9-BBNOTf or Bu₂OTf, N(iPr)₂Et, CH₂Cl₂, 0 °C, 551-553, -78 °C to rt; (ii) Et₂Zn, CH₂Cl₂, 0 °C, 2 h; (iii) Zn, NH₄Cl, MeOH, rt; (iv) NaOMe (0.5 M in MeOH) CH₂Cl₂, rt, 5 min; (v) Hg(OCOCF₃)₂, CH₂Cl₂, rt, 24 h then aq. NaCl then NaBH₄, NaOH (3.5 M), MeOH, rt, 2 min then 1 M HCl quench.

Scheme 107 Total synthesis of (+)-Prelactone B, E and V 566-568
2.12 Conclusion

Novel methodology for the asymmetric synthesis of highly substituted δ-lactones containing four contiguous stereocenters from syn-aldol cyclopropanes has been demonstrated. An asymmetric aldol reaction followed by the directed cyclopropanation reaction furnishes syn-aldol cyclopropanes 434 in moderate to high yield, with subsequent removal of the chiral auxiliary affording the corresponding methyl ester cyclopropane products 435. The key step involves mercury mediated cyclopropane ring-opening of the methyl ester cyclopropanes to furnish an intermediate that undergoes concomitant cyclisation to afford organomercurial δ-lactones 436. These intermediates subsequently undergo reductive demercuration in basic sodium borohydride to afford the highly substituted δ-lactones 437.

The scope of the novel methodology has been investigated, with variation at the \( R_1 \) and \( R_2 \) substituents. A highly substituted δ-lactone with an \( O\)-benzyl synthetic handle has also been successfully synthesised for use as a building block for natural product synthesis. This novel methodology has also been applied to the total synthesis of (+)-Prelactone B, E and V in good yield and excellent diastereoselectivity. Uses for this research could potentially include use as precursors to generate stereotetrads for natural product synthesis; determination of the stereochemistry in unassigned stereotetrad structures for natural products; and preparation of unnatural analogues of important polyketides and the synthesis of polyketide libraries.\(^{198}\)
3 Results and Discussion

Dihydroxylation Based Approach for the Asymmetric Syntheses of Highly Substituted Hydroxy-γ-Butyrolactones

3.1 Introduction

Highly substituted γ-butyrolactones are found as fragments in many natural products that display a broad range of biological activity. One of the most relevant examples is Vitamin C, L-ascorbic acid 569, an essential nutrient that functions as an antioxidant and a cofactor in many vital enzymatic pathways. Many naturally occurring γ-butyrolactones also possess interesting pharmacological properties such as antibacterial, antifungal, anti-inflammatory and cytotoxic activities. For example, (-)-Stemoamide 570 was isolated from the root of Stemona tuberos, which is used in traditional Chinese and Japanese medicine for the treatment of respiratory diseases. Substituted γ-butyrolactones are also responsible for the distinctive flavours of many alcoholic drinks such as whiskey, cognac and wine.

![natural products containing γ-butyrolactones fragments](image)

Figure 9 Natural products containing γ-butyrolactones fragments
Highly substituted γ-butyrolactones have also been utilised as chiral building blocks for the synthesis of natural products containing multiple contiguous stereocentres.\textsuperscript{210-216} For example, Tatsuta and co-workers used a highly substituted γ-butyrolactone as a precursor in their total synthesis of the tetracyclic antibiotic (−)-Tetrodecamycin \textsuperscript{578}. Enantiomerically pure lactone \textsuperscript{575} was reduced with lithium borohydride to afford straight chain diol \textsuperscript{576} in high yield. This underwent a series of well established synthetic procedures to furnish intermediate \textsuperscript{577}, which was used to complete the first total synthesis of the natural product (−)-Tetrodecamycin \textsuperscript{578}.\textsuperscript{217}

\textit{Reagents and conditions: (i) LiBH\textsubscript{4}, THF, 65 °C, 38 h.}

\textbf{Scheme 109} Highly substituted γ-butyrolactone \textsuperscript{575} as a precursor for the synthesis of (−)-Tetrodecamycin \textsuperscript{578}

The ubiquitous nature of trisubstituted γ-butyrolactones in Nature, as well as their versatile synthetic utility has led to the development of a wide range of methodology for their asymmetric synthesis.\textsuperscript{218-225} Hydroxy-γ-butyrolactones are an important subset within this compound class, and consequently a number of approaches have been established for their asymmetric synthesis.\textsuperscript{226-235} Many of these strategies rely on diastereoselective addition of an enolate to an appropriately substituted electrophile.\textsuperscript{228-229,231}
3.2 Dihydroxylation Approaches for the Asymmetric Synthesis of Highly Substituted Hydroxy-γ-Butyrolactones

A popular approach is dihydroxylation of β,γ-unsaturated carbonyl systems using osmium tetroxide, followed by spontaneous intramolecular lactonisation to afford a γ-butyrolactone skeleton. For example, Shirai and co-workers developed novel methodology for the asymmetric synthesis of hydroxy-γ-butyrolactones containing three contiguous stereocentres. Lactam 579 was treated with standard Upjohn dihydroxylation conditions of OsO₄ and N-methyl-morpholine-N-oxide (NMO) to afford a diastereomeric mixture of diols 580 and 581, which subsequently underwent an acid-catalysed ring switch reaction to afford a mixture of trisubstituted-γ-butyrolactones 582 and 583.

Reagents and conditions: (i) cat. OsO₄, NMO, quinuclidine, CH₂Cl₂, 0 °C; (ii) p-TsOH·H₂O, C₆H₆, rt.

Scheme 110 Synthesis of trisubstituted γ-butyrolactones 582 and 583 via dihydroxylation followed by an acid-catalysed lactonisation reaction

Jenkinson and co-workers have synthesised C-3 and C-4 branched sugar lactones via dihydroxylation of Wittig products 584. The best results were obtained using tartaric acid as a ligand, which was shown to increase the rate of reaction and alter selectivity. The resultant mixture of diols 585 and 586 was separated via column chromatography followed by acid
Dihydroxylation Based Approach for the Asymmetric Syntheses of Highly Substituted Hydroxy-γ-Butyrolactones

catalysed acetal deprotection and subsequent lactonisation to afford 587 and 588 in good yields.\(^{237}\)

\[
\begin{align*}
\text{HO} & \quad \text{CO}_2\text{Me} \\
\text{C}_\text{12}\text{H}_{25} & \quad \text{Et} \\
584 & \quad \text{CO}_2\text{Me} \\
\rightarrow & \quad \text{HO} \\
\text{HO} & \quad \text{H} \\
\text{HO} & \quad \text{H} \\
\text{HO} & \quad \text{H} \\
\text{HO} & \quad \text{H} \\
\text{585} & \quad \text{586} \\
\text{59% yield} & \quad \text{36% yield} \\
\rightarrow & \quad \text{HO} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{HO} \\
\text{587} & \quad \text{588} \\
\text{75% yield} & \quad \text{79% yield}
\end{align*}
\]

Reagents and conditions: (i) \(K_2\text{OsO}_4,\ NMO,\ H_2\text{O},\ ^1\text{BuOH},\ \text{tartaric acid}\); (ii) Dowex (50W X8, \(H^+\)), \(H_2\text{O}\).

Scheme 111 Synthesis of branched sugar lactones via dihydroxylation methodology

Sharpless and co-workers completed a stereoselective synthesis of both enantiomers of Muricatacin using dihydroxylation methodology. Treatment of 589 with AD-mix-\(\alpha\) afforded lactone 590 in 84\% yield, whilst AD-mix-\(\beta\) afforded 591 in 82\% yield, both in >95\% ee.\(^{238}\)

\[
\begin{align*}
\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{C}_\text{12}\text{H}_{25} & \quad \text{HO} \\
589 & \quad \text{HO} \\
\rightarrow & \quad \text{AD-mix-\(\alpha\)} \\
\text{590} & \quad \text{591} \\
(+)-\text{Muricatacin} & \quad (-)-\text{Muricatacin}
\end{align*}
\]

Scheme 112 Total synthesis of (+)- and (-)- Muricatacin 590 and 591 via Sharpless Asymmetric Dihydroxylation
3.3 Previous Work and Initial Results

The Bull group have previously shown that \(\beta,\gamma\)-alkenyl-\(\beta\)-hydroxy-\(N\)-acyloxazolidin-2-one 592 undergoes an epoxidation/lactonisation sequence when treated with catalytic VO(acac)\(_2\) and tert-butylhydroperoxide to afford highly substituted hydroxy-\(\gamma\)-butyrolactone 595. Initially, the epoxidation reaction proceeds with high levels of diastereoccontrol to afford unstable intermediate 593. This undergoes an intramolecular epoxide ring opening reaction via nucleophilic attack of the exocyclic carbonyl of the oxazolidin-2-one fragment through a neighbouring group participation mechanism (593) to generate iminium intermediate 594, with clean inversion of stereochemistry at the C-5 position. Hydrolysis of iminium intermediate 594 furnishes the highly substituted hydroxy-\(\gamma\)-butyrolactone 595 in high yield and diastereoselectivity with release of the SuperQuat auxiliary 445.\(^{242-243}\)

\[
\text{Reagents and conditions: (i) VO(acac)}_2 (10 \text{ mol\%}), \text{^1BuOOH, benzene, rt, 12h.}
\]

**Scheme 113** Epoxidation/lactonisation sequence to afford hydroxy-\(\gamma\)-butyrolactone 595

Following on from this work, the Bull group decided to investigate another approach using Upjohn dihydroxylation conditions,\(^{244}\) with the aim of accessing complementary diastereomers of this type of hydroxy-\(\gamma\)-butyrolactone. The epoxidation/lactonisation sequence described above leads to inversion of configuration at the C-5 position. However, dihydroxylation of alkene 596 was predicted to lead to *anti*-diastereoselectivity with respect to the \(\beta\)-hydroxyl...
group to afford unstable triol 597, which would spontaneously lactonise to furnish diastereomeric hydroxy-γ-butyrolactone 598 and SuperQuat auxiliary 445.243

Scheme 114 Dihydroxylation/lactonisation sequence to afford hydroxy-γ-butyrolactones 598

The stereochemical configuration of hydroxy-γ-butyrolactone 595 produced in the epoxidation/lactonisation sequence had previously been unequivocally assigned as (3S,4S,5S) using X-ray crystallographic analysis.242-243 The corresponding dihydroxylation/lactonisation sequence of β-alkenyl-β-hydroxy-N-acyloxazolidin-2-one 592 was investigated to confirm that the configuration at the C-5 position would be inverted, leading to a different diastereomer of hydroxy-γ-butyrolactone 595. Aldol 592 was treated with standard Upjohn conditions of 10 mol% OsO₄ and N-methylmorpholine-N-oxide (NMO) in acetone:H₂O (8:1) at room temperature to afford a new hydroxy-γ-butyrolactone 599 in 69% yield and in >49:1 dr.

Scheme 115 Dihydroxylation/lactonisation sequence of unsaturated aldol 592 to afford hydroxy-γ-butyrolactone 599 with strong ¹H NOE interactions in 599 confirming stereochemistry
Dihydroxylation Based Approach for the Asymmetric Syntheses of Highly Substituted Hydroxy-γ-Butyrolactones

\(^{1}\)H NOE spectroscopic analysis was used to assign the stereochemical configuration of the new hydroxy-γ-butyrolactone 599. This revealed a strong interaction between the C-3 proton and the methylene protons of the C-5 ethyl group, as well as a strong interaction between the C-4 proton and the C-5 CH₂OH methylene protons, indicating a (3S,4S,5R) configuration. This stereochemical assignment is consistent with the expected anti-diastereoselectivity of the dihydroxylation of unsaturated aldol 592 with respect to the β-hydroxyl group.

Therefore, the epoxidation/lactonisation sequence of unsaturated aldol 592 leads to (3S,4S,5S)-hydroxy-γ-butyrolactone 595. However, application of the dihydroxylation/lactoniation methodology to the same unsaturated aldol product 592 leads to (3S,4S,5R)-hydroxy-γ-butyrolactone 599, which is the complementary C-5 diastereoisomer. The Bull group have previously focused on the synthesis of this type of hydroxy-γ-butyrolactone with variation at both the α-position and of the alkene substituents. However, no direct comparison has been carried out for dihydroxylation of different isomers of alkene with the same substituents.²⁴³

This chapter will therefore focus on a direct comparison between dihydroxylation reactions of alkenes containing different substitution patterns for the synthesis of functionalised hydroxy-γ-butyrolactones containing multiple contiguous stereocentres, with the major diastereoisomer of each lactone produced being controlled by its alkene substitution pattern.
3.4 Asymmetric Synthesis of Unsaturated syn-Aldol Products

A series of aldol products was prepared according to the methodology previously described in Chapter 2. The alkene geometry of the unsaturated aldol products was varied using the same substituents in order to investigate the effect of the alkene substitution pattern on the stereochemical outcome of the dihydroxylation/lactonisation reaction. The CH$_2$OBn group was chosen as a suitable substituent since both cis- and trans-alkenes could be accessed using the methodology previously described in Chapter 2. The resultant lactones containing a terminal O-benzyl fragment represent particularly useful synthetic building blocks for the synthesis of polyketide synthetic targets.

![Scheme 116 Synthesis of α,β-unsaturated syn-aldol products 601](image)

Reagents and conditions: (i) Bu$_2$BOTf/ 9-BBNOTf, N(Pr)$_2$Et/NEt$_3$, CH$_2$Cl$_2$, 0 °C then aldehyde 600, -78 °C.

The synthesis of non-commercially available aldehydes was carried out using established literature procedures. Aldehyde 604 was synthesised in three steps from butane-1,4-diol 602. Mono-benzyl protection of 602 followed by Swern oxidation, produced aldehyde 603 in 75% yield. This was treated with 37% aqueous formaldehyde solution and dimethylamine hydrochloride in a Mannich/elimination type reaction to furnish 4-(benzylxy)-2-methylenebutanal 604 in 78% yield.

![Scheme 117 Synthesis of aldehyde 604](image)

Reagents and conditions: (i) NaH, BnBr, THF, reflux then H$_2$O; (ii) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, -55 °C, 15 min then NEt$_3$, 15 min then H$_2$O; (iii) CH$_3$O (37% solution in H$_2$O), NEt$_3$:HCl, 70 °C, 24 h.
Aldehyde 610 was synthesised from 2-(benzyloxy)ethanol 605 in four steps following a literature procedure.\textsuperscript{246} Swern oxidation of 605 produced aldehyde 606 in 91\% yield, which was treated with (carbethoxyethylidene)triphenylphosphorane 607 in a Horner-Wadsworth-Emmons reaction to afford 608 in 65\% yield. Reduction of ester 608 with DIBAL followed by another Swern oxidation furnished aldehyde 610 in 92\% yield.

\[
\text{HO-OBn} \xrightarrow{(i)} \text{O} \xrightarrow{(ii)} \text{O} \xrightarrow{(iii)} \text{O} \xrightarrow{(iv)} \text{HO-OBn}
\]

\textbf{Scheme 118 Synthesis of aldehyde 610}

Reagents and conditions: (i) (COCl)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, -55 °C, 15 min then NEt\textsubscript{3}, 15 min then H\textsubscript{2}O; (ii) 607, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 30 min; (iii) DIBAL, Et\textsubscript{2}O, -78 °C, 1 h then 0 °C, 1 h; (iv) (COCl)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, -55 °C, 15 min then NEt\textsubscript{3}, 15 min then H\textsubscript{2}O.

The synthesis of (E)-4-(benzylloxy)but-2-enal 537 and (Z)-4-(benzylloxy)but-2-enal 535\textsuperscript{187} and their aldol products 536 and 538 have previously been described in Chapter 2.
**Table 7** Unsaturated syn-aldol products with variation of alkene geometry

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Aldol Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="611.png" alt="Image" /></td>
<td><img src="53.png" alt="Image" /> 613</td>
<td>53%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="604.png" alt="Image" /> O\text{Bn}</td>
<td><img src="53.png" alt="Image" /> 614</td>
<td>78%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="537.png" alt="Image" /> O\text{Bn}</td>
<td><img src="53.png" alt="Image" /> 538</td>
<td>89%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4</td>
<td><img src="535.png" alt="Image" /> O\text{Bn}</td>
<td><img src="53.png" alt="Image" /> 536</td>
<td>88%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td><img src="610.png" alt="Image" /> O\text{Bn}</td>
<td><img src="53.png" alt="Image" /> 615</td>
<td>46%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>6</td>
<td><img src="612.png" alt="Image" /></td>
<td><img src="53.png" alt="Image" /> 616</td>
<td>92%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

<sup>a</sup>χp refers to SuperQuat auxiliary; <sup>b</sup>isolated yield after column chromatography
3.5 Upjohn Dihydroxylation

The Upjohn dihydroxylation reaction was first reported in 1976 for the preparation of cis-1,2-diols from alkenes using catalytic osmium tetroxide and stoichiometric N-methyl-morpholine-N-oxide (NMO) as the re-oxidant. It was developed as an alternative to using stoichiometric quantities of toxic, volatile and expensive osmium tetroxide. It is one of the most widely used reactions in organic synthesis due to its mildness, generality and specificity.

![Scheme 119 General Upjohn dihydroxylation](image)

3.5.1 Mechanism of Upjohn Dihydroxylation

Osmium tetroxide 619 adds across the alkene bond 617 in a [3+2] cycloaddition reaction, generating an osmate ester 620, which is subsequently hydrolysed with two equivalents of water 621 to afford a cis-1,2-diol 618 and reduced dihydroxydioxoosmium 622. This osmium species is re-oxidised by NMO 623, which regenerates the osmium tetroxide catalyst 619.

![Scheme 120 Mechanism of the Upjohn dihydroxylation](image)
The mechanism of the reaction is controversial and has been the subject of intense investigation. Until recently, there was disagreement between two proposed pathways. Originally, Criegee proposed a concerted [3+2] cycloaddition of the O=Os=O bond to the alkene bond to form an osmate ester. In 1977, Sharpless challenged this mechanism by proposing a stepwise [2+2] cycloaddition of the alkene bond to the Os=O bond to form an osmaoxetane ester, which subsequently rearranges to produce the five membered cyclic osmate ester in the rate determining step.

It has subsequently been shown in several studies that the concerted [3+2] cycloaddition is the favoured pathway. It has been shown that the high activation barrier of the [2+2] cycloaddition makes it highly improbable, with this conclusion being supported by computational modelling and experimental kinetic isotope effects.

### 3.5.2 Synthesis of Highly Substituted Hydroxy-γ-Butyrolactones

Unsaturated syn-aldol products were treated with catalytic osmium tetroxide and stoichiometric \( N \)-methyl-morpholine-\( N \)-oxide (NMO) in acetone: \( H_2O \) (8:1) at room temperature. The resulting mixture was stirred for twenty four hours, filtered through Celite® and purified via flash column chromatography to afford a series of hydroxy-\( \gamma \)-butyrolactones in good yield and generally high diastereoselectivity (Table 8).
Dihydroxylation Based Approach for the Asymmetric Syntheses of Highly Substituted Hydroxy-γ-Butyrolactones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol (613-616, 536, 538)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Trial (626-631) (not isolated)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Lactone (632-637)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="613" alt="Aldol" /> 53%, &gt;95% de</td>
<td><img src="626" alt="Triol" /></td>
<td><img src="632" alt="Lactone" /></td>
<td>3:1</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td><img src="614" alt="Aldol" /> 78%, &gt;95% de</td>
<td><img src="627" alt="Triol" /> OBn</td>
<td><img src="633" alt="Lactone" /> OBn</td>
<td>10:1</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td><img src="538" alt="Aldol" /> 89%, &gt;95% de</td>
<td><img src="628" alt="Triol" /></td>
<td><img src="634" alt="Lactone" /> OBn</td>
<td>4:1</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td><img src="536" alt="Aldol" /> 88%, &gt;95% de</td>
<td><img src="629" alt="Triol" /></td>
<td><img src="635" alt="Lactone" /></td>
<td>2:1</td>
<td>74%</td>
</tr>
<tr>
<td>5</td>
<td><img src="615" alt="Aldol" /> 46%, &gt;95% de</td>
<td><img src="630" alt="Triol" /></td>
<td><img src="636" alt="Lactone" /> OBn</td>
<td>&gt;49:1</td>
<td>93%</td>
</tr>
<tr>
<td>6</td>
<td><img src="616" alt="Aldol" /> 92%, &gt;95% de</td>
<td><img src="631" alt="Triol" /></td>
<td><img src="637" alt="Lactone" /></td>
<td>5:1</td>
<td>41%</td>
</tr>
</tbody>
</table>

<sup>a</sup>χ<sub>p</sub> refers to SuperQuat auxiliary.  
<sup>b</sup>Major diastereoisomer formed.  
<sup>c</sup>Configuration of hydroxy-γ- 
butyrolactones confirmed by <sup>1</sup>H NOE spectroscopic analysis.  
<sup>d</sup>Determined by analysis of the crude <sup>1</sup>H NMR spectra.  
<sup>e</sup>Isolated yields after purification by column chromatography.

Table 8 Dihydroxylation of aldols 613-616, 536, 538 to afford hydroxy-γ-butyrolactones 632-637
The stereochemical configuration of each of the hydroxy-γ-butyrolactones 632-637 was determined by $^1$H NOE spectroscopic analysis and X-ray crystallography, as well as by comparison with literature precedent for each of the alkene substitution patterns. In depth analysis of how the configuration of these lactones was assigned is discussed in the next section of this chapter.

Reaction of acrolein aldol 613 under Upjohn dihydroxylation conditions provided a 3:1 mixture of diastereomers in 79% yield, the major diastereomer 632 being formed with anti-diastereocontrol. It was found that dihydroxylation/lactonisation reaction of 1,1-disubstituted aldol 614 proceeded with good levels of anti-diastereoselectivity to afford hydroxy-γ-butyrolactone 633 in a 10:1 mixture of diastereomers and 87% yield. A noticeable difference in selectivity was observed between dihydroxylation of 1,2-trans-disubstituted aldol 538 and 1,2-cis-disubstituted aldol 536, with the trans-system giving a higher level of anti-diastereoselectivity than the cis-system. 1,2-trans-Disubstituted aldol 538 underwent dihydroxylation/lactonisation to form hydroxy-γ-butyrolactone 634 in 77% yield with a 4:1 diastereomeric ratio. Conversely, 1,2-cis-disubstituted aldol 536 was found to undergo dihydroxylation/lactonisation with poor levels of diastereocntrol in a 2:1 mixture in favour of the anti-diastereomer 635 in 74% yield, with the opposite C-6 configuration to that observed for reaction of the 1,2-trans-disubstituted aldol 538. Pleasingly, reaction of (E)-1,1,2-trisubstituted aldol 615 produced excellent levels of anti-diastereoselectivity, providing hydroxy-γ-butyrolactone 636 in 93% yield as a single diastereomer in a >49:1 ratio. However, the dihydroxylation reaction of 1,2,2-trisubstituted aldol 616 proceeded with reduced diastereoselectivity resulting in a 5:1 mixture, with the major hydroxy-γ-butyrolactone 637 having the opposite C-5 configuration to that observed for previous examples. Consequently, the 1,2,2-trisubstituted aldol 616 preferentially undergoes dihydroxylation with syn-diastereoselectivity, before lactonisation to afford (3S,4S,5R)-hydroxy-γ-butyrolactone 637 in 41% yield.
3.6 Assignment of Stereochemistry of Hydroxy-γ-Butyrolactones

3.6.1 Literature Examples

There are numerous examples of Upjohn dihydroxylation reactions in the literature and the topic has been extensively reviewed.\textsuperscript{173,255-258} It has been shown that 1-monosubstituted,\textsuperscript{259-260} 1,1-disubstituted,\textsuperscript{261} 1,2-trans-disubstituted,\textsuperscript{259-260} and 1,1,2-trisubstituted\textsuperscript{262} alkene systems undergo Upjohn dihydroxylation with anti-diastereoselectivity with respect to the hydroxyl group.

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme.png}
\end{center}
\caption{Literature examples of Upjohn dihydroxylation reactions of allylic alcohols with different alkene substitution patterns giving anti-diastereoselectivity}
\end{scheme}
However, 1,2-cis-disubstituted\textsuperscript{259-260} and 1,2,2-trisubstituted\textsuperscript{259-260} alkene systems have been shown to undergo dihydroxylation with modest levels of syn-diastereoselectivity.

\[ \text{Scheme 123} \text{ Literature examples of Upjohn dihydroxylation reactions of allylic alcohols with different alkene substitution patterns giving syn-diastereoselectivity} \]

3.6.2 Stereochemical Models

Several models have been proposed to predict and rationalise the observed diastereoselectivity of osmium catalysed dihydroxylation reactions of allylic alcohols.\textsuperscript{261,263} These include models described by Kishi,\textsuperscript{264-265} Houk\textsuperscript{184,266-268} and Vedejs.\textsuperscript{269-270} All of these stereochemical models are based on the assumption that the step that determines product diastereoselectivity involves competitive attack of the osmium reagent onto one of the two faces of the alkene, in an irreversible [3+2] cycloaddition to produce an osmate ester.\textsuperscript{263}

\[ \text{Figure 10} \text{ Proposed stereochemical models for anti-diastereoselectivity in OsO}_4 \text{ dihydroxylation} \]
Kishi proposed an empirical model based on minimisation of both $A^{1,3}$ strain and electrostatic repulsion between the OsO$_4$ and the C-O bond. Allylic strain is minimised by positioning the smallest substituent ($H_1$) of the stereogenic centre parallel to the double bond. The OsO$_4$ then approaches from the opposite side to the C-O bond to avoid electrostatic repulsion between the allylic oxygen and the incipient O=Os=O bond to afford a diol with with anti-diastereoselectivity.$^{263-265}$

![Scheme 124 Kishi model for anti-diastereoselectivity in dihydroxylation of allylic alcohols](image)

Houk used computational techniques in an extension of the transition state model developed to rationalise the stereochemical outcome of nitrile oxide cycloadditions.$^{267}$ Houk suggested an ‘inside alkoxy’ model,$^{271}$ in which the hydroxyl group is directed towards the incoming OsO$_4$ reagent. The alkyl substituent $R^1$ is positioned anti to the attacking oxidant to avoid steric hindrance. Houk calculated that this conformation is the lowest energy state because electrostatic repulsions between the electron rich alkoxy group and the unfavourable $\sigma/\pi$ interactions of the alkene are minimised. It follows that as the size of $R^1$ increases, the diastereoselectivity also increases, with this model predicting anti diastereoselectivity.$^{184,266-268}$

![Scheme 125 Houk model for anti-diastereoselectivity in dihydroxylation of allylic alcohols](image)
Vedejs suggested that steric interactions between the substrate and the oxidant are dominant in determining the diastereoselectivity. The favoured transition state positions the smallest substituent (H₂A) perpendicular to the alkene diastereoface undergoing dihydroxylation. The large alkyl substituent R¹ is placed on the opposite face of OsO₄ attack to minimise steric hindrance. The stereogenic proton (H₂A) minimises steric interactions with the incoming OsO₄ and consequently this model also predicts anti-diastereoselectivity.²⁶³,²⁶⁹-²⁷⁰

![Scheme 126 Vedejs model for anti-diastereoselectivity in dihydroxylation of allylic alcohols](image)

Although a vast number of highly diastereoselective substrate directed dihydroxylations have been reported, the stereocontrol is yet to be fully understood. The use of a single model is insufficient as it does not succeed in predicting the stereochemical outcome for dihydroxylation of all alkene substitution patterns.²⁶³ For example, Evans found disagreement between Kishi’s model and experimental data on the dihydroxylation of 1,1-disubstituted alkenes.²⁶¹ It was observed that the diastereoselectivity increases as the size of the R¹ alkyl group increases, which directly contradicts the Kishi model prediction. Therefore, Evans suggested that this data set is better explained using the model proposed by Houk.²⁶¹

Rationalising the diastereoselectivity of 1,2-cis-disubstituted alkenes is also problematic.²⁶³ Kishi reported enhanced anti-diastereoselectivity for 1,2-cis-disubstituted alkenes compared with 1,2-trans-disubstituted alkenes.²⁶³⁻²⁶⁵ However, Donohoe found that 1,2-cis-disubstituted systems gave syn-diastereoselectivity.²⁶⁰ These observations are hard to explain using the models previously described. Donohoe proposed that the Kishi model may be used if the OsO₄ approaches from the same side as the free hydroxyl group. This is further enhanced if the alkyl group R¹ is large, which may allow steric interactions to override electronic factors.²⁶⁰
Another consideration is that many experimental observations leading to these models are based on dihydroxylation of protected allylic alcohols, and relatively little work has been undertaken on unprotected allylic alcohols. Therefore, it was decided that evaluation of the steric and electronic features of any given substrate would need to be analysed on an individual basis to predict the stereochemical outcome of dihydroxylation.

3.6.3 $^1$H NOE Spectroscopic Analysis

The stereochemistry of hydroxy-$\gamma$-butyrolactones 632-637 was assigned using $^1$H NOE spectroscopy and the conclusions then compared with literature examples for the dihydroxylation of each type of substitution pattern.

Figure 11 Strong interactions in the $^1$H NOE spectra of the hydroxy-$\gamma$-butyrolactones (632-637)
The $^1$H NOE spectrum of hydroxy-$\gamma$-butyrolactone $632$ derived from 1-monosubstituted aldol $613$ showed strong interaction between the C-3 proton and the C-5 proton, confirming these protons lie on the same face of the lactone ring. There is also a strong interaction between the C-4 proton and the C-5 CH$_2$OH methylene protons, indicating a $(3S,4S,5R)$ configuration. This assignment is consistent with $anti$-diastereoselectivity observed in literature examples of osmium catalysed dihydroxylations for this type of alkene substitution pattern.$^{259-260}$

The stereochemistry of hydroxy-$\gamma$-butyrolactone $633$, derived from 1,1-disubstitued aldol $614$, was unequivocally determined to be $(3S,4S,5R)$ through X-ray crystallographic analysis (Figure 12). Additionally, the $^1$H NOE spectrum of this lactone revealed strong interactions between the C-3 proton and C-5 methylene protons of the O-benzyl substituent, as well as between the C-3 methyl protons and the C-5 CH$_2$OH methylene protons, confirming the configuration of the C-5 stereocentre. This assignment is also consistent with the literature precedent for $anti$-diastereoselective dihydroxylation of 1,1-disubstituted alkenes by Evans and co-workers.$^{261}$

![Figure 12 X-ray crystal structure of $(3S,4S,5R)$-633](image)

The $^1$H NOE spectrum of hydroxy-$\gamma$-butyrolactone $634$, derived from 1,2-trans-disubstituted aldol $538$, showed strong interaction between the C-3 proton and the C-5 proton, confirming these protons lie on the same face of the lactone ring. The stereochemistry was assigned as $(3S,4S,5S)$, which corresponds to an $anti$-diastereoselective dihydroxylation and this is supported by the literature examples reported by Donohoe and co-workers.$^{259-260}$
The $^1$H NOE spectrum for the major diastereomer 635 from the dihydroxylation/lactonisation of 1,2-cis-disubstituted alkene 536 revealed a strong interaction between the C-3 proton and C-5 proton, proving that these protons are on the same face of the lactone. Therefore, the stereochemistry was assigned as (3S,4S,5S), which corresponds to anti-diastereoselectivity. This is in contrast with the findings of Donohoe and co-workers, who found that simple 1,2-cis-disubstituted allylic alcohols gave low levels of syn-diastereoselectivity in a 2:1 mixture using Upjohn conditions. However, the low levels of diastereoselectivity observed in both cases suggests that the directing effects of the allylic alcohol in 1,2-cis-disubstituted systems is limited, so it is therefore not surprising that different substrates result in different selectivities with poor diastereomeric ratios.

The $^1$H NOE spectrum of hydroxy-$\gamma$-butyrolactone 636 from aldol 615 showed strong interactions between protons C-3 and C-5 methyl protons as well as between C-3 methyl group and C-5 CHO proton, leading to a stereochemical assignment of (3S,4S,5S) corresponding to anti-diastereoselectivity. The high levels of anti-diastereoselectivity of >49:1 are consistent with results for the dihydroxylation of (E)-1,1,2-trisubstituted systems in the literature.

The stereochemistry of the major diastereomer 637 of the dihydroxylation/lactonisation reaction of 1,2,2-trisubstituted aldol 616 was determined as (3S,4S,5R), which corresponds to syn-diastereoselectivity. The $^1$H NOE spectrum showed a strong interaction between methyl protons on the C-3 and C-5 proton, proving that these protons lie on the same face of the lactone ring. This observation is consistent with results published by Donohoe and co-workers for the dihydroxylation 1,2,2-trisubstituted allylic alcohols. The $^1$H NMR spectrum of the major diastereomer revealed a vicinal coupling constant between protons on C-4 and C-5 of $^3J = 7.4$ Hz, which is indicative of a syn-relationship between these protons. Conversely, the $^1$H NMR spectrum of the minor diastereomer showed a vicinal coupling constant between the C-3 proton and the C-5 proton of $^3J = 4.0$ Hz, which is consistent with an anti-relationship between these protons in this diastereoisomer.
3.7 Reassignment of Literature Published by Dias and Co-workers

Dias and co-workers had previously described the dihydroxylation/lactonisation of a small series of closely related Evans derived \( \gamma \)-alkenyl-O-silyl aldol products (638-641).\(^{239}\) Surprisingly, the configuration of the resulting O-silyl-\( \gamma \)-butyrolactones (642-645) was reported as (3S,4S,5S), which was different to the results we had obtained. Remarkably, lactones 647 and 649 as reported must have arisen from an *unprecedented* antarafacial dihydroxylation reaction occurring with syn-diastereoselectivity to the \( \beta \)-O-silyl hydroxyl group (Scheme 128).

![Scheme 128](image-url)

Scheme 128 Dias and co-workers’ dihydroxylation/lactonisation of O-TBS protected unsaturated aldols 638-641
This led the Bull group to investigate the effect of the O-silyl group on these type of dihydroxylation/lactonisation reactions.\textsuperscript{243} Therefore, unsaturated aldol 592 was O-TBS protected using TBS-OTf and 2,6-lutidine and subjected to the standard Upjohn dihydroxylation/lactonisation conditions, resulting in the O-TBS γ-butyrolactone 651 in a 3:1 dr. This mixture was then deprotected using TBAF to provide hydroxy-γ-butyrolactone 599 in 65% yield and 3:1 dr (Scheme 129). The \textsuperscript{1}H, \textsuperscript{13}C, and NOE spectra were identical to those of the lactone we had previously formed from dihydroxylation/lactonisation of the unprotected aldol 592.

\includegraphics{scheme129}

\textit{Reagents and conditions}: (i) OsO\textsubscript{4} (10 mol\%), NMO, acetone:H\textsubscript{2}O (8:1); (ii) TBAF, CH\textsubscript{2}Cl\textsubscript{2}.

\textbf{Scheme 129} Dihydroxylation/lactonisation of unprotected aldol 592 and O-TBS aldol 650 afford the same major diastereoisomer of hydroxy-γ-butyrolactone 599.

In light of this result, it was proposed that both the free hydroxyl and O-silyl protected unsaturated aldol derivatives of 592 undergo dihydroxylation with anti-diastereoselectivity to the stereodirecting group. Therefore, it is suggested that the stereochemical assignments of the O-silyl-γ-butyrolactones (646-649) previously reported by Dias and co-workers are incorrect and propose that the configuration of these lactones should be reassigned as shown in Scheme 130.

It should be noted that Dias and co-workers subsequently reported formation of (3S,4S,5R)-stereochemistry for γ-butyrolactone 646 derived from the dihydroxylation/lactonisation of aldol 638, which was used for a natural product synthesis.\textsuperscript{272} This assignment is different to that reported in their original paper, but is consistent with our results.
Dihydroxylation Based Approach for the Asymmetric Syntheses of Highly Substituted Hydroxy-γ-Butyrolactones

Scheme 130 Proposed reassignment of configuration of reported O-silyl-γ-butyrolactones 652-655
3.8 Improving the Diastereoselectivity - Sharpless Asymmetric Dihydroxylation

Upjohn dihydroxylation conditions followed by concomitant lactonisation gave high levels of diastereoselectivity for the majority of alkene substitution patterns described. However, 1,2-cis-disubstituted aldol 536 resulted in a disappointing 2:1 mixture of diastereomers in favour of anti-diastereoselectivity. Therefore, it was proposed that Sharpless asymmetric dihydroxylation conditions273-274 should be investigated to try to improve the diastereoselectivity of this reaction.

3.8.1 Sharpless Asymmetric Dihydroxylation – AD mix

Sharpless asymmetric dihydroxylations are usually performed with pre-mixed reagents known as AD-mix. The components of this mixture are K₂OsO₂(OH)₄, K₃Fe(CN)₆, K₂CO₃ and a chiral quinine ligand. The K₂OsO₂(OH)₄ acts as a source of OsO₄, which is generated in situ. Potassium ferricyanide functions as the re-oxidant in the catalytic cycle and potassium carbonate as a buffer. Coordination of the chiral amine ligands, (DHQ)₂PHAL 656 and (DHQ)₂PHAL 657, to the osmium catalyst leads to formation of a chiral complex, which can distinguish between the pro-chiral faces of the alkene substrate, resulting in enantioselective cis-diol formation on one face of the alkene in preference to the other. These chiral ligands 656 and 657 consist of two naturally derived dihydroquinine alkaloid units linked together by a phthalazine linker. AD-mix-α contains (DHQ)₂PHAL and AD-mix-β contains (DHQD)₂PHAL, with a catalytic quantity of OsO₄ sometimes being added to initiate the dihydroxylation reaction.275

![Figure 13 Chiral quinine ligands in AD-mix for Sharpless Asymmetric Dihydroxylation](image-url)
3.8.2 Sharpless Asymmetric Dihydroxylation – Predicting the Enantioselectivity

The enantioselectivity of the Sharpless asymmetric dihydroxylation can be predicted using the pictorial mnemonic (Scheme 131), where \( R^L \) = large group, \( R^M \) = medium group and \( R^S \) = small group.\(^{256,276}\)

![Scheme 131](image)

Scheme 131 Stereochemical mnemonic for predicting enantioselectivity of Sharpless asymmetric dihydroxylation with AD-mix

The model is best suited to predicting the enantioselectivity of dihydroxylation reactions of trans-alkenes, but cannot usually be used to predict the stereoselective outcome of the dihydroxylation of 1,2-cis-disubstituted alkenes.\(^{256,276}\) Indeed, it is notoriously difficult to obtain high levels of enantioselectivity for the dihydroxylation of simple 1,2-cis-disubstituted alkenes. However, Sharpless found that cis-1,2-disubstituted alkenes undergo dihydroxylation with AD-mix in comparable levels of enantioselectivity with that observed for other substitution patterns if a free allylic alcohol is present. It was proposed that hydrogen bonding by a free hydroxyl group to the oxo group on the osmium species may be responsible for the enhanced enantioselectivity observed for allylic alcohols.\(^{277-278}\) Sharpless suggested that the stereochemical mnemonic should be altered for 1,2-cis-disubstituted alkenes if the \( R^L \) group is substituted for a hydrogen group.\(^{277-278}\)

3.8.3 Sharpless Asymmetric Dihydroxylation of 1,2-cis-Disubstituted Aldol 536

The substrate directed Upjohn conditions led to a dihydroxylation/lactonisation sequence to afford lactone 635 in a 2:1 mixture, the major diastereomer of which corresponded to anti-diastereoselectivity with respect to its \( \beta \)-hydroxyl group. In an attempt to improve this, aldol 536 was treated with AD-mix in a 1:1 mixture of tert-butanol and water along with methylsulfonamide, an additive shown to increase the rate of reaction.\(^{275}\) However, the
reaction was only initiated once an equal volume of dichloromethane was added to aid solubility and a catalytic amount of OsO₄ was added.

Treatment of cis-1,2-disubstituted aldol 536 with AD-mix-β led to an enhancement of stereochemistry observed for dihydroxylation under Upjohn conditions, to afford hydroxy-γ-butyrolactone 635 in a 17:1 mixture of diastereomers and 95% yield in favour of the anti-product. Pleasingly, treatment of aldol 536 with AD-mix-α led to reversal of diastereoselectivity compared with the Upjohn dihydroxylation conditions to afford a 1:4 mixture of diastereomers, with the major lactone 658 being formed as the result of dihydroxylation with syn-diastereoselectivity with respect to the β-hydroxyl group of 536.

These results are consistent with those obtained by Sharpless and co-workers on the dihydroxylation of a simplified (Z)-O-benzyl allylic alcohol. The diastereoselectivity expected using the stereochemical model for cis-1,2-disubstituted alkenes shows that dihydroxylation with AD-mix-β is the 'matched' reaction and should lead to anti-diastereoselectivity. The mnemonic predicts that dihydroxylation with AD-mix-α is the ‘mismatched’ reaction and therefore should have a preference for syn-diastereoselectivity.
However, it has been shown using Upjohn dihydroxylation that the substrate already has a preference for anti-diastereoselectivity. Therefore, it was surprising that the ‘mismatched’ reaction led to reversal of the diastereoselectivity.

**Scheme 133** Modified stereochemical mnemonic for predicting enantioselectivity of Sharpless asymmetric dihydroxylation for 1,2-cis-disubstituted aldol 536

Fortunately, the hydroxy-γ-butyrolactones 635 and 658 were separable using flash column chromatography. This allows either diastereomer of lactone to be prepared and isolated in high enantiomeric purity for potential applications in natural product synthesis.
3.9 Total Synthesis of 2-Deoxy-D-Ribonolactone

The synthetic utility of the dihydroxylation/lactonisation methodology was then demonstrated for the synthesis of 2-Deoxy-D-ribonolactone 663, which is a by-product of oxidative DNA damage.\cite{279-280} It has been synthesised several times previously\cite{281-284} and has also been shown to be a useful synthetic precursor.\cite{285-289} 2-Deoxy-D-ribonolactone 663 is also of interest because its nucleoside derivatives can potentially act as a universal base and non-hydrogen bonding isosteres of nucleobases for chemical biology applications.\cite{290} Therefore, α-chloropropionyl-N-acyl-oxaolidin-2-one 660 was treated under Evans’ asymmetric aldol conditions with acrolein 611 to afford syn-aldol 661 in a 45% yield and in >95% de. This underwent dechlorination with zinc dust and ammonium chloride in methanol to provide the allylic alcohol 662 in 82% yield.\cite{197} Allylic alcohol 662 was then subjected to the standard Upjohn dihydroxylation/lactonisation conditions to afford 2-Deoxy-D-ribonolactone 663 as a 9:1 mixture of diastereoisomers in 87% yield. The spectroscopic data of 663 was consistent with that reported previously.\cite{281-284}

![Scheme 134 Asymmetric synthesis of 2-Deoxy-D-ribonolactone 663](image_url)

Reagents and conditions: (i) Bu$_2$OTf, N(Pr)$_2$Et, CH$_2$Cl$_2$, 0 °C, 611, -78 °C to rt; (ii) Zn, NH$_4$Cl, MeOH, rt; (iii) OsO$_4$ (10 mol%), NMO, acetone:H$_2$O (8:1).
3.10 Conclusion

A method of preparing hydroxy-γ-butyrolactones (632-637) containing multiple contiguous stereocentres in high yield with good diastereoselectivity has been developed. Osmium tetroxide mediated dihydroxylation of a range of β-alkenyl-β-hydroxy-N-acyloxazolidin-2-ones (613-616, 536, 538) results in formation of triols that undergo spontaneous intramolecular 5-exo-trig cyclisation reactions to afford hydroxy-γ-butyrolactones.

![Scheme 135](image)

The configurations of the resulting hydroxy-γ-butyrolactones (632-637) were established using $^1$H NOE spectroscopic analysis, which revealed that the diastereoselectivity of these directed dihydroxylation reactions is dependent on the alkene substitution pattern. It was found that 1-substituted, 1,1-disubstituted, (E)-1,2-disubstituted, (Z)-1,2-disubstituted, and 1,1,2-trisubstituted alkenes undergo dihydroxylation with anti-diastereoselectivity to their β-hydroxyl groups, whereas a 1,2,2-trisubstituted alkene gave the syn-diastereoisomer.

Sharpless asymmetric dihydroxylation conditions were employed to improve the poor levels of diastereoselectivity observed for the dihydroxylation/lactonisation of the (Z)-1,2-disubstituted aldol (536). The synthetic utility of this directed dihydroxylation/lactonisation methodology has also been demonstrated for the synthesis of 2-Deoxy-D-ribonolactone 663.
4 Experimental

General Experimental

All reactions were performed under a nitrogen atmosphere using starting materials and solvents obtained from commercial sources without further purification. Chemicals were purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar and Fluka. Dry solvents were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether boiling at 40-60 °C.

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Advance 250 MHz or a Bruker Advance 300 MHz spectrometer at 303K. The spectra were recorded in CDCl$_3$ solution with chemical shifts reported relative to the residual CDCl$_3$ as an internal standard. Chemical shift is reported in parts per million (ppm) and all coupling constants, $J$, are reported in Hertz (Hz). The multiplicity of the signals is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; dhep, doublet of heptets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; dtd, doublet of triplet of doublets; ddq; doublet of doublet of quartets; td, triplet of doublets; tq, triplet of quartets; qd, quartet of doublets; quin, quintet; sex, sextet; hep, heptet. Diastereomeric excesses (de) were determined by crude $^1$H NMR spectra analysis, with >95% de reported where the minor diastereoisomer was undetectable.

Thin layer chromatography was performed using aluminium backed plates coated with Merck Kieselgel 60 GF$_{254}$ or Macherey-Nagal SilG/UV$_{254}$nm silica gel. Plates were visualised under UV light (254 nm) and stained with phosphomolybdc acid or potassium permanganate followed by heating. Normal phase flash silica column chromatography was performed using Fisher 60Å silica gel (35-70 μm). Infra-red spectra were recorded on a PerkinElmer 100 FT-IR spectrometer. Spectra were recorded as thin films. Mass spectra were recorded using an electrospray Time-of-Flight MicroTOF$^\text{TM}$ mass spectrometer. Masses were recorded in either positive or negative mode. Samples were introduced as either flow injection or syringe pump. Samples were diluted with HPLC grade acetonitrile or methanol. Capillary melting points were determined on a Büchi 535 melting point apparatus and are reported uncorrected. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 mL.
4.1 Compounds from Chapter 2

4.1.1 Synthesis of N-Acyl-Oxazolidin-2-ones 95, 471-473, 515

(S)-4-Benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, 95

n-BuLi (6.43 mL, 16.0 mmol, 2.5 M solution in hexane) was added to a solution of (S)-4-benzyl-5,5-dimethyloxazolidin-2-one 445 (3.00 g, 14.6 mmol) in dry THF (90 mL) at -78 °C under nitrogen and was stirred for 30 minutes. Propionyl chloride (1.40 mL, 16.0 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO$_4$ and concentrated to afford crude product. The crude product was purified via recrystallisation from diethyl ether and hexane to afford (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (3.52 g, 13.4 mmol) as a white solid in 92% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.31-7.17 (5H, m, Ph), 4.48 (1H, dd, $J = 9.6$, 3.9 Hz, CHN), 3.12 (1H, dd, $J = 14.3$, 3.9 Hz, CHH$_2$H$_2$Ph), 2.94-2.81 (3H, m, CH$_3$H$_2$Ph and COCH$_3$), 1.34 (3H, s, C(CH$_3$)(CH$_3$)), 1.33 (3H, t, $J = 7.33$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 174.4, 152.8, 137.1, 129.2, 128.8, 126.9, 82.3, 63.6, 35.5, 29.5, 28.7, 22.4, 8.5; IR cm$^{-1}$ $\nu = 1765$ (C=O$_{\text{ox}}$), 1703 (C=O); HRMS: $m/z$ (ES) 262.1446, C$_{15}$H$_{20}$NO$_3$ [M+H]$^+$ requires 262.1443; $[\alpha]^{25}_D = -42.0$ (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(S)-4-Benzyl-5,5-dimethyl-3-(3-methylbutanoyl)oxazolidin-2-one, 4713

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{O} \\
& \quad \text{C} & \quad \text{C} & \quad \text{C}
\end{align*}
\]

\(n\text{-BuLi} (1.71 \text{ mL}, 4.29 \text{ mmol}, 2.5 \text{ M solution in hexane})\) was added to a solution of (S)-4-benzyl-5,5-dimethyloxazolidin-2-one 445 (0.80 g, 3.90 mmol) in dry THF (30 mL) at -78 °C under nitrogen and was stirred for 30 minutes. Isovaleryl chloride (0.52 mL, 4.29 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO\(_4\) and concentrated to afford crude product. The crude product was purified using flash silica chromatography \([\text{CH}_2\text{Cl}_2, \ R_f \ 0.71]\) to afford (S)-4-benzyl-5,5-dimethyl-3-(3-methylbutanoyl)oxazolidin-2-one 471 (0.81 g, 2.80 mmol) as a colourless oil that solidified on standing in 72% yield. \(^1\text{H NMR (300 MHz, CDCl}_3\)} \(\delta = 7.31-7.17 (5\text{H, m, Ph}), 4.49 (1\text{H, dd, } J = 9.5, 3.9 \text{ Hz, CHN}), 3.11 (1\text{H, dd, } J = 14.3, 3.9 \text{ Hz, CH}_2\text{H}_3\text{Ph and COCH}_3), 2.13 (1\text{H, hep, } J = 6.8 \text{ Hz, CH(CH}_3)_2), 1.34 (3\text{H, s, C(CH}_3)(CH}_3)), 1.33 (3\text{H, s, C(CH}_3)(CH}_3)), 0.95 (3\text{H, d, } J = 1.5 \text{ Hz, CH(CH}_3)(CH}_3)), 0.93 (3\text{H, d, } J = 1.5 \text{ Hz, CH(CH}_3)(CH}_3)); \(^{13}\text{C NMR (75 MHz, CDCl}_3\)} \(\delta = 173.0, 152.7, 137.1, 129.1, 128.8, 126.9, 82.1, 63.5, 44.1, 35.5, 28.6, 25.2, 22.6, 22.5, 22.4); \ IR \text{ cm}^{-1} \nu = 1770 (\text{C=O ox}), 1694 (\text{C=O}); \text{ HRMS: } m/z \text{ (ES) 290.1758, C}_{17}\text{H}_{24}\text{NO}_3 \ [\text{M+H}]^+\) requires 290.1756; \(\alpha^\circ \text{D}^{25} = -38.0 \ (c = 0.5 \text{ g/100 mL in CHCl}_3)\).
Experimental

(S)-4-Benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one, 472

n-BuLi (1.71 mL, 4.29 mmol, 2.5 M solution in hexane) was added to a solution of (S)-4-benzyl-5,5-dimethyloxazolidin-2-one 445 (0.80 g, 3.89 mmol) in dry THF (30 mL) at -78 °C under nitrogen and was stirred for 30 minutes. Phenylacetyl chloride (0.56 mL, 4.29 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [CH₂Cl₂, Rf 0.61] to afford (S)-4-benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one 472 (0.96 g, 3.89 mmol) as a colourless oil, which solidified on standing in 76% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.33-7.15 (10H, m, Phox and Ph), 4.46 (1H, dd, J = 9.6, 3.8 Hz, CHN), 4.25 (2H, s, COCH₂Ph), 3.11 (1H, dd, J = 14.4, 3.8 Hz, CH₂H₂Ph), 2.82 (1H, J = 14.4, 9.6 Hz, CH₂H₂Ph), 1.34 (3H, s, C(CH₃)(CH₂)), 1.29 (3H, s, C(CH₃)(CH₂)); ¹³C NMR (75 MHz, CDCl₃) δC = 171.6, 152.7, 137.0, 133.8, 129.8, 129.2, 128.8, 128.7, 127.3, 126.9, 82.5, 63.9, 41.9, 35.3, 28.7, 22.4; IR cm⁻¹ ν = 1765 (C=Oox), 1712 (C=O); HRMS: m/z (ES) 324.1605, C₂₀H₂₂NO₃ [M+H]⁺ requires 324.1599; [α]D²⁵ = -36.0 (c = 0.5 g/100 mL in CHCl₃).
**Experimental**

(S)-4-Benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyloxazolidin-2-one, 473

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{OMe}
\end{align*}
\]

\(n\text{-BuLi (2.14 mL, 5.36 mmol, 2.5 M solution in hexane)}\) was added to a solution of (S)-4-benzyl-5,5-dimethyloxazolidin-2-one 445 (1.00 g, 4.87 mmol) in dry THF (30 mL) at -78 °C under nitrogen and was stirred for 30 minutes. 4-Methoxyphenylacetyl chloride (0.82 mL, 5.36 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO\(_4\) and concentrated to afford crude product. The crude product was purified using flash silica chromatography [CH\(_2\)Cl\(_2\), \(R_f\) 0.79] to afford (S)-4-benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyloxazolidin-2-one 473 (1.34 g, 3.80 mmol) as a colourless oil, which crystallised on standing in 78% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta \) = 7.31-7.19 (7H, m, Ph and C\(_6\)H\(_2\)H\(_2\)OMe), 6.87 (2H, d, \(J = 8.8 \text{ Hz, C}_6\)H\(_2\)H\(_2\)OMe), 4.50 (1H, dd, \(J = 9.8, 3.7 \text{ Hz, CHN})

\text{4.22 (2H, s, CH}_2\text{Ar}, 3.79 (3H, s, OCH}_3\text{), 3.13 (1H, dd, J = 14.4, 3.7 Hz, CH}_3\text{H}_8\text{Ph), 2.85 (1H, dd, J = 14.4, 9.6 Hz, CH}_3\text{H}_8\text{Ph), 1.36 (3H, s, C(CH}_3\text{)(CH}_3\text{)), 1.32 (3H, s, C(CH}_3\text{)(CH}_3\text{));} \]

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta \) = 171.9, 158.8, 152.7, 136.9, 130.8, 129.1, 128.7, 126.8, 125.8, 114.1, 82.4, 63.8, 55.3, 40.9, 35.3, 28.6, 22.4; IR cm\(^{-1}\) \(\nu = 1765 \) (C=O\(_{\text{ox}}\)), 1711 (C=O); HRMS: \(m/z\) (ES) 376.1515, \(C_{21}H_{23}\text{NNaO}_4\) [M+Na\(^{+}\)] requires 376.1524; \([\alpha]_{D}^{15} = -30.0 \text{ (c = 0.77 g/100 mL in CHCl}_3\text{).} \)
Experimental

\((S)-4\text{-}{\text{Benzyl-3-propionyloxazolidin-2-one, 515}}^{166}\)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{H}_3
\end{array}
\]

\(n\text{-BuLi (4.96 mL, 12.42 mmol, 2.5 M solution in hexane) was added to a solution of (S)-4-benzyl-oxazolidin-2-one 444 (2.00 g, 11.29 mmol) in dry THF (60 mL) at -78 \, ^\circ\text{C} \text{under nitrogen and was stirred for 30 minutes. Propionyl chloride (1.08 mL, 12.42 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO}_4\text{ and concentrated to afford crude product. The crude product was purified via recrystallisation in diethyl ether and hexane to afford (S)-4-benzyl-3-propionyloxazolidin-2-one 515 (1.90 g, 8.12 mmol) as a white crystalline solid in 72\% yield.}^{1}\text{H NMR (300 MHz, CDCl}_3) \delta_H = 7.30-7.15 (5H, m, Ph), 4.66-4.58 (1H, m, CHN), 4.17-4.08 (2H, m, CH}_2O), 3.24 (1H, dd, \(J = 13.3, 3.2 \, \text{Hz, CH}_2HPh), 2.98-2.69 (2H, m, CH}_2CH}_3), 2.73 (1H, dd, \(J = 13.3, 9.5 \, \text{Hz, CH}_2HPh), 1.15 (3H, t, \(J = 7.3 \, \text{Hz, CH}_2CH}_3);^{13}\text{C NMR (75 MHz, CDCl}_3) \delta_C = 174.0, 153.5, 135.4, 129.4, 128.9, 127.3, 66.2, 55.2, 37.9, 29.2, 8.3; \text{IR } \text{cm}^{-1} \nu = 1785 (\text{C}=\text{O}_\text{ox}), 1701 (\text{C}=\text{O}); \text{HRMS: } m/z (\text{ES}) 256.0948, \text{C}_{13}\text{H}_{15}\text{NNaO}_3 [\text{M+Na}]^+ \text{requires 256.0949}; [\alpha]_{D}^{25} = +90.4 \, (c = 0.95 \text{ g/100 mL in CHCl}_3).\]
4.1.2 Synthesis of Syn-Aldol Products 474-481, 517

Asymmetric Syn-Aldol Reaction – General Procedure 1

The appropriate acylated auxiliary 95, 471-473, 515 (1 equiv.) was dissolved in dry dichloromethane at 0 °C under nitrogen. Dibutylboron triflate (1.1 equiv., 1.0 M in dichloromethane) was added dropwise. After 30 minutes, N,N-diisopropylethylamine (1.3 equiv.) was added and the resulting solution was stirred for 30 minutes. The reaction was cooled to -78 °C. The appropriate aldehyde (1.3 equiv.) was added in one portion and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution (Na₂HPO₄/NaH₂PO₄) (10 mL) and was stirred for 10 minutes. Hydrogen peroxide (4 mL) and methanol (8 mL) were then added and the solution was stirred for a further two hours. The methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product, which was purified as described.
The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (1.50 g, 5.74 mmol), dibutylboron triflate (6.31 mL, 6.31 mmol, 1 M in dichloromethane), diisopropylethylamine (1.28 mL, 7.46 mmol) and crotonaldehyde (0.61 mL, 7.46 mmol) in dichloromethane (25 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.54] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 474 (1.80 g, 5.45 mmol) as a colourless gum in 95% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 7.39–7.17 (5H, m, Ph), 5.74 (1H, dqq, J = 15.5, 6.5, 1.0 Hz, CH=CHCH$_3$), 5.48 (1H, ddd, J = 15.5, 6.5, 1.5 Hz, CH=CHCH$_3$), 4.60 (1H, dd, J = 9.0, 4.5 Hz, CHN), 4.53 (1H, m, CHOH), 3.91 (1H, qd, J = 7.0, 4.5 Hz, COCH), 3.05 (1H, dq, J = 14.5, 4.5 Hz, CH$_2$H$_5$Ph), 2.90 (1H, dd, J = 14.5, 9.0, CH$_3$H$_5$Ph), 2.60 (1H, d, J = 2.5 Hz, OH), 1.70 (3H, d, J = 6.5 Hz, CH=CHCH$_3$), 1.39 (3H, s, CH$_3$C(CH$_3$)$_2$), 1.38 (3H, s, (CH$_3$)$_2$C(CH$_3$)$_2$), 1.15 (3H, d, J = 7.0 Hz, CH$_3$CH); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 176.9, 152.9, 137.1, 130.6, 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 cm$^{-1}$ ν = 3508 (OH), 1775 (C=O ox), 1696 (C=O); HRMS: m/z (ES) 332.1855, C$_{19}$H$_{29}$N$_2$O$_4$ [M+NH$_4$]$^+$ requires 332.1856; [α]$_D$$^{25}$ = -24.0 (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(S)-4-Benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 475

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (1.00 g, 3.83 mmol), dibutylboron triflate (4.21 mL, 4.21 mmol, 1 M in dichloromethane), diisopropylethylamine (0.87 mL, 4.97 mmol) and cinnamaldehyde (0.62 mL, 4.97 mmol) in dichloromethane (12 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.46] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one 475 (1.31 g, 3.29 mmol) as a white solid in 86% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H$ = 7.40-7.20 (10H, m, Ph$_{ox}$ and Ph), 6.66 (1H, d, $J = 16.0$ Hz, CH=CHPh), 6.19 (1H, dd, $J = 15.9$, 5.9 Hz, CH=CHPh), 4.62-4.59 (1H, m, CHO), 4.54 (1H, dd, $J = 8.8$, 4.6 Hz, CHN), 4.01 (1H, qd, $J = 6.8$, 4.3 Hz, CH$_2$), 3.07 (1H, dd, $J = 14.4$, 4.6 Hz, CH$_2$), 2.91 (1H, dd, $J = 14.2$, 8.7 Hz, CH$_3$), 2.83 (1H, broad s, OH), 1.38 (3H, s, C(CH$_3$)$_2$(CH$_3$)), 1.31 (3H, s, C(CH$_3$)$_2$(CH$_3$)), 1.20 (3H, d, $J = 7.4$ Hz, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C$ = 176.7, 152.6, 136.7, 131.7, 129.2, 128.8, 128.7, 128.6, 127.8, 127.04, 126.7, 82.5, 73.1, 63.5, 43.1, 35.6, 28.4, 22.3, 11.8; IR cm$^{-1}$: $\nu$ = 3444 (OH), 1769 (C=O$_{ox}$), 1683 (C=O); HRMS: m/z (ES) 416.1828, C$_{24}$H$_{27}$NNaO$_4$ [M+Na]$^+$ requires 416.1837; $[\alpha]^{25}_D$ = +74.0 (c = 0.5 g/100 mL in CHCl$_3$).
(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 476

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and 3-methyl-2-butenal (0.38 mL, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.65] to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 476 (0.85 g, 2.46 mmol) as a colourless oil in 81% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.33-7.19 (5H, m, Ph), 5.23 (1H, m, CH=C(CH$_3$)$_2$), 4.59 (1H, dd, $J = 8.7, 5.0$ Hz, CHO), 4.51 (1H, dd, $J = 8.8, 4.6$ Hz, CHN), 3.97-3.89 (1H, m, CHCH$_3$), 3.05 (1H, dd, $J = 14.3, 4.5$ Hz, CH$_3$H$_5$Ph), 2.89 (1H, dd, $J = 14.2, 9.0$ Hz, CH$_3$H$_5$Ph), 2.32 (1H, broad s, OH), 1.71 (3H, d, $J = 1.3$ Hz, C=C(CH$_3$)(CH$_3$)), 1.67 (3H, d, $J = 1.3$ Hz, C=C(CH$_3$)(CH$_3$)), 1.19 (3H, s, OC(CH$_3$)(CH$_3$)), 1.17 (3H, s, OC(CH$_3$)(CH$_3$)), 1.17 (3H, d, $J = 7.0$ Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 176.4, 152.7, 136.9, 136.8, 129.3, 128.8, 129.3, 128.8, 127.0, 124.3, 82.3, 69.6, 63.5, 43.1, 35.6, 28.3, 26.0, 22.2, 18.5, 12.4; IR cm$^{-1}$: $\nu = 3505$ (OH), 1772 (C=O), 1692 (C=O); HRMS: $m/z$ (ES) 368.1843, C$_{20}$H$_{27}$NNaO$_4$ [M+Na]$^+$ requires 368.1837; $\alpha$$_D^{25} = -28.0$ (c = 0.5 g/100 mL in CHCl$_3$).
(S)-4-Benzyl-3-((2S,3R,E)-3-hydroxy-2-methylundec-4-enoyl)-5,5-dimethyloxazolidin-2-one, 477

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and trans-2-nonenal (0.66 mL, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.68] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methylundec-4-enoyl)-5,5-dimethyloxazolidin-2-one 477 (0.81 g, 2.02 mmol) as a colourless oil in 66% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 7.31-7.18 (5H, m, Ph), 5.76-5.66 (1H, m, CH=CH$_2$), 5.43 (1H, dd, $J$ = 15.4, 6.4 Hz, CH=CH$_2$), 4.51 (1H, dd, $J$ = 9.0, 4.5 Hz, CHN), 4.34 (1H, app. t, $J$ = 5.0 Hz, CHO), 3.89 (1H, app. t, $J$ = 5.0 Hz, CHO), 3.89 (1H, app. t, $J$ = 5.0 Hz, CHO), 3.20 (1H, dd, $J$ = 14.3, 4.5 Hz, CH$_3$), 3.05 (1H, dd, $J$ = 14.3, 4.5 Hz, CH$_3$), 2.88 (1H, dd, $J$ = 14.3, 9.0 Hz, CH$_3$), 2.68 (1H, broad s, OH), 2.04-1.97 (2H, m, C=CH$_3$), 1.37-1.24 (14H, m, C$_7$H$_8$ and C(CH$_3$)$_2$), 1.13 (3H, d, $J$ = 9.0 Hz, CH$_3$), 0.88-0.84 (3H, m, C$_9$H$_{15}$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 176.5, 152.5, 136.7, 133.6, 129.1, 128.9, 128.7, 126.9, 82.3, 73.1, 63.4, 42.9, 35.4, 32.3, 31.7, 29.1, 28.9, 28.3, 22.6, 22.2, 14.1, 11.7; IR cm$^{-1}$ ν = 3501 (OH), 1773 (C=O$_{ax}$), 1696 (C=O); HRMS: m/z (ES) 424.2451, C$_{24}$H$_{35}$NNaO$_4$ [M+Na]$^+$ requires 424.2463; [α]$_D^{25}$ = -18.0 (c = 0.5 g/100 mL in CHCl$_3$).
The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and trans-4-nitrocinamaldehyde (0.70 g, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography \([\text{CH}_2\text{Cl}_2], R_f 0.14\) to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)-5,5-dimethyloxazolidin-2-one 478 (0.89 g, 2.03 mmol) as an orange solid in 66% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H = 8.16$ (2H, d, $J = 8.8$ Hz, C$_6$H$_2$H$_2$NO$_2$), 7.50 (2H, d, $J = 8.8$ Hz, C$_6$H$_2$H$_2$NO$_2$), 7.33-7.21 (5H, m, Ph), 6.75 (1H, d, $J = 15.6$ Hz, CH=CHC$_6$H$_4$NO$_2$), 6.35 (1H, dd, $J = 16.0$, 5.2 Hz, CH=CHC$_6$H$_4$NO$_2$), 4.70-4.67 (1H, m, OH), 4.56 (1H, dd, $J = 8.7$, 5.0 Hz, CHN), 3.99 (1H, qd, $J = 7.1$, 3.4 Hz, CHCH$_3$), 3.13-3.09 (1H, broad s, OH), 2.98 (1H, dd, $J = 14.3$, 4.8 Hz, CH$_3$H$_8$Ph), 2.92 (1H, dd, $J = 14.6$, 8.8 Hz, CH$_3$H$_8$Ph), 1.41 (3H, s, C(CH$_3$)(CH$_3$)), 1.35 (3H, s, C(CH$_3$)(CH$_3$)), 1.18 (3H, d, $J = 7.1$ Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C = 176.73$, 152.5, 147.1, 143.3, 136.5, 133.7, 129.3, 129.2, 128.8, 127.2, 127.1, 124.1, 82.6, 72.2, 63.4, 42.8, 35.6, 28.5, 22.3, 11.5; IR cm$^{-1}$ $\nu = 3512$ (OH), 1774 (C=O); HRMS: m/z (ES) 461.1657, C$_{24}$H$_{26}$N$_2$NaO$_6$ [M+Na]$^+$ requires 461.1688; $[\alpha]_D^{25} = -18.0$ (c = 0.5 g/100 mL in CHCl$_3$).
(S)-4-Benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)oxazolidin-2-one, 517

(S)-4-Benzyl-3-propionyloxazolidin-2-one 515 (0.80 g, 3.43 mmol) was dissolved in dry dichloromethane (10 mL) at 0 °C under nitrogen and was stirred for 30 minutes. 9-Borabicyclo[3.3.1]nonyl triflate (7.54 mL, 3.77 mmol, 0.5 M in hexane) was added dropwise. After 30 minutes, diisopropylethylamine (0.78 mL, 4.46 mmol) was added and the resulting solution was stirred for 30 minutes before being cooled to -78 °C. trans-4-Nitrocinamaldehyde (0.79 g, 4.46 mmol) was added in one portion and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution (Na₂PO₄/NaH₂PO₄) (10 mL) and was stirred for 10 minutes. Hydrogen peroxide (4 mL) and methanol (8 mL) were then added and the solution was stirred for a further two hours. The methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.45] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)oxazolidin-2-one 517 (0.97 g, 2.36 mmol) as a fluffy yellow solid in 69% yield. ¹H NMR (300 MHz, CDCl₃) δ_H = 8.11 (2H, d, J = 8.7 Hz, C₆H₉H₂NO₂), 7.46 (2H, d, J = 8.7 Hz, C₆H₉H₂NO₂), 7.31-7.13 (5H, m, Ph), 6.73 (1H, d, J = 15.9, 1.3 Hz, CH=CHC₆H₄NO₂), 6.32 (1H, dd, J = 15.9, 5.1 Hz, CH=CHC₆H₄NO₂), 4.72-4.64 (2H, m, CH and CHO), 4.21-4.14 (2H, m, OCH₂), 3.92 (1H, qd, J = 7.0, 3.1 Hz, CHCH₃), 3.20 (1H, dd, J = 13.5, 3.4 Hz, CH₃CH₂Ph), 2.85 (1H, broad s, OH), 2.76 (1H, dd, J = 13.4, 9.4 Hz, CH₃CH₂Ph), 1.23 (3H, d, J = 7.1 Hz, CHCH₂); ¹³C NMR (75 MHz, CDCl₃) δ_C = 176.7, 153.2, 147.1, 143.2, 134.9, 133.7, 129.5, 129.3, 129.1, 127.6, 127.1, 124.1, 71.9, 66.5, 55.1, 42.6, 37.9, 11.2; IR cm⁻¹ v = 3540 (OH), 1773 (C=O), 1686 (C=O); HRMS: m/z (ES) 433.1358, C₂₂H₂₂N₄O₆ [M+Na]⁺ requires 433.1375; [α]D²⁵ = +58.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(S)-4-Benzyl-3-((2S,3R,E)-3-hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 479

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

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and trans-4-methoxycinnamaldehyde (0.64 g, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:CH\(_2\)Cl\(_2\), R\(_f\) 0.05] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 479 (0.72 g, 1.70 mmol) as a yellow solid in 56% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.33-7.20\) (7H, m, Ph and C\(_6\)H\(_2\)OMe), 6.83 (2H, d, J = 8.9 Hz, C\(_6\)H\(_2\)OMe), 6.58 (1H, d, J = 15.8 Hz, CH=CHC\(_6\)H\(_4\)OMe), 6.06 (1H, dd, J = 15.8, 6.2 Hz, CH=CHC\(_6\)H\(_4\)OMe), 4.59-4.51 (2H, m, CHOH and CHN), 4.02 (1H, qd, J = 7.0, 4.2 Hz, CHCH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 3.06 (1H, dd, J = 14.3, 4.6 Hz, CH\(_2\)Ph), 2.90 (1H, dd, J = 14.4, 8.9 Hz, CH\(_2\)OMe), 2.73 (1H, d, J = 2.2 Hz, OH), 1.38 (3H, s, C(CH\(_3\))(CH\(_3\))), 1.30 (3H, s, C(CH\(_3\))(CH\(_3\))), 1.20 (3H, d, J = 6.9 Hz, CHCH\(_3\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 176.7, 156.0, 152.6, 136.9, 134.3, 129.2, 128.8, 127.1, 114.0, 82.3, 75.7, 63.5, 55.5, 43.4, 35.4, 28.3, 26.0, 22.4, 20.6, 13.6, 12.4; IR cm\(^{-1}\) \(\nu = 3509\) (OH), 1770 (C=O), 1692 (C=O), 1511 (OCH\(_3\)) HRMS: \(m/z\) (ES) 446.1926, C\(_{25}\)H\(_{30}\)NNaO\(_5\) \([\text{M+Na}]^+\) requires 446.1943; \([\alpha]_{D}^{25} = +8.0\) (c = 0.5 g/100 mL in CHCl\(_3\)).
Experimental

\((S)-4\text{-benzyl-3-((2S,3R,E)-3-hydroxy-2-isopropylhex-4-enoyl})-5,5\text{-dimethyloxazolidin-2-one, 480}\)

\[
\begin{array}{c}
\text{O} & \text{O} & \text{OH} \\
\text{N} & \text{C} & \text{C} \\
\text{Ph} & \text{CH}_2 & \text{CH}_2
\end{array}
\]

The title compound was prepared according to General Procedure 1 from \((S)-4\text{-benzyl-5,5-dimethyl-3-(3-methylbutanoyl)oxazolidin-2-one 471}\) (0.50 g, 1.73 mmol), dibutylboron triflate (1.90 mL, 1.90 mmol, 1 M in dichloromethane), diisopropylethylamine (0.39 mL, 2.25 mmol) and crotonaldehyde (0.19 mL, 2.25 mmol) in dichloromethane (8 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.48] to afford \((S)-4\text{-benzyl-3-((2S,3R,E)-3-hydroxy-2-isopropylhex-4-enoyl})-5,5\text{-dimethyloxazolidin-2-one 480}\) (0.51 g, 1.42 mmol) as a colourless gum in 82% yield. \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta_H = 7.26-7.15 \text{ (5H, m, Ph)}, 5.74-5.58 \text{ (2H, m, CH\textsubscript{2}=CHCH\textsubscript{3})}, 4.54 \text{ (1H, dd, } J = 10.0, 3.7 \text{ Hz, CHN)}, 4.36 \text{ (1H, app. t, } J = 6.9 \text{ Hz, CHOH)}, 4.09 \text{ (1H, dd, } J = 8.8, 6.7 \text{ Hz, CH(\textsubscript{Pr}))}, 3.09 \text{ (1H, dd, } J = 14.3, 3.7 \text{ Hz, CH\textsubscript{2}H\textsubscript{2}Ph)}, 2.83 \text{ (1H, dd, } J = 14.4, 9.8 \text{ Hz, CH\textsubscript{2}H\textsubscript{2}Ph)}, 2.05-1.92 \text{ (1H, m, CH(CH\textsubscript{3})(CH\textsubscript{3})}), 1.81 \text{ (1H, broad s, OH)}, 1.66 \text{ (3H, d, } J = 5.1 \text{ Hz, CH=CHCH\textsubscript{3}}), 1.28 \text{ (6H, s, C(CH\textsubscript{3})(CH\textsubscript{3})}), 0.92 \text{ (3H, d, } J = 6.7 \text{ Hz, CH(CH\textsubscript{3})(CH\textsubscript{3})}), 0.84 \text{ (3H, d, } J = 6.7 \text{ Hz, CH(CH\textsubscript{3})(CH\textsubscript{3})}); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta_C = 174.4, 153.5, 137.1, 130.2, 129.8, 129.2, 128.8, 126.9, 82.1, 73.4, 64.0, 53.8, 35.7, 28.4, 28.3, 22.3, 20.6, 20.1, 18.0; \)IR cm\textsuperscript{-1} \(\nu = 3498 \text{ (OH)}, 1772 \text{ (C=O\textsubscript{ox})}, 1690 \text{ (C=O)}; \)HRMS: m/z (ES) 382.1984, C\textsubscript{21}H\textsubscript{29}N\textsubscript{Na}O\textsubscript{4} [M+Na]\textsuperscript{+} requires 382.1994; \([\alpha]\)\textsubscript{D}\textsuperscript{25} = -14.0 \text{ (c = 0.5 g/100 mL in CHCl\textsubscript{3})}.
Experimental

(S)-4-Benzyl-3-((2S,3R,E)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 481

The title compound was prepared according to General Procedure 1 from (S)-4-benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyl-oxazolidin-2-one 473 (0.35 g, 0.99 mmol), 9-BBN triflate (2.17 mL, 1.09 mmol, 0.5 M in hexane), diisopropylethylamine (0.22 mL, 1.28 mmol) and crotonaldehyde (0.10 mL, 1.28 mmol) in dichloromethane (6 mL). The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, R_f 0.25] to afford (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 481 (0.30 g, 0.71 mmol) as a colourless gum in 72% yield.

_{1}H NMR (300 MHz, CDCl_3) δ_H = 7.35 (2H, d, J = 9.0 Hz, C_6H_5CH_3), 7.19-7.11 (5H, m, Ph), 6.88 (2H, d, J = 9.0 Hz, C_6H_5CH_3CH_2OMe), 5.84-5.73 (1H, m, CH=CHCH_3), 5.48 (1H, ddd, J = 15.3, 7.2, 1.6 Hz, CH=CHCH_3), 5.13-5.00 (1H, m, CH_2CH_2OMe), 4.65 (1H, app. t, J = 7.5 Hz, CHO), 4.50 (1H, ddd, J = 9.2, 4.1 Hz, CHN), 3.81 (3H, s, OCH_3), 2.90 (1H, dd, J = 14.4, 4.1 Hz, CH_2CH_2CH_3), 2.70 (1H, dd, J = 14.4, 9.2 Hz, CH_2CH_2CH_3), 2.08 (1H, broad s, OH), 1.67 (3H, dd, J = 6.5, 1.4 Hz, CHCH_3), 1.34 (3H, s, C(CH_3)(CH_3)), 1.31 (3H, s, C(CH_3)(CH_3)); _{13}C NMR (75 MHz, CDCl_3) δ_C = 173.0, 159.4, 152.1, 136.7, 131.1, 130.6, 129.6, 129.1, 128.7, 126.8, 126.2, 114.2, 82.2, 74.1, 63.5, 55.4, 54.4, 35.1, 28.4, 22.2, 17.9; IR cm⁻¹ ν = 3504 (OH), 1766 (C=O), 1693 (C=O), 1511 (OCH_3); HRMS: m/z (ES) 446.1945, C_{25}H_{29}NNaO_5 [M+Na]^+ requires 446.1943; [α]_{D}^{25} = -74.0 (c = 0.5 g/100 mL in CHCl_3).
4.1.3 Synthesis of anti-Aldol Product 483

(S)-4-Benzyl-3-((2R,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 483

Based on a literature procedure,\(^{166}\) (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (1.00 g, 3.83 mmol), MgCl\(_2\) (0.036 g, 0.38 mmol) and NaSbF\(_6\) (0.30 g, 1.15 mmol) were dissolved in dry ethyl acetate (21.5 mL) at room temperature under nitrogen. Triethylamine (1.06 mL, 7.65 mmol) was added dropwise followed by cinnamaldehyde (0.58 mL, 4.59 mmol) and chlorotrimethylsilane (0.73 mL, 5.74 mmol). The reaction was stirred at room temperature for 24 hours. The suspension was diluted with diethyl ether and was passed through a plug of silica. The filtrate was concentrated and redissolved in methanol (15 mL) with two drops of trifluoroacetic acid. The solution was stirred at room temperature for 30 minutes and was concentrated to afford a yellow oil. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, \(R_f\) 0.21] to afford (S)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one 483 (1.23 g, 3.13 mmol) as a colourless oil in 82% yield. \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \(\delta_H = 7.29-7.09\) (10H, m Ph and Ph\(_{ox}\)), 6.53 (1H, d, \(J = 15.9\) Hz, CH=CHPh), 6.15 (1H, dd, \(J = 15.9, 6.7\) Hz, CH=CHPh), 4.43 (1H, dd, \(J = 9.8, 3.6\) Hz, CHN), 4.34 (1H, app. t, \(J = 7.1\) Hz, CHO\(_{OH}\)), 4.03 (1H, app. quin., \(J = 6.9\) Hz, CHCH\(_3\)), 3.08 (1H, dd, \(J = 14.6, 3.6\) Hz, CH\(_3\)Ph), 3.00 (1H, broad s, OH), 2.67 (1H, dd, \(J = 14.6, 9.8\) Hz, CH\(_3\)Ph), 1.23 (3H, s, C(CH\(_3\))(CH\(_3\))), 1.21 (3H, s, C(CH\(_3\))(CH\(_3\))), 1.14 (3H, d, \(J = 6.9\) Hz, CHCH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta_C = 176.5, 152.6, 137.0, 136.4, 131.9, 129.5, 128.9, 128.6, 128.5, 127.7, 126.7, 126.5, 82.2, 75.3, 63.8, 43.5, 35.0, 28.4, 22.2, 14.4; IR cm\(^{-1}\) \(\nu = 3377\) (OH), 1774 (C=O\(_{ax}\)), 1687 (C=O); HRMS: \(m/z\) (ES) 416.1826, C\(_{24}\)H\(_{27}\)NNaO\(_4\) [M+Na]\(^+\) requires 416.1837; \([\alpha]_D^{25} = -68.0\) (c = 0.5 g/100 mL in CHCl\(_3\)).
4.1.4  *Synthesis of syn-Cyclopropyl Aldol Products* 493-501, 518

Directed Syn-Cyclopropanation – General Procedure 2

![Chemical Structure](attachment:image.png)

The appropriate *syn*-aldol product 474-481, 483, 517 (1 equiv.) was dissolved in dichloromethane and stirred at 0 °C under nitrogen. Diethylzinc (5 equiv., 1 M in hexane) was added in one portion followed by diiodomethane (5 equiv.). The reaction was stirred for two hours in the absence of light. The reaction was quenched with saturated sodium sulphite (5 mL) and stirred for 10 minutes before sufficient 1 M HCl was added to dissolve the white precipitate. The aqueous layer was separated and extracted with dichloromethane and the combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated to afford the crude product, which was purified as described.
(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 493

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 474 (0.72 g, 2.17 mmol), diethylzinc (10.86 mL, 10.86 mmol, 1 M in hexane) and diiodomethane (0.87 mL, 10.86 mmol) in dichloromethane (30 mL). The crude product was purified via recrystallisation in diethyl ether and hexane to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one 493 (0.63 g, 1.82 mmol) as a white crystalline solid in 84% yield. mp = 98-101 °C (Et₂O, hexane); ¹H NMR (300 MHz, CDCl₃) δH = 7.31-7.18 (5H, m, Ph), 4.51 (1H, dd, J = 9.0, 4.3 Hz, CHN), 3.98 (1H, qd, J = 7.1, 3.8 Hz, (C=O)CH), 3.19 (1H, dd, J = 8.3, 3.7 Hz, CHO), 3.07 (1H, dd, J = 14.3, 4.2 Hz, CH₃H₆Ph), 2.88 (1H, dd, J = 14.3, 9.2 Hz, CH₃H₆Ph), 2.43 (1H, broad s, OH), 1.36 (3H, s, C(CH₃)(CH₃)), 1.23 (3H, d, J = 7.1 Hz, (C=O)CHCH₃), 1.01 (3H, d, J = 5.8 Hz, cyclopropyl-CH₃), 0.75-0.60 (2H, m, CHOHCH₃H₆ and cyclopropyl-CHCH₃), 0.54-0.48 (1H, m, cyclopropyl-CH₃H₆), 0.33-0.27 (1H, m, cyclopropyl-CH₃H₆); ¹³C NMR (75 MHz, CDCl₃) δC = 176.8, 152.6, 136.9, 129.2, 128.8, 127.0, 82.3, 76.2, 63.6, 43.1, 35.5, 28.6, 23.2, 22.4, 18.4, 11.8, 11.7, 11.0; IR cm⁻¹ ν = 3485 (OH), 1775 (C=O), 1685 (C=O); HRMS: m/z (ES) 368.1827, C₂₀H₂₇NNaO₄ [M+Na]+ requires 368.1837; [α]₀⁺ = +4.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethylloxazolidin-2-one, 494

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethylloxazolidin-2-one 475 (0.70 g, 1.78 mmol), diethylzinc (8.90 mL, 8.90 mmol, 1 M in hexane) and diiodomethane (0.72 mL, 8.90 mmol) in dichloromethane (30 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.28] to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethylloxazolidin-2-one 494 (0.69 g, 1.93 mmol) as a white crystalline solid in 98% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_h$ = 7.33-7.05 (10H, m, Ph$_{ox}$ and Ph), 4.44 (1H, dd, $J = 9.2, 4.1$ Hz, CH$_2$), 4.05 (1H, qd, $J = 7.1, 4.4$ Hz, CHCH$_3$), 3.46 (1H, dd, $J = 8.0, 4.4$ Hz, CHO$_2$), 3.09 (1H, dd, $J = 14.3, 4.2$ Hz, CH$_2$H$_3$Ph), 2.87 (1H, dd, $J = 14.3, 9.3$ Hz, CH$_2$H$_3$Ph), 2.51 (1H, broad s, OH), 1.94-1.88 (1H, m, cyclopropyl-Ph), 1.38-1.31 (1H, m, CHOCHCH$_3$H$_3$), 1.35 (3H, s, C(CH$_3$)(CH$_3$)), 1.26 (3H, d, $J = 7.0$ Hz, CHCH$_3$), 1.16 (3H, s, CH$_2$H$_3$), 1.12-1.06 (1H, m, cyclopropyl-CH$_2$H$_3$), 1.02-0.96 (1H, m, cyclopropyl-CH$_2$H$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_c$ = 176.6, 152.5, 142.3, 136.8, 129.2, 128.8, 128.5, 127.0, 126.0, 125.8, 82.3, 75.5, 63.5, 43.4, 35.4, 28.2, 26.5, 22.3, 21.3, 14.0, 12.4; IR cm$^{-1}$ $\nu = 3497$ (OH), 1769 (C=O$_{ox}$), 1692 (C=O); HRMS: $m/z$ (ES) 430.1977, C$_{25}$H$_{29}$NNaO$_4$ [M+Na]$^+$ requires 430.1994; $[\alpha]_D^{25}$ = +74.0 ($c = 0.5$ g/100 mL in CHCl$_3$).
The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethylazolidin-2-one 476 (0.58 g, 1.68 mmol), diethylzinc (8.39 mL, 8.40 mmol, 1 M in hexane) and diiodomethane (0.67 mL, 8.40 mmol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.47] to afford (S)-4-benzyl-3-((2S,3R)-3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylazolidin-2-one 495 (0.59 g, 1.64 mmol) as a colourless oil in 98% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H = 7.31-7.18$ (5H, m, Ph), 4.51 (1H, dd, $J = 9.2$, 4.3 Hz, CHN), 3.94 (1H, qd, $J = 7.1$, 3.4 Hz, CHCH$_3$), 3.51 (1H, dd, $J = 9.3$, 3.4 Hz, CHO), 3.08 (1H, dd, $J = 14.4$, 4.2 Hz, CH$_3$H$_8$Ph), 2.88 (1H, dd, $J = 14.3$, 9.3 Hz, CH$_3$H$_8$Ph), 2.63 (1H, broad s, OH), 1.36 (3H, s, OC(CH$_3$)(CH$_3$)), 1.35 (3H, s, OC(CH$_3$)(CH$_3$)), 1.23 (3H, d, $J = 7.1$ Hz, CHCH$_3$), 1.05 (3H, s, CH-cyclopropyl-(CH$_3$)(CH$_3$)), 1.03 (3H, s, CH-cyclopropyl-(CH$_3$)(CH$_3$)), 0.86-0.78 (1H, m, CH-cyclopropyl-(CH$_3$)(CH$_3$)), 0.57-0.53 (1H, m, cyclopropyl-CH$_3$H$_8$), 0.31-0.28 (1H, m, cyclopropyl-CH$_3$H$_8$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C = 177.3$, 152.5, 136.8, 129.2, 128.8, 127.0, 82.3, 72.8, 63.6, 42.9, 35.5, 28.6, 27.6, 27.3, 22.3, 20.7, 18.5, 16.5, 11.4; IR cm$^{-1}$ $\nu = 3598$ (OH), 1760 (C=O$_{ox}$), 1700 (C=O); HRMS: $m/z$ (ES) 382.1981, C$_{21}$H$_{29}$NNaO$_4$ [M+Na]$^+$ requires 382.1994; $[\alpha]_{D}^{25} = +6.0$ (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(S)-4-Benzyl-3-((2S,3R)-3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one, 496

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methylundec-4-enoyl)-5,5-dimethyloxazolidin-2-one 477 (0.43 g, 1.04 mmol), diethylzinc (5.17 mL, 5.173 mmol, 1 M in hexane) and diiodomethane (0.42 mL, 5.17 mmol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.40] to afford (S)-4-benzyl-3-((2S,3R)-3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one 496 (0.42 g, 1.01 mmol) as a colourless oil in 98% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.30-7.17 (5H, m, Ph), 4.51 (1H, dd, $J$ = 9.3, 4.0 Hz, CHN), 3.97 (1H, qd, $J$ = 7.1, 3.3 Hz, CH$_2$OH), 3.21 (1H, dd, $J$ = 8.4, 3.3 Hz, CHOH), 3.08 (1H, dd, $J$ = 14.3, 4.1 Hz, CH$_3$H$_8$Ph), 2.87 (1H, dd, $J$ = 14.3, 9.3 Hz, CH$_3$H$_8$Ph), 2.53 (1H, broad s, OH), 1.36-1.13 (19H, m, C$_5$H$_{10}$CH$_3$, d, $J$ = 7.1 Hz, C(CH$_3$)(CH$_3$)), 0.88-0.84 (3H, m, C$_3$H$_{10}$CH$_3$), 0.78-0.63 (2H, m, CHOHCH$_2$H$_8$ and cyclopropyl-CH-alkyl), 0.54-0.48 (1H, m, cyclopropyl-CH$_3$H$_8$), 0.36-0.30 (1H, m, cyclopropyl-CH$_3$H$_8$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 176.9, 152.4, 136.8, 129.1, 128.7, 126.9, 82.2, 75.8, 63.5, 42.9, 35.4, 33.7, 31.9, 29.4, 29.2, 28.5, 22.7, 22.3, 22.1, 16.6, 14.2, 11.3, 10.7; IR cm$^{-1}$ ν = 3527 (OH), 1763 (C=O$_\alpha$), 1699 (C=O); HRMS: m/z (ES) 438.2600, C$_{25}$H$_{37}$NNaO$_4$ [M+Na]$^+$ requires 438.2620; $[\alpha]_{D}^{25}$ = +2.0 ($c$ = 0.5 g/100 mL in CHCl$_3$).
(S)-4-Benzyl-3-((S)-2-((R)-hydroxy((1S,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one, 497

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-isopropylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 480 (0.66 g, 1.84 mmol), diethylzinc (9.18 mL, 9.18 mmol, 1 M in hexane) and diiodomethane (0.73 mL, 9.18 mmol) in dichloromethane (30 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.11] to afford (S)-4-benzyl-3-((S)-2-((R)-hydroxy((1S,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one 497 (0.68 g, 1.82 mmol) as a colourless oil in 97% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta_H = 7.28-7.13\) (5H, m, Ph), 4.56 (1H, dd, \(J = 10.3, 3.3\) Hz, CHN), 4.17 (1H, dd, \(J = 8.5, 6.5\) Hz, (C=O)CH), 3.30 (1H, dd, \(J = 8.9, 6.5\) Hz, CHOH), 3.16 (1H, dd, \(J = 14.4, 3.3\) Hz, CH\(_A\)H\(_B\)Ph), 2.80 (1H, dd, \(J = 14.4, 10.3\) Hz, CH\(_A\)H\(_B\)Ph), 2.21 (1H, m, CH(CH\(_3\))\((CH_3)\)), 1.93 (1H, broad s, OH), 1.29 (3H, s, C(CH\(_3\))\((CH_3)\)), 1.27 (3H, s, C(CH\(_3\))\((CH_3)\)), 0.99 (3H, d, \(J = 6.0\) Hz, cyclopropyl-CH\(_3\) ), 0.96 (3H, d, \(J = 6.7\) Hz, CH(CH\(_3\))\((CH_3)\)), 0.94-0.87 (1H, m, CHCH\(_3\)), 0.88 (3H, d, \(J = 6.7\) Hz, CH(CH\(_3\))\((CH_3)\)), 0.74-0.66 (1H, m, CHOHCH\(_A\)H\(_B\)), 0.43-0.37 (1H, m, cyclopropyl-CH\(_A\)H\(_B\) ), 0.24-0.18 (1H, m, cyclopropyl-CH\(_A\)H\(_B\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta_C = 174.6, 153.3, 137.1, 129.1, 128.8, 126.8, 81.8, 75.4, 64.0, 54.1, 35.5, 28.6, 28.4, 23.3, 22.4, 20.9, 20.7, 18.5, 12.7, 10.4; IR cm\(^{-1}\)ν = 3526 (OH), 1771 (C=O); HRMS: \(m/\epsilon\) (ES) 396.2161 \(C_{22}H_{33}NNaO_4\) [M+Na]\(^+\) requires 396.2150; \([\alpha]^\text{25}_{D}\) = +18.0 (\(c = 0.5\) g/100 mL in CHCl\(_3\)).
Experimental

\((S)-4\text{-benzyl-3-}((2S,3R)\text{-3-hydroxy-2-methyl-3-}((1S,2S)\text{-2-}(4\text{-nitrophenyl})\text{cyclopropyl})\text{propanoyl})\text{-5,5-dimethyloxazolidin-2-one, 498}\)

The title compound was prepared according to General Procedure 2 from \((S)-4\text{-benzyl-3-}((2S,3R,E)\text{-3-hydroxy-2-methyl-5-}(4\text{-nitrophenyl})\text{pent-4-enoyl})\text{-5,5-dimethyloxazolidin-2-one 478}\) (0.20 g, 0.46 mmol), diethylzinc (2.28 mL, 2.28 mmol, 1 M in hexane) and diiodomethane (0.18 mL, 2.28 mmol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, \(R_f 0.25\)] to afford \((S)-4\text{-benzyl-3-}((2S,3R)\text{-3-hydroxy-2-methyl-3-}((1S,2S)\text{-2-}(4\text{-nitrophenyl})\text{cyclopropyl})\text{propanoyl})\text{-5,5-dimethyloxazolidin-2-one 498}\) (0.19 g, 0.42 mmol) as a yellow oil in 98% yield. 

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.11 (2H, d, J = 8.9 \text{ Hz, } C_6H_2H_2NO_2), 7.33-7.22 (5H, m, Ph), 7.17 (2H, d, J = 8.9 \text{ Hz, } C_6H_2H_2NO_2), 4.49 (1H, dd, J = 8.9, 4.6 Hz, CHN), 4.02 (1H, qd, J = 7.0, 3.5 Hz, CHCH\(_3\)), 3.60 (1H, dd, J = 7.1, 3.5 Hz, CHOH), 3.05 (1H, dd, J = 14.2, 4.6 Hz, CH\(_2\)H\(_2\)CH\(_3\)) 2.89 (1H, dd, J = 14.2, 9.0 Hz, CH\(_2\)H\(_2\)CH\(_3\)), 2.04-1.98 (1H, m, cyclopropyl-C\(_6\)H\(_4\)NO\(_2\)), 1.65 (1H, broad s, OH), 1.46-1.38 (1H, m, CHOHC\(_2\)H\(_3\)), 1.38-1.27 (1H, m, cyclopropyl-CH\(_2\)H\(_3\)), 1.27 (3H, s, C(CH\(_3\))\(_2\)), 1.22 (3H, d, J = 7.0 Hz, CHCH\(_3\)), 1.14-1.07 (1H, m, cyclopropyl-CH\(_3\)H\(_3\)), \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 176.5, 152.5, 151.0, 146.0, 136.6, 129.1, 128.8, 127.0, 126.3, 123.8, 82.4, 74.0, 63.4, 43.2, 35.4, 28.3, 27.9, 22.2, 20.9, 15.2, 12.0; IR cm\(^{-1}\) \(\nu = 3512 \text{ (OH), 1769 (C=O)}\); HRMS: \(m/z\) (ES) 475.1835, C\(_{25}\)H\(_{28}\)N\(_2\)NaO\(_6\) \([M+Na]^+\) requires 475.1845; \([\alpha]^{25}_D = +68.0 \text{ (c = 0.5 g/100 mL in CHCl}_3\).}
Experimental

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoyl)-oxazolidin-2-one, 518

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)oxazolidin-2-one 517 (0.20 g, 0.49 mmol), diethylzinc (2.44 mL, 2.44 mmol, 1 M in hexane) and diiodomethane (0.20 mL, 2.44 mmol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.12] to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoyl)oxazolidin-2-one 518 (0.167 g, 0.39 mmol) as an orange oil in 81% yield. 1H NMR (300 MHz, CDCl3) δH = 8.03 (2H, d, J = 8.9 Hz, C6H2H2NO2), 7.29-7.18 (3H, m, Ph), 7.10 (2H, d, J = 8.4 Hz, C6H2H2NO2), 7.11-7.08 (2H, m, Ph), 4.58-4.50 (1H, m, CH), 4.07-3.97 (2H, m, CH2H2CHN and CH3), 3.87 (1H, app. t, J = 8.4 Hz, CH2H2CHN), 3.50 (1H, dd, J = 7.4, 4.1 Hz, CHO), 3.13 (1H, dd, J = 13.4, 3.2 Hz, CH2H2Ph), 2.70 (1H, dd, J = 13.4, 9.2 Hz, CH2H2Ph), 2.51 (1H, broad s, OH), 1.94-1.90 (1H, m, cyclopropyl-aryl), 1.46-1.38 (1H, m, CHOCHCH2H3), 1.27-1.18 (3H, d, J = 7.0 Hz, CHCH3), 1.25-1.18 (1H, m, cyclopropyl-CH2H3), 1.06-1.00 (1H, m, cyclopropyl-CH2H3); 13C NMR (75 MHz, CDCl3) δC = 176.3, 153.3, 150.8, 146.2, 135.0, 129.5, 129.1, 127.6, 126.3, 123.9, 74.8, 66.2, 55.2, 43.1, 27.9, 28.0, 21.0, 15.6, 12.0; IR cm⁻¹ ν = 3556 (OH), 1756 (C=O); HRMS: m/z (ES) 447.1529, C23H24N2NaO6 [M+Na]+ requires 447.1532; [α]25D = +176.0 (c = 0.5 g/100 mL in CHCl3).
Experimental

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-3-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoyl)-5,5-dimethyl-oxazolidin-2-one, 499

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 479 (0.66 g, 1.56 mmol), diethylzinc (7.79 mL, 7.79 mmol, 1 M in hexane) and diiodomethane (0.63 mL, 7.79 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.09] to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-3-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoyl)-5,5-dimethyl-oxazolidin-2-one 499 (0.49 g, 1.12 mmol) as a colourless oil in 72% yield. 

$^1$H NMR (300 MHz, CDCl_3) δ_H = 7.33-7.19 (5H, m, Ph), 6.99 (2H, d, J = 8.7 Hz, C_6H_5H_2OMe), 6.79 (2H, d, J = 8.7 Hz, C_6H_5H_2OMe), 4.45 (1H, dd, J = 9.2, 4.2 Hz, CHN), 4.06 (1H, qd, J = 7.0, 4.2 Hz, CHCH_3), 3.76 (3H, s, OCH_3), 3.44 (1H, dd, J = 8.0, 4.2 Hz, CHOH), 3.09 (1H, dd, J = 14.3, 4.2 Hz, CHCH_3), 2.87 (1H, dd, J = 14.3, 9.3 Hz, CHCH=CHCH_3), 2.47 (1H, broad s, OH), 1.88-1.82 (1H, m, cyclopropyl-aryl), 1.36 (3H, s, C(CH_3)(CH_3)), 1.26 (3H, d, J = 7.0 Hz, CHCH_3), 1.31-1.21 (1H, m, CHOHCHCH_3H_3), 1.19 (3H, s, C(CH_3)(CH_3)), 1.06-1.00 (1H, m, cyclopropyl-CHCH_3), 0.95-0.89 (1H, m, cyclopropyl-CHCH_3); $^{13}$C NMR (75 MHz, CDCl_3) δ_C = 176.7, 158.0, 152.6, 136.9, 134.3, 129.2, 128.8, 127.1, 127.0, 114.0, 82.3, 75.7, 63.5, 55.5, 43.4, 35.4, 28.3, 26.0, 22.4, 20.6, 13.6, 12.3; IR cm$^{-1}$ ν = 3490 (OH), 1769 (C=O), 1692 (C=O); HRMS: m/z (ES) 460.2107, C_{26}H_{33}NNaO_5 [M+Na]$^+$ requires 460.2099; [α]$^{25}_D$ = +62.0 (c = 0.5 g/100 mL in CHCl_3).
(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-(4-methoxyphenyl)-3-((15S)-2-methylcyclopropyl)propanoyl)-5,5-dimethylazolidin-2-one, 500

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethylazolidin-2-one 481 (0.30 g, 0.71 mmol), diethylzinc (3.54 mL, 3.54 mmol, 1 M in hexane) and diiodomethane (0.28 mL, 3.54 mmol) in dichloromethane (25 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.32] to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-(4-methoxyphenyl)-3-((15S)-2-methylcyclopropyl)propanoyl)-5,5-dimethylazolidin-2-one 500 (0.21 g, 0.48 mmol) as a colourless oil in 68% yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.35 (2H, d, $J = 8.7$ Hz, C$_6$H$_2$H$_2$OMe), 7.28-7.16 (5H, m, Ph), 6.87 (2H, d, $J = 8.7$ Hz, C$_6$H$_2$H$_2$OMe), 5.11 (1H, broad d, $J = 3.5$ Hz, (C=O)CH), 4.56 (1H, dd, $J = 9.8$, 3.5 Hz, CHN), 3.80 (3H, s, OCH$_3$)$_3$, 3.55 (1H, dd, $J = 7.8$, 5.8 Hz, CHOCH), 2.96 (1H, dd, $J = 14.5$, 3.2 Hz, CH$_3$), 2.68 (1H, dd, $J = 14.5$, 9.5 Hz, CH$_3$)CH$_3$), 2.61 (1H, broad s, OH), 1.36 (3H, s, C(CH$_3$)(CH$_3$)), 1.29 (3H, s, C(CH$_3$)(CH$_3$)), 1.01 (3H, d, $J = 6.0$ Hz, CHCH$_3$), 0.79-0.70 (1H, m, CHCH$_3$), 0.59-0.51 (2H, m, CHOCHCH$_3$H$_8$ and cyclopropyl-CH$_2$H$_8$), 0.30-0.23 (1H, m, cyclopropyl-CH$_2$H$_8$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 174.0, 159.2, 151.9, 136.8, 131.3, 129.0, 128.8, 126.9, 126.2, 114.0, 82.0, 76.3, 63.5, 55.3, 54.0, 34.8, 28.8, 23.8, 22.4, 18.5, 11.7, 11.3; IR cm$^{-1}$ ν = 3506 (OH), 1770 (C=O), 1693 (C=O); HRMS: m/z (ES) 460.2093, C$_{26}$H$_{31}$NNaO$_5$ [M+Na]$^+$ requires 460.2099; $[\alpha]_D^{25}$ = -112.0 ($c = 0.5$ g/100 mL in CHCl$_3$).
Experimental

(S)-4-Benzyl-3-((2R,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one, 501

The title compound was prepared according to General Procedure 2 from (S)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyl oxazolidin-2-one 483 (1.23 g, 3.13 mmol), diethylzinc (15.6 mL, 15.63 mmol, 1 M in hexane) and diiodomethane (1.26 mL, 15.63 mmol) in dichloromethane (60 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.11] to afford (S)-4-benzyl-3-((2R,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one 501 (1.26 g, 3.09 mmol) as a colourless oil in 99% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.31-7.14 and 7.05-7.03 (10H, m, Ph and Ph$_{ox}$), 4.50 (1H, dd, $J$ = 9.8, 3.5 Hz, CH$_N$), 4.17 (1H, app. quin., $J$ = 7.0 Hz, CHCH$_3$), 3.38 (1H, app. t, $J$ = 7.4 Hz, CHO$_H$), 3.09 (1H, dd, $J$ = 14.7, 3.3 Hz, CH$_B$H$_A$Ph), 2.93 (1H, broad s, OH), 2.62 (1H, dd, $J$ = 14.5, 9.9 Hz, CH$_A$H$_B$Ph), 1.94-1.88 (1H, m, cyclopropyl-Ph), 1.30-1.17 (m, 10H, C(CH$_3$)$_2$CH$_3$ and CHCH$_3$ and cyclopropyl-CH$_3$H$_B$), 1.11-0.98 (2H, m, CHOCHCH$_A$H$_B$ and cyclopropyl-CH$_B$H$_B$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 177.1, 152.5, 142.1, 137.0, 128.9, 128.6, 128.4, 126.7, 125.6, 82.1, 77.2, 63.7, 44.1, 34.8, 28.5, 28.3, 22.2, 21.4, 14.6, 13.0; IR cm$^{-1}$ ν = 3500 (OH), 1770 (C=O$_{ox}$), 1695 (C=O); HRMS: m/z (ES) 430.2023, C$_{25}$H$_{29}$NNaO$_4$ [M+Na]$^+$ requires 430.1994; $[\alpha]_{D}^{25}$ = +64.0 ($c$ = 0.5 g/100 mL in CHCl$_3$).
4.1.5 *Synthesis of Methyl Esters* **506-514**

**Synthesis of Methyl Ester – General Procedure 3**

![Chemical Structure](attachment:image.png)

The appropriate syn-aldol cyclopropane product **493-501, 518** (1 equiv.) was dissolved in dichloromethane under nitrogen. A solution of sodium methoxide (1 equiv., 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated to afford crude product, which was purified as described.
Experimental

(2S,3R)-Methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoate, 506

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoyl)-5,5-dimethylloxazolidin-2-one 493 (0.43 g, 1.25 mmol) and sodium methoxide (2.49 mL, 1.25 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Hexane, Rf 0.14] to afford (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-methylcyclopropyl)propanoate 506 (0.16 g, 0.93 mmol) as a colourless oil in 76% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 3.69 (3H, s, OCH$_3$), 3.08 (1H, dd, $J$ = 8.7, 5.1 Hz, CHOH), 2.67 (1H, qd, $J$ = 7.0, 5.1 Hz, (C=O)CH), 2.26 (1H, broad s, OH), 1.24 (3H, d, $J$ = 7.0 Hz, (C=O)CHCH$_3$), 0.98 (3H, d, $J$ = 5.9 Hz, cyclopropyl-CH$_3$), 0.69-0.54 (2H, m, CHOHC$_2$H$_3$ and CHCH$_3$), 0.54-0.46 (1H, m, cyclopropyl-CH$_2$H$_3$), 0.31-0.26 (1H, m, cyclopropyl-CH$_3$H$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 175.9, 76.8, 51.8, 45.6, 23.9, 18.3, 12.4, 11.4, 11.3; IR cm$^{-1}$ $\nu$ = 3444 (OH), 1718 (C=O); HRMS: m/z (ES) 195.0995 C$_9$H$_{16}$NaO$_3$ [M+Na]$^+$ requires 195.0997; $[\alpha]_{D}^{25}$ = +32.0 (c = 0.5 g/100 mL in CHCl$_3$).
(2S,3R)-Methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate, 507

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-dimethylloxazolidin-2-one 494 (0.50 g, 1.23 mmol) and sodium methoxide (2.45 mL, 1.23 mmol, 0.5 M in methanol) in dichloromethane (50 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.49] to afford (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate 507 (0.27 g, 1.15 mmol) as a white crystalline solid in 94% yield. 

$^1$H NMR (300 MHz, CDCl$_3$) δ H = 7.28-7.23 (2H, m, Ph), 7.18-7.13 (1H, m, Ph), 7.06-7.04 (2H, m, Ph), 3.61 (3H, s, OCH$_3$), 3.44 (1H, dd, 8.0, 4.7 Hz, CHOH), 2.76 (1H, qd, J = 7.2, 4.7 Hz, CHCH$_3$), 2.51 (1H, broad s, OH), 1.87-1.80 (1H, m, cyclopropyl-Ph), 1.38-1.31 (1H, m, CHOHC$_{H_A}CH_B$), 1.28 (3H, d, J = 7.2 Hz, CHCH$_3$), 1.12-1.05 (1H, m, cyclopropyl-CH$_A$H$_B$), 1.01-0.95 (1H, m, cyclopropyl-CH$_A$H$_B$); 

$^{13}$C NMR (75 MHz, CDCl$_3$) δ C = 176.0, 142.1, 128.5, 126.0, 125.9, 75.8, 51.9, 45.3, 26.4, 21.3, 14.0, 12.1; IR cm$^{-1}$ ν = 3439 (OH), 1730 (C=O); 

HRMS: m/z (ES) 257.1148, C$_{14}$H$_{18}$NaO$_3$ [M+Na]$^+$ requires 257.1153; $[^{25}D] = +74.0$ (c = 0.5 g/100 mL in CHCl$_3$).
(2S,3R)-Methyl 3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate, 508

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((2S,3R)-3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylloxazolidin-2-one 495 (0.20 g, 0.56 mmol) and sodium methoxide (1.11 mL, 0.56 mmol, 0.5 M in methanol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.47] to afford (2S,3R)-methyl 3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate 508 (0.09 g, 0.49 mmol) as a colourless liquid in 89% yield. ^1H NMR (300 MHz, CDCl_3) δ_H = 3.71 (3H, s, OCH_3), 3.49 (1H, dd, J = 9.6, 4.1 Hz, CHOH), 2.64 (1H, qd, J = 7.1, 4.4 Hz, (C=O)CH), 2.25 (1H, s, OH), 1.26 (3H, d, J = 7.1 Hz, CHCH_3), 1.06 (3H, s, (CH_3)(CH_3)), 1.03 (3H, s, (CH_3)(CH_3)), 0.82-0.74 (1H, m, CHOHCHCH_3H), 0.59-0.55 (1H, m, cyclopropyl-CH_3H), 0.34-0.31 (1H, m, cyclopropyl-CH_3H); ^13C NMR (75 MHz, CDCl_3) δ_C = 176.0, 73.2, 51.9, 45.5, 28.3, 27.3, 20.7, 18.6, 16.9, 11.3; IR cm⁻¹ ν = 3451 (OH), 1721 (C=O); HRMS: m/z (ES) 209.1136, C_{10}H_{18}NaO_3 [M+Na]^+ requires 209.1153; [α]_D^{25} = +46.0 (c = 0.5 g/100 mL in CHCl_3).
(2S,3R)-Methyl 3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate, 509

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((2S,3R)-3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylloxazolidin-2-one 496 (0.43 g, 1.05 mmol) and sodium methoxide (2.10 mL, 1.05 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.41] to afford (2S,3R)-methyl 3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate 509 (0.19 g, 0.78 mmol) as a colourless liquid in 74% yield. ¹H NMR (300 MHz, CDCl₃) δH = 3.70 (3H, s, OCH₃), 3.16 (1H, dd, J = 8.6, 4.3 Hz, CHOH), 2.68 (1H, qd, J = 7.1, 4.3 Hz, CHCH₂), 2.15 (1H, broad s, OH), 1.27 (3H, d, J = 7.1 Hz, CHCH₃), 1.30-1.11 (10H, m, C₅H₁₀), 0.90-0.85 (3H, m, C₅H₁₀CH₃), 0.74-0.47 (3H, m, CHCH₃, CHOHC₆H₄, cyclopropyl-CH₂H₃, 0.37-0.31 (1H, m, cyclopropyl-CH₂H₃); ¹³C NMR (75 MHz, CDCl₃) δC = 176.1, 176.5, 51.9, 45.2, 33.7, 32.0, 29.5, 29.3, 22.8, 22.6, 17.2, 14.2, 11.7, 10.6; IR cm⁻¹ ν = 3473 (OH), 1736 (C=O); HRMS: m/z (ES) 265.1777, C₁₄H₂₆NaO₃ [M+Na]^+ requires 265.1779; [α]D²⁵ = +38.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(S)-Methyl-2-((R)-hydroxy((15,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoate, 510

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((S)-2-((R)-hydroxy((15,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one 497 (0.41 g, 1.10 mmol) and sodium methoxide (2.19 mL, 1.10 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The reaction was stirred for 24 hours before quenching with brine. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.39] to afford (S)-methyl-2-((R)-hydroxy((15,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoate 510 (0.18 g, 0.90 mmol) as a colourless liquid in 82% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 3.69 (3H, s, OCH$_3$), 3.18 (1H, app. t, J = 8.0 Hz, CHO$_2$), 2.53 (1H, dd, J = 8.0, 6.1 Hz, (C=O)CH), 2.21 (1H, app. sex., J = 6.8 Hz, CHCH(CH$_3$)(CH$_3$)), 1.70 (1H, broad s, OH), 1.00-0.97 (9H, m, CH(CH$_3$)(CH$_3$) and cyclopropyl-CH$_3$), 0.78-0.64 (2H, m, CHOHCHCH$_2$H$_8$ and CHCH$_3$), 0.50-0.44 (1H, m, cyclopropyl-CH$_3$H$_8$), 0.30-0.24 (1H, m, cyclopropyl-CH$_2$H$_6$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 173.9, 74.9, 58.4, 51.2, 27.3, 25.3, 21.6, 18.9, 18.4, 12.6, 10.9; IR cm$^{-1}$ ν = 3451 (OH), 1731 (C=O); HRMS: m/z (ES) 223.1293, C$_{11}$H$_{20}$NaO$_3$ [M+Na]$^+$ requires 223.1305; $\left[\alpha\right]_{D}^{25} = +12.0\ (c = 0.5\ g/100\ mL\ in\ CHCl_3).$
Experimental

(2S,3R)-Methyl-3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoate, 511

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoyl)oxazolidin-2-one 498 (0.40 g, 0.94 mmol) and sodium methoxide (1.88 mL, 0.94 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [2:3 EtOAc:Petroleum ether, Rf 0.20] to afford (2S,3R)-methyl3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoate 511 (0.20 g, 0.72 mmol) as an orange crystalline solid in 76% yield. ¹H NMR (300 MHz, CDCl₃) δH = 8.10 (2H, d, J = 8.9 Hz, C₆H₄H₂NO₂), 7.15 (2H, d, J = 8.8 Hz, C₆H₄H₂NO₂), 3.61 (3H, s, OCH₃), 3.54 (1H, dd, J = 7.2, 4.6 Hz, CHO), 2.73 (1H, qd, J = 7.1, 4.7 Hz, (C=O)CH), 2.47 (1H, broad s, OH), 1.99-1.92 (1H, m, CH-aryl), 1.44-1.35 (1H, m, CHOHC₆H₄H), 1.30-1.22 (1H, m, cyclopropyl-CH₂H₆), 1.26 (3H, d, J = 7.1 Hz, (C=O)CHCH₃), 1.10-1.04 (1H, m, cyclopropyl-CH₂H₆); ¹³C NMR (75 MHz, CDCl₃) δC = 175.8, 150.7, 146.2, 126.3, 123.9, 74.6, 52.0, 45.3, 28.0, 21.2, 15.1, 12.2; IR cm⁻¹ ν = 3483 (OH), 1706 (C=O); HRMS: m/z (ES) 302.1003, C₁₄H₁₇NNaO₅ [M+Na⁺] requires 302.1004; [α]D²⁵ = +114.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(2S,3R)-Methyl-3-hydroxy-3-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoate, 512

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-(2S,3R)-3-hydroxy-3-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoyl)-5,5-dimethylloxazolidin-2-one 499 (0.08 g, 0.18 mmol) and sodium methoxide (0.37 mL, 0.18 mmol, 0.5 M in methanol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.29] to afford (2S,3R)-methyl-3-hydroxy-3-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoate 512 (0.03 g, 0.11 mmol) as a white crystalline solid in 62% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H$ = 6.97 (2H, d, $J = 8.7$ Hz, $C_6H_2H_2COMe$), 6.80 (2H, d, 8.7 Hz, $C_6H_2H_2COMe$), 3.77 (3H, s, $C_6H_4COCH_3$), 3.61 (3H, s, O$CH_3$), 3.39 (1H, dd, $J = 8.2$, 4.7 Hz, $CHOH$), 2.75 (1H, qd, $J = 7.1$, 4.7 Hz, $CHCH_3$), 2.44 (1H, broad s, OH), 1.82-1.75 (1H, m, cyclopropyl-aryl), 1.30-1.21 (1H, m, $CHOHCHCH_2H_8$), 1.27 (3H, d, $J = 7.1$ Hz, $CHCH_3$), 1.04-0.98 (1H, m, cyclopropyl-$CH_2H_8$), 0.91-0.87 (1H, m, cyclopropyl-$CH_2H_8$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C$ = 175.9, 157.9, 134.0, 127.1, 114.0, 76.0, 55.4, 51.9, 45.4, 25.9, 20.6, 13.5, 12.2; IR cm$^{-1}$ $\nu$ = 3508 (OH), 1721 (C=O); HRMS: $m/z$ (ES) 287.1246, $C_{15}H_{20}O_4 [M+Na]^+$ requires 287.1259; [$\alpha$]$_D^{25} = +90.0$ (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(2S,3R)-Methyl-3-hydroxy-2-(4-methoxyphenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoate, 513

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-(2S,3R)-3-hydroxy-2-(4-methoxyphenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl-oxazolidin-2-one 500 (0.09 g, 0.21 mmol) and sodium methoxide (0.41 mL, 0.21 mmol, 0.5 M in methanol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.13] to afford (2S,3R)-methyl-3-hydroxy-2-(4-methoxyphenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoate 513 (0.03 g, 0.11 mmol) as a white crystalline solid in 55% yield. ^1H NMR (300 MHz, CDCl₃) δ_H = 7.32 (2H, d, J = 8.7 Hz, C₆H₄H₂COMe), 6.88 (2H, d, J = 8.7 Hz, C₆H₄H₂COMe), 3.80 (3H, s, C₆H₄COCH₃), 3.72-3.69 (1H, m, CH-aryl), 3.70 (3H, s, OCH₃), 3.47-3.40 (1H, m, CHOH), 2.14 (1H, broad s, OH), 0.99 (3H, d, J = 6.0 Hz, CHCH₃), 0.73-0.56 (3H, m, CHOHCHCH₃H₂, CHCH₃ and cyclopropyl-CH₃H₂), 0.33-0.26 (1H, m, cyclopropyl-CH₃H₂); ^13C NMR (75 MHz, CDCl₃) δ_C = 173.6, 159.3, 130.4, 127.5, 114.2, 77.0, 57.4, 55.4, 52.0, 24.2, 18.3, 11.7, 11.6; IR cm⁻¹ v = 3436 (OH), 1727 (C=O); HRMS: m/z (ES) 287.1248, C_{15}H_{20}NaO₄ [M+Na]^+ requires 287.1259; [α]_D^{25} = -32.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(2R,3R)-Methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate, 514

The title compound was prepared according to General Procedure 3 from (S)-4-benzyl-3-
((2R,3R)-3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoyl)-5,5-
dimethylloxazolidin-2-one 510 (1.23 g, 3.02 mmol) and sodium methoxide (6.03 mL, 3.02 mmol, 0.5 M in methanol) in dichloromethane (35 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.11] to afford (2R,3R)-methyl 3-
hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate 514 (0.55 g, 2.35 mmol) as a colourless oil in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H = 7.28$-$7.23$ (2H, m, Ph), 7.18-$7.13$ (1H, m, Ph), 7.06-$7.03$ (2H, m, Ph), 3.69 (3H, s, OCH$_3$), 3.39 (1H, app. t, $J = 7.7$, CHOH), 3.12 (1H, broad s, OH), 2.72 (1H, app. quin., $J = 7.2$ Hz, CHCH$_3$), 1.92-$1.85$ (1H, m, cyclopropyl-Ph), 1.24 (3H, d, $J = 7.2$ Hz, CHCH$_3$ and 1H, m, CHOCHCHCH$_2$H$_3$), 1.10-$1.04$ (1H, m, cyclopropyl-CH$_2$H$_3$), 1.00-$0.94$ (1H, m, cyclopropyl-CH$_2$H$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C = 176.1$, 142.0, 128.3, 125.7, 76.2, 51.7, 46.4, 27.4, 21.6, 13.9, 12.6; IR cm$^{-1}$ v = 3456 (OH), 1719 (C=O); HRMS: m/z (ES) 257.1138, C$_{14}$H$_{18}$NaO$_3$ [M+Na]$^+$ requires 257.1153; $[\alpha]_{D}^{25}$ = -24.0 (c = 0.5 g/100 mL in CHCl$_3$).
Mercury trifluoroacetate (2.5 equiv.) was added in one portion to a stirred solution of the appropriate methyl ester syn-aldol cyclopropane \(506-514\) (1 equiv.) in dichloromethane. The resulting yellow solution was stirred at ambient temperature for 24 hours under nitrogen, before being quenched with brine and stirred for a further one hour. The organic layer was extracted with brine and the aqueous layer was extracted further with ethyl acetate. The organic layers were combined, dried over \(\text{MgSO}_4\) and concentrated to afford the corresponding organomercurial \(\delta\)-lactone. This was subsequently dissolved in methanol and cooled to 0 °C under nitrogen. Sodium borohydride (3 equiv.) was dissolved in 3.5 M sodium hydroxide and was added in one portion to the solution of organomercurial \(\delta\)-lactone. The resulting dark grey solution was stirred for two minutes at 0 °C and was then quenched with 1 M HCl solution to pH 2. The methanol was evaporated, the aqueous layer was saturated with NaCl and the resulting brine solution was extracted with three portions of ethyl acetate. The organic extracts were combined, dried over \(\text{MgSO}_4\) and concentrated to afford the corresponding tetrasubstituted \(\delta\)-lactone. The crude product was purified using flash silica chromatography to remove the mercury residues to afford the clean product.
The title compound was prepared according to General Procedure 4 from (2S,3R)-methyl 3-hydroxy-2-methyl-3-((15,2S)-2-methylcyclopropyl)propanoate 506 (0.10 g, 0.58 mmol) and mercury trifluoroacetate (0.62 g, 1.45 mmol) in dichloromethane (10 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.066 g, 1.74 mmol) dissolved in 3.5 M NaOH (2.8 mL) and methanol (3 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.20] to afford (3S,4R,5R,6S)-4-hydroxy-3,5,6-trimethyltetrahydro-2H-pyran-2-one 526 (0.065 g, 0.41 mmol) as a white solid in 71% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 3.99 (1H, dq, $J = 10.3, 6.2$ Hz, OCH$\text{CH}_{3}$), 3.29 (1H, app. t, $J = 10.0$ Hz, $\text{CH}_{2}$OH), 2.39 (1H, dq, $J = 10.0, 7.1$ Hz, CO$\text{CH}_{3}$), 1.95 (1H, broad s, OH), 1.64 (1H, ddq, $J = 10.3, 10.0, 6.5$ Hz, CHO$\text{CH}_{2}$OH$\text{CH}_{2}$CH$\text{CH}_{3}$), 1.40 (3H, d, $J = 2.1$ Hz, CO$\text{CH}_{3}$), 1.40 (3H, d, $J = 6.2$ Hz, OCH$\text{CH}_{2}$), 1.09 (3H, d, $J = 6.5$ Hz, CHO$\text{CH}_{2}$O$\text{CH}_{2}$CH$\text{CH}_{3}$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 173.2, 78.7, 75.4, 44.7, 43.1, 20.0, 14.0, 13.3; IR cm$^{-1}$ ν = 3423 (OH), 1711 (C=O); HRMS: m/z (ES) 181.0834, C$_8$H$_{14}$NaO$_3$ [M+Na]$^+$ requires 181.0840; $[\alpha]^{25}_D$ = -38.0 (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(3S,4R,5R,6R)-4-Hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one, 527

The title compound was prepared according to General Procedure 4 from (2S,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate 507 (0.27 g, 1.14 mmol) and mercury trifluoroacetate (1.21 g, 2.84 mmol) in dichloromethane (50 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.13 g, 3.41 mmol) dissolved in 3.5 M NaOH (5.6 mL) and methanol (6 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.08] to afford (3S,4R,5R,6R)-4-hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one 527 (0.20 g, 0.92 mmol) as a white solid in 81% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 7.39-7.28 (5H, m, Ph), 4.76 (1H, d, $J = 10.8$ Hz, C$\text{H}_\text{Ph}$), 3.48 (1H, app. t, $J = 10.1$ Hz, C$\text{H}_\text{OH}$), 2.57 (1H, dq, $J = 10.0$, 7.0 Hz, COCH$_3$), 2.16 (1H, broad s, OH), 2.04 (1H, ddq, $J = 10.8$, 10.1, 6.5 Hz, CHOCHCH$_3$), 1.48 (3H, d, $J = 7.0$ Hz, COCH$_3$), 0.92 (3H, d, $J = 6.6$ Hz, CHOCHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 173.1, 137.8, 129.1, 128.8, 127.5, 84.8, 75.5, 44.9, 42.8, 14.0, 13.3; IR cm$^{-1}$ ν = 3426 (OH), 1686 (C=O); HRMS: m/z (ES) 243.0986, C$_{13}$H$_{16}$NaO$_3$ [M+Na]$^+$ requires 243.0976; [$\alpha$]$_D^{25}$ = +6.0 (c = 0.5 g/100 mL in CHCl$_3$).
(3S,4R,5R)-4-Hydroxy-3,5,6,6-tetramethyltetrahydro-2H-pyran-2-one, 528

The title compound was prepared according to General Procedure 4 from (2S,3R)-methyl 3-((S)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate 508 (0.17 g, 0.91 mmol) and mercury trifluoroacetate (0.99 g, 2.34 mmol) in dichloromethane (30 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.10 g, 2.74 mmol) dissolved in 3.5 M NaOH (4.6 mL) and methanol (5 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.09] to afford (3S,4R,5R)-4-hydroxy-3,5,6,6-tetramethyltetrahydro-2H-pyran-2-one 528 (0.081 g, 0.48 mmol) as a colourless gum in 52% yield.

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 3.45 (1H, app. t, $J = 9.9$ Hz, CHOH), 2.36 (1H, dq, $J = 9.7$, 7.0 Hz, COCH$_3$), 2.12 (1H, broad s, OH), 1.83 (1H, dq, $J = 10.8$, 6.8 Hz, CHOCH$_3$(CH$_3$)C(CH$_3$)(CH$_3$)), 1.43 (3H, s, C(CH$_3$)(CH$_3$)), 1.39 (3H, d, $J = 7.0$ Hz, COCH$_3$), 1.24 (3H, s, C(CH$_3$)(CH$_3$)), 1.11 (3H, d, $J = 6.8$ Hz, CHOCH$_3$(CH$_3$)C(CH$_3$)(CH$_3$)); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 173.5, 83.9, 73.3, 45.3, 44.8, 28.9, 23.6, 14.1, 12.9; IR cm$^{-1}$ ν = 3430 (OH), 1686 (C=O); HRMS: m/z (ES) 173.1157, C$_9$H$_{17}$O$_3$ [M+H]$^+$ requires 173.1177; $[\alpha]_D^{25}$ = -52.0 (c = 0.5 g/100 mL in CHCl$_3$).
(3S,4R,5R,6S)-6-Hexyl-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-one, 529

The title compound was prepared according to General Procedure 4 from (2S,3R)-methyl 3-((1S,2S)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate 509 (0.14 g, 0.58 mmol) and mercury trifluoroacetate (0.61 g, 1.44 mmol) in dichloromethane (25 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.066 g, 1.73 mmol) dissolved in 3.5 M NaOH (2.9 mL) and methanol (3 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.17] to afford (3S,4R,5R,6S)-6-hexyl-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-one 529 (0.087 g, 0.38 mmol) as a white solid in 66% yield. 

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 3.89 (1H, m, OCC$_6$H$_{13}$), 3.28 (1H, t, $J = 10.0$ Hz, COCH$_3$), 3.27 (1H, dq, $J = 10.0$, 7.0 Hz, COCH$_3$), 1.93 (1H, broad s, OCH), 1.82-1.48 (5H, complex m, CHOCH$_3$CH$_3$CHC$_6$H$_{13}$ and C$_2$H$_4$CH$_3$), 1.44 (3H, d, $J = 7.0$ Hz, COCH$_3$), 1.33-1.28 (6H, m, C$_4$H$_8$CH$_2$), 1.08 (3H, d, $J = 6.5$ Hz, CHOCH$_3$CH$_3$CHC$_6$H$_{13}$), 0.90-0.86 (3H, m, C$_3$H$_6$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 173.4, 82.0, 75.2, 44.4, 40.5, 33.0, 31.7, 29.2, 24.2, 22.6, 14.1, 13.8, 13.3; IR cm$^{-1}$ $\nu$ = 3518 (OH), 1707 (C=O); HRMS: $m/z$ (ES) 251.1613, C$_{13}$H$_{24}$NaO$_3$ [M+Na]$^+$ requires 251.1623; $[\alpha]_D^{25}$ = -50.0 (c = 0.5 g/100 mL in CHCl$_3$).
The title compound was prepared according to General Procedure 4 from (S)-methyl-2-((R)-hydroxy((1S,2S)-2-methylcyclopropyl)methyl)-3-methylbutanoate 510 (0.11 g, 0.55 mmol) and mercury trifluoroacetate (0.58 g, 1.37 mmol) in dichloromethane (20 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.062 g, 1.65 mmol) dissolved in 3.5 M NaOH (2.7 mL) and methanol (3 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.20] to afford (3S,4R,5R,6S)-4-hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2H-pyran-2-one 530 (0.073 g, 0.40 mmol) as a colourless gum in 72% yield. 1H NMR (300 MHz, CDCl3) δH = 3.95 (1H, dq, J = 10.3, 6.3 Hz, OCCH3), 3.48 (1H, dd, J = 10.1, 7.5 Hz, CHO), 2.45 (1H, dd, J = 7.6, 3.8 Hz, COCH), 2.42-2.33 (1H, m, J = 6.9, 3.8 Hz, CH(CH3)2), 1.77 (1H, broad s, OH), 1.59 (1H, app. tq, J = 10.2, 6.6 Hz, CHCHCH3), 1.36 (3H, d, J = 6.3 Hz, COCH3), 1.11 (3H, d, J = 6.8 Hz, CH(CH3)(CH3)), 1.08 (3H, d, J = 6.6 Hz, COCHCHCH3), 1.06 (3H, d, J = 6.8 Hz, CH(CH3)(CH3)); 13C NMR (75 MHz, CDCl3) δC = 172.3, 77.3, 72.2, 56.4, 43.0, 29.9, 20.5, 19.8, 19.6, 13.4; IR cm⁻¹ ν = 3412 (OH), 1702 (C=O); HRMS: m/z (ES) 209.1152, C10H18NaO3 [M+Na]+ requires 209.1153; [α]D²⁵ = -32.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(3S,4R,5R,6R)-4-Hydroxy-3,5-dimethyl-6-(4-nitrophenyl)tetrahydro-2H-pyran-2-one, 531

The title compound was prepared according to General Procedure 4 from (2S,3R)-methyl-3-hydroxy-2-methyl-3-((1S,2S)-2-(4-nitrophenyl)cyclopropyl)propanoate 511 (0.11 g, 0.40 mmol) and mercury trifluoroacetate (0.43 g, 1.01 mmol) in dichloromethane (15 mL). The reaction was stirred for five days before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.046 g, 1.21 mmol) dissolved in 3.5 M NaOH (2.0 mL) and methanol (3 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.17] to afford (3S,4R,5R,6R)-4-hydroxy-3,5-dimethyl-6-(4-nitrophenyl)tetrahydro-2H-pyran-2-one 531 (0.055 g, 0.21 mmol) as a white solid in 51% yield. $^1$H NMR (300 MHz, CDCl3) $\delta$H = 8.24 (2H, d, $J = 8.8$ Hz, C$_6$H$_2$H$_2$CNO$_2$), 7.49 (2H, d, $J = 8.8$ Hz, C$_6$H$_2$H$_2$CNO$_2$), 4.90 (1H, d, $J = 10.8$ Hz, CHAr), 3.50 (1H, app. t, $J = 10.0$ Hz, CHO$_2$), 2.61 (1H, dq, $J = 9.9$, 7.0 Hz, COCH), 1.99 (1H, ddq, $J = 10.8$, 10.2, 6.5 Hz, CHArCH$_3$), 1.47 (3H, d, $J = 7.0$ Hz, COCH$_3$), 0.92 (3H, d, $J = 6.5$ Hz, CHArCH$_3$); $^{13}$C NMR (75 MHz, CDCl3) $\delta$C = 172.7, 148.3, 144.8, 128.4, 124.0, 83.4, 75.2, 44.9, 42.9, 13.9, 13.1; IR cm$^{-1}$ $\nu = 3477$ (OH), 1713 (C=O); HRMS: m/z (ES) 288.0821, C$_{13}$H$_{15}$NNaO$_5$ [M+Na]$^+$ requires 288.0847; $[\alpha]_{D}^{25} = -8.0$ (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(3R,4R,5R,6R)-4-Hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one, 532

The title compound was prepared according to General Procedure 4 from (2R,3R)-methyl 3-hydroxy-2-methyl-3-((1S,2S)-2-phenylcyclopropyl)propanoate 514 (0.250 g, 1.07 mmol) and mercury trifluoroacetate (1.13 g, 2.67 mmol) in dichloromethane (25 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.12 g, 3.20 mmol) dissolved in 3.5 M NaOH (5.3 mL) and methanol (6 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.25] to afford (3R,4R,5R,6R)-4-hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one 532 (0.18 g, 0.82 mmol) as a white solid in 77% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 7.34 (5H, app. s, Ph), 4.71 (1H, d, $J$ = 10.7 Hz, CHPh), 3.87 (1H, app. t, $J$ = 3.9 Hz, CHO), 2.82 (1H, qd, $J$ = 6.8, 4.3 Hz, COCH$_3$), 2.74 (1H, broad s, OH), 2.13 (1H, m, CHCH$_3$CHPh), 1.32 (3H, d, $J$ = 6.9 Hz, COCH$_3$), 0.92 (3H, d, $J$ = 7.1 Hz, CHOCHCH$_3$CHPh); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 174.6, 137.7, 128.9, 128.6, 127.6, 84.1, 75.0, 44.7, 39.4, 15.6, 11.2; IR cm$^{-1}$ ν = 3423 (OH), 1709 (C=O); HRMS: m/z (ES) 243.0983, C$_{13}$H$_{16}$NaO$_3$ [M+Na]$^+$ requires 243.0997; $[\alpha]_{D}^{25}$ = -24.0 (c = 0.5 g/100 mL in CHCl$_3$).
4.1.7 Synthesis of Compounds for Highly Substituted δ-Lactones with a Synthetic Handle

(Z)-4-(Benzyloxy)but-2-en-1-ol, 534

Based on a literature procedure, sodium hydride (0.48 g, 11.35 mmol, 60% dispersion in mineral oil) was added portionwise to N,N-dimethylformamide (40 mL) at -20 °C under nitrogen. The resulting suspension was stirred for five minutes before (Z)-but-2-ene-1,4-diol (1.00 mL, 11.35 mmol) was added dropwise. The solution was stirred for a further 20 minutes before benzyl bromide (1.45 mL, 11.35 mmol) was added dropwise. The resulting solution was then stirred at -20 °C for five hours. The reaction was warmed to room temperature and was quenched with water (60 mL). The mixture was extracted three times with ether, combined organic extracts were dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, Rₜ 0.45] to afford (Z)-4-(benzyloxy)but-2-en-1-ol 534 (1.55 g, 8.70 mmol) as a colourless liquid in 73% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.27-7.17 (5H, m, Ph), 5.78-5.61 (2H, m, CH=CH), 4.44 (2H, s, OCH₂Ph), 4.08 (2H, d, J = 5.9 Hz, CH₂O), 4.01 (2H, d, J = 5.9 Hz, CH₂O), 1.91 (1H, broad s, OH); ¹³C NMR (75 MHz, CDCl₃) δC = 138.0, 132.5, 128.6, 128.5, 128.0, 127.9, 72.7, 65.8, 58.9; IR cm⁻¹ ν = 3295 (OH); HRMS: m/z (ES) 201.0885, C₁₁H₁₄NaO₂ [M+Na]⁺ requires 201.0891.
Experimental

(Z)-4-(Benzyloxy)but-2-enal, 535

Based on a literature procedure,\textsuperscript{187} oxalyl chloride (0.26 mL, 3.09 mmol) was dissolved in dry dichloromethane (10 mL) at -55 °C under nitrogen. Dimethylsulfoxide (0.39 mL, 5.61 mmol) was added and the resulting solution was stirred for two minutes. (Z)-4-(benzyloxy)but-2-en-1-ol 534 (0.50 g, 2.81 mmol) in dichloromethane (1 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for 15 minutes at -55 °C. Triethylamine (1.96 mL, 14.03 mmol) was then added and the resulting solution was stirred for a further 15 minutes at -55 °C. The thick white slurry was warmed to room temperature and was quenched with the addition of water (10 mL). The layers were separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were washed with 1 M HCl (10 mL) and saturated NaHCO\textsubscript{3} before being dried over MgSO\textsubscript{4} and concentrated. The crude product was purified using flash silica chromatography [1:8 EtOAc:Petroleum ether, R\textsubscript{f} 0.25] to afford (Z)-4-(benzyloxy)but-2-enal 535 (0.42 g, 2.39 mmol) as a colourless liquid in 84% yield. The pure material was initially a 50:50 mixture of cis and trans alkene, but after cooling in the fridge overnight at 4 °C, the cis isomer was present in a 99:1 ratio. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta_{\text{H}} = 10.05 \text{ (1H, d, } J = 6.8 \text{ Hz, CHO)}, 7.37-7.31 \text{ (5H, m, Ph)}, 6.64 \text{ (1H, dt, } J = 11.6, 5.8 \text{ Hz, CH=CHCHO}), 6.06 \text{ (1H, ddt, } J = 11.6, 6.8, 1.9 \text{ Hz, CHCHO}), 4.59 \text{ (2H, s, OCH\textsubscript{2}Ph)}, 4.53 \text{ (2H, dd, } J = 5.5, 1.9 \text{ Hz, CH\textsubscript{2}OBn}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta_{\text{C}} = 191.6, 147.7, 137.4, 129.9, 128.7, 128.2, 127.9, 73.2, 67.1.\)
Experimental

(S)-4-Benzyl-3-((2S,3R,Z)-6-(benzoxyl)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl oxazolidin-2-one, 536

Based on a literature procedure,187 (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.50 g, 1.91 mmol) was dissolved in dry dichloromethane (20 mL) at -10 °C under nitrogen and was stirred for 20 minutes. Dibutylboron triflate (2.29 mL, 2.30 mmol, 1.0 M in dichloromethane) was added dropwise followed by triethylamine (0.35 mL, 2.49 mmol) and the resulting solution was stirred for 30 minutes at 0 °C. The reaction was cooled to -78 °C and (Z)-4-(benzoxyl)but-2-enal 535 (0.37 g, 2.11 mmol) was added dropwise. The solution was stirred at -78 °C for 45 minutes and then warmed to 0 °C and stirred for a further three hours. The reaction was cooled to -10 °C and pH 7 buffer solution (Na\textsubscript{2}PO\textsubscript{4}/NaH\textsubscript{2}PO\textsubscript{4}) (10 mL) was added followed by methanol (8 mL) and hydrogen peroxide (4 mL). The methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO\textsubscript{3} and brine. The combined organic extracts were dried over MgSO\textsubscript{4} and concentrated. The crude product was purified using flash silica chromatography [1:2 EtOAc:Petroleum ether, R\textsubscript{f} 0.63] to afford (S)-4-benzyl-3-((2S,3R,Z)-6-(benzoxyl)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 536 (0.74 g, 1.68 mmol) as a colourless gum, which crystallised on standing to form white crystals in 88% yield. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta_H = 7.29 - 7.12 \) (10H, m, Ph), 5.71-5.52 (2H, m, C=CH), 4.63-4.49 (1H, m, CH\textsubscript{OH}), 4.44-4.39 (3H, m, C\textsubscript{H}\textsubscript{2}OBn and C\textsubscript{H}N), 4.10 (1H, ddd, J = 12.7, 6.5, 1.3 Hz, CH\textsubscript{A}H\textsubscript{B}OBn), 4.00 (1H, ddd, J = 12.6, 5.5, 1.3 Hz, CH\textsubscript{A}H\textsubscript{B}OBn), 3.87 (1H, m, CH\textsubscript{CH\textsubscript{3}}), 2.97 (1H, dd, J = 14.3, 4.5 Hz, CH\textsubscript{2}HPh), 2.81 (1H, dd, J = 14.3, 9.0 Hz, CH\textsubscript{2}HPh), 2.73 (1H, broad s, OH), 1.30 (3H, s, C(CH\textsubscript{3})\textsubscript{3}(CH\textsubscript{3})), 1.26 (3H, s, C(CH\textsubscript{3})\textsubscript{3}(CH\textsubscript{3})), 1.11 (3H, d, J = 7.0 Hz, CHCH\textsubscript{3}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta_C = 175.9, 152.6, 138.1, 136.7, 132.1, 129.6, 129.2, 128.7, 128.5, 127.9, 127.8, 126.9, 82.4, 72.5, 69.0, 66.2, 63.4, 43.1, 35.5, 28.4, 22.2. 12.4; IR cm\textsuperscript{-1} ν = 3477 (OH), 1771 (C=O\textsubscript{\alpha}), 1692 (C=O); HRMS: m/z (ES) 460.2097, C\textsubscript{26}H\textsubscript{31}NNaO\textsubscript{5} [M+Na]\textsuperscript{+} requires 460.2099; [\textgreek{alpha}]\textsubscript{D}\textsuperscript{25} = -12.0 (c = 0.5 g/100 mL in CHCl\textsubscript{3}).
(E)-4-(Benzyloxy)but-2-enal, 537

Based on a literature procedure, oxalyl chloride (0.26 mL, 3.09 mmol) was dissolved in dry dichloromethane (10 mL) at -55 °C under nitrogen. Dimethylsulphoxide (0.39 mL, 5.61 mmol) was added and the resulting solution was stirred for two minutes. (Z)-4-(benzyloxy)but-2-en-1-ol 534 (0.50 g, 2.81 mmol) in dichloromethane (1 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for 15 minutes at -55 °C. Triethylamine (1.96 mL, 14.03 mmol) was then added and the resulting solution was stirred for a further 15 minutes at -55 °C. The thick white slurry was warmed to room temperature and was quenched with the addition of water (10 mL). The layers were separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were washed with 1 M HCl (10 mL) and saturated NaHCO₃ before being dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:8 EtOAc:Petroleum ether, Rf 0.25] to afford a 50:50 mixture of cis 535 and trans 537 alkene (0.42 g, 2.39 mmol) as a colourless liquid in 84% yield. The pure material was dissolved in dichloromethane (1 mL) with a catalytic amount of p-TSA and left at room temperature overnight to isomerise to the trans isomer (E)-4-(benzyloxy)but-2-enal 537 in a 99:1 ratio. ^1H NMR (300 MHz, CDCl₃) δH = 9.58 (1H, d, J = 7.9 Hz, CHO), 7.39-7.28 (5H, m, Ph), 6.85 (1H, dt, J = 15.8, 4.1 Hz, CH=CHCHO), 6.41 (1H, ddt, J = 15.8, 7.9, 1.9 Hz, CHCHO), 4.60 (2H, s, OCH₂Ph), 4.29 (2H, dd, J = 4.1, 1.9 Hz, CH₂OBn); ^13C NMR (75 MHz, CDCl₃) δC = 193.4, 153.2, 137.5, 131.9, 128.6, 128.1, 127.8, 73.1, 68.7; IR cm⁻¹ ν = 1681 (C=O); HRMS: m/z (ES) 199.0737, C₁₁H₁₂NaO₂ [M+Na]^⁺ requires 199.0734.
(S)-4-Benzyl-3-((2S,3R,E)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl oxazolidin-2-one, 538

Based on a literature procedure, (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (1.95 g, 7.46 mmol) was dissolved in dry dichloromethane (50 mL) at -10 °C under nitrogen and was stirred for 20 minutes. Dibutylboron triflate (8.97 mL, 8.95 mmol, 1.0 M in dichloromethane) was added dropwise followed by triethylamine (1.35 mL, 9.70 mmol) and the resulting solution was stirred for 30 minutes at 0 °C. The reaction was cooled to -78 °C and (E)-4-(benzyloxy)but-2-enal 537 (1.45 g, 8.21 mmol) was added dropwise. The solution was stirred at -78 °C for 45 minutes and then warmed to 0 °C and stirred for a further three hours. The reaction was cooled to -10 °C and pH 7 buffer solution (Na$_2$PO$_4$/Na$_2$HPO$_4$) (30 mL) was added followed by methanol (24 mL) and hydrogen peroxide (12 mL). The methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO$_3$ and brine. The combined organic extracts were dried over MgSO$_4$ and concentrated. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petalroleum ether, R$_f$ 0.19] to afford (S)-4-benzyl-3-((2S,3R,E)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl oxazolidin-2-one 538 (2.91 g, 6.65 mmol) as a yellow oil in 89% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ = 7.27-7.15 (10H, m, Ph and Ph$_{ox}$), 5.83 (1H, dtd, J = 15.6, 5.4, 1.0 Hz, CH=CHCH$_2$OBn), 5.68 (1H, dd, J = 15.6, 5.4 Hz, CH=CHCH$_2$OBn), 4.84-4.38 (4H, m, CH$_2$OBn, CHN, CHOH), 3.96 (2H, d, J = 5.4 Hz, CH$_2$OBn), 3.86 (1H,qd, J = 7.0, 4.2 Hz, CHCH$_3$), 2.99 (1H, dd, J = 14.2, 4.6 Hz, CH$_2$H$_8$Ph), 2.82 (1H, dd, J = 14.4, 9.0 Hz, CH$_2$H$_8$Ph), 2.76 (1H, broad s, OH), 1.30 (3H, s, C(CH$_3$)(CH$_3$)), 1.28 (3H, s, C(CH$_3$)(CH$_3$)), 1.10 (3H, d, J = 7.1 Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ = 176.3, 152.4, 138.2, 136.6, 132.0, 129.1, 128.7, 128.6, 128.3, 127.7, 127.6, 126.8, 82.3, 72.2, 72.1, 70.0, 63.3, 42.7, 35.4, 28.3, 22.1, 11.6; IR cm$^{-1}$ ν = 3473 (OH), 1771 (C=O); HRMS: m/z (ES) 460.2064, C$_{26}$H$_{31}$NNaO$_5$ [M+Na]$^+$ requires 460.2099; $[^{25}$D$]_D$ = -28.0 (c = 0.5 g/100 mL in CHCl$_3$).
Experimental

(S)-4-Benzyl-3-((2S,3R)-3-((1S,2R)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylazolidin-2-one, 539

(S)-4-Benzyl-3-((2S,3R)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethylazolidin-2-one 536 (0.50 g, 1.14 mmol) was dissolved in dichloromethane (25 mL) and stirred at -5 °C under nitrogen. Diethylzinc (5.71 mL, 5.71 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (0.46 mL, 5.74 mmol). The reaction was stirred for two hours under nitrogen in the absence of light before being quenched with saturated sodium sulfite (5 mL). Sufficient 1 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. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, Rf 0.40] to afford (S)-4-benzyl-3-((2S,3R)-3-((1S,2R)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylazolidin-2-one 539 (0.46 g, 1.02 mmol) as a colourless gum in 89% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.28-7.17 (10H, m, Ph and Phox), 4.49-4.41 (3H, m, OC₃H₂Ph and CHN), 3.94 (1H, qd, J = 7.1, 3.0 Hz, CHCH₃), 3.67 (1H, dd, J = 8.1, 3.0 Hz, CHOH), 3.51 (1H, dd, J = 10.3, 6.6 Hz, CH₃HoOBn), 3.41 (1H, dd, J = 10.3, 7.5 Hz, CH₃HoOBn), 3.01 (1H, dd, J = 14.3, 4.3 Hz, CH₃HoPh), 2.83 (1H, dd, J = 14.3, 9.1 Hz, CH₃HoPh), 1.31 (3H, s, C(CH₃)Ph), 1.24 (3H, s, C(CH₃)Ph), 1.23 (3H, d, J = 7.0 Hz, CHCH₃), 1.20-1.05 (2H, m, CHOCHCH₃H₆ and cyclopropyl-CHCH₂OBn), 0.80 (1H, app. dt, J = 8.4, 4.8 Hz, cyclopropyl-CH₃H₆), 0.41 (1H, app. dd, J = 10.7, 5.7 Hz, cyclopropyl-CH₃H₆); ¹³C NMR (75 MHz, CDCl₃) δC = 177.5, 152.2, 138.6, 136.8, 129.2, 128.8, 128.4, 127.7, 127.6, 127.0, 82.3, 72.7, 71.1, 70.3, 63.5, 43.3, 35.5, 28.5, 22.3, 19.2, 15.7, 11.3, 8.1; IR cm⁻¹ ν = 3519 (OH), 1771 (C=Oν), 1689 (C=O); HRMS: m/z (ES) 474.2223, C₂₇H₃₃NNaO₅ [M+Na]⁺ requires 474.2256; [α]D²⁵ = -8.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(S)-4-Benzyl-3-(((2S,3R)-3-((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyl-oxazolidin-2-one, 541

(S)-4-Benzyl-3-(((2S,3R)-3-((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyl-oxazolidin-2-one 538 (0.50 g, 1.14 mmol) was dissolved in dichloromethane (25 mL) and stirred at -5 °C under nitrogen. Diethylzinc (5.71 mL, 5.71 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (0.46 mL, 5.71 mmol). The reaction was stirred for two hours under nitrogen in the absence of light before being quenched with saturated sodium sulfite (5 mL). Sufficient 1 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. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, Rf 0.16] to afford (S)-4-benzyl-3-(((2S,3R)-3-((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyl-oxazolidin-2-one 541 (0.49 g, 1.09 mmol) as a colourless gum in 95% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.27-7.10 (10H, m, Ph and Ph₂O), 4.45-4.38 (1H, m, CHN), 4.44 (1H, s, OCH₂-HPh), 4.43 (1H, s, OCH₂-HPh), 3.91 (1H, qd, J = 7.1, 3.4 Hz, CH₂), 3.32-3.19 (3H, m, CH₂OBn and CHOH), 3.00 (1H, dd, J = 14.3, 4.3 Hz, CH₃-HPh), 2.80 (1H, dd, J = 14.3, 9.2 Hz, CH₃-HPh), 2.49 (1H, broad s, OH), 1.29 (3H, s, C(CH₃)(CH₃)), 1.25 (3H, s, C(CH₃)(CH₃)), 1.18 (3H, d, J = 7.1 Hz, CHCH₃), 1.10-0.99 (1H, m, cyclopropyl-CH₂OBn), 0.89-0.81 (1H, m, CHOHCH₂H₆), 0.63-0.58 (1H, m, cyclopropyl-CH₃H₆), 0.49-0.43 (1H, m, cyclopropyl-CH₃H₆); ¹³C NMR (75 MHz, CDCl₃) δC = 176.8, 152.4, 138.6, 136.7, 129.1, 128.7, 128.4, 127.6, 127.5, 126.9, 82.3, 74.7, 73.3, 72.5, 63.5, 43.0, 35.4, 28.4, 22.3, 20.3, 16.0, 11.5, 8.9; IR cm⁻¹ ν = 3504 (OH), 1769 (C=O); HRMS: m/z (ES) 474.2237, C₂₇H₃₅NNaO₅ [M+Na⁺] requires 474.2256; [α]D²⁵ = -20.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(2S,3R)-Methyl 3-((1S,2R)-2-((benzyl)oxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoate, 540

(5)-4-Benzyl-3-((2S,3R)-3-((1S,2R)-2-((benzyl)oxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl]-5,5-dimethylloxazolidin-2-one 539 (0.20 g, 0.43 mmol) was dissolved in dichloromethane (6 mL) under nitrogen. A solution of sodium methoxide (0.87 mL, 0.43 mmol, 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, Rₚ 0.40] to afford (2S,3R)-methyl 3-((1S,2R)-2-((benzyl)oxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoate 540 (0.09 g, 0.32 mmol) as a colourless oil in 75% yield. \(^1\)H NMR (300 MHz, CDCl₃) δH = 7.27-7.20 (5H, m, Ph), 4.46 (1H, d, J = 11.8 Hz, OCH₂H₃Ph), 4.39 (1H, d, J = 11.8 Hz, OCH₂H₃Ph), 3.65-3.58 (5H, m, OC₃H₃, C₃H₂OBn and C₃H₂OH), 3.25 (1H, dd, J = 10.0, 8.9 Hz, CH₃H₆OBn), 2.83 (1H, qd, J = 7.3, 2.8 Hz, CHCH₃), 2.52 (1H, broad s, OH), 1.26-1.15 (1H, m, CHOHCH₂H₆OBn), 1.21 (3H, d, J = 7.2 Hz, CHCH₃), 1.10-1.01 (1H, m, cyclopropyl-CHCH₂OBn), 0.81 (1H, app. td, J = 8.4, 4.8 Hz, cyclopropyl-CH₂H₆), 0.36 (1H, dd, J = 10.7, 5.6 Hz, cyclopropyl-CH₃H₆); \(^13\)C NMR (75 MHz, CDCl₃) δC = 176.7, 138.2, 128.5, 127.9, 127.8, 73.1, 71.5, 70.5, 51.9, 44.4, 19.3, 15.8, 10.2, 8.2; IR cm⁻¹ ν = 3457 (OH), 1728 (C=O); HRMS: m/z (ES) 301.1397, 
C₁₆H₂₂NaO₄ [M+Na]⁺ requires 301.1416; \([α]_{D}^{25} = +38.0 (c = 0.5 g/100 mL in CHCl₃).\)
(2S,3R)-Methyl-3-((15S,2S)-2-(benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoate, 542

(S)-4-Benzyl-3-((2S,3R)-3-((15S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethylloxazolidin-2-one 541 (0.39 g, 0.86 mmol) was dissolved in dichloromethane (12 mL) under nitrogen. A solution of sodium methoxide (1.73 mL, 0.86 mmol, 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.21] to afford (2S,3R)-methyl 3-((15S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoate 542 (0.21 g, 0.76 mmol) as a colourless oil in 88% yield. 1H NMR (300 MHz, CDCl₃) δH = 7.30-7.19 (5H, m, Ph), 4.46 (1H, d, J = 12.1 Hz, OCH₃H₆Ph), 4.41 (1H, d, J = 12.1 Hz, OCH₃H₆Ph), 3.60 (3H, s, OCH₃), 3.26-3.19 (3H, m, CHO and CH₂OBn), 2.63 (2H, qd, J = 7.1, 4.8 Hz, CHCH₃ and OH), 1.21 (3H, d, J = 7.1 Hz, CHCH₃), 1.03-0.92 (1H, m, CHOCHCH₂H₆), 0.84-0.77 (1H, m, cyclopropyl-CH₂OBn), 0.62-0.57 (1H, m, cyclopropyl-CH₃H₂); 13C NMR (75 MHz, CDCl₃) δC = 175.9, 138.4, 128.3, 127.5, 127.5, 75.2, 73.1, 72.5, 51.7, 45.2, 20.8, 16.3, 11.8, 8.7; IR cm⁻¹ ν = 3451 (OH), 1729 (C=O); HRMS: m/z (ES) 301.1408, C₁₆H₂₂NaO₄ [M+Na]+ requires 301.1415; [α]D²⁵ = +30.0 (c = 0.5 g/100 mL in CHCl₃).
The title compound was prepared according to General Procedure 4 from \((2S,3R)-methyl-3-((1S,2S)-2-(benzyloxymethyl)cyclopropyl)-3-hydroxy-2-methylpropanoate\) 542 (0.10 g, 0.36 mmol) and mercury trifluoroacetate (0.38 g, 0.90 mmol) in dichloromethane (12 mL). The reaction was stirred for 24 hours before being quenched with brine. The organomercurial δ-lactone underwent reductive demercuration with sodium borohydride (0.041 g, 1.08 mmol) dissolved in 3.5 M NaOH (3.7 mL) and methanol (4 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rf 0.11] to afford \((3S,4R,5R,6R)-6-((benzyloxy)methyl)-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-one\) 544 (0.078 g, 0.30 mmol) as a white solid in 82% yield. 

\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta_H = 7.37-7.26 (5\text{H, m, Ph}), 4.63 (1\text{H, d, } J = 12.0 \text{ Hz, } \text{O}H_a\text{H}_b\text{Ph}), 4.51 (1\text{H, d, } J = 12.0 \text{ Hz, } \text{O}H_a\text{H}_b\text{Ph}), 3.98 (1\text{H, dt, } J = 10.4, 3.0 \text{ Hz, COOCH}), 3.73 (1\text{H, dd, } J = 11.2, 2.4 \text{ Hz, CH}_a\text{H}_b\text{OBn}), 3.65 (1\text{H, dd, } J = 11.2, 3.3 \text{ Hz, CH}_a\text{H}_b\text{OBn}), 3.30 (1\text{H, app. t, } J = 10.2 \text{ Hz, CHOH}), 2.40 (1\text{H, dq, } J = 10.1, 7.1 \text{ Hz, COCHCH})_3, 2.11 (1\text{H, broad s, OH}), 2.10 (1\text{H, ddq, } J = 10.4, 10.2, 6.5 \text{ Hz, CHOHCHCH})_3, 1.39 (3\text{H, d, } J = 7.0 \text{ Hz, COCHCH})_3, 1.07 (3\text{H, d, } J = 6.5 \text{ Hz, CHOHCHCH})_3; \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta_C = 173.3, 137.9, 128.6, 127.9, 127.8, 81.7, 75.0, 73.7, 69.6, 44.4, 37.2, 13.7, 13.4; \text{ IR cm}^{-1} \nu = 3413 (\text{OH}), 1712 (\text{C=O}); \text{ HRMS: } m/z (\text{ES}) 265.1439, \text{ C}_{15}\text{H}_{21}\text{O}_4 [\text{M+H}]^+ \text{ requires 265.1439}; [\alpha]_{D}^{25} = -28.0 \text{ (c = 0.5 g/100 mL in CHCl}_3).\)
4.1.8 Synthesis of Compounds for N-Protected (S,S)-2-Aminomethyl-1-
Cyclopropanecarboxylic Acid

(S)-4-Benzyl-3-((2S,3R)-3-((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-
methylpropanoyl)-5,5-dimethyloxazolidin-2-one 541 (2.56 g, 5.67 mmol) was dissolved in
toluene (200 mL) at 0 °C under nitrogen. LiHMDS (12.48 mL, 12.48 mmol, 1 M in THF) was
added dropwise and the resulting solution was stirred for three hours. The reaction was
quenched with saturated ammonium chloride, diluted with diethyl ether and the layers were
separated. The organic layer was extracted with brine, dried over MgSO₄ and concentrated to
afford the crude product. The crude product was purified using flash silica chromatography
[1:9 EtOAc:Petroleum ether, Rᵣ 0.32] to afford (1S,2S)-2-((benzyloxy)methyl)cyclopropanecarbaldehyde 545 (0.99 g, 5.22 mmol) as a colourless oil in
92% yield. ¹H NMR (360 MHz, CDCl₃) δ_H = 9.17 (1H, d, J = 5.0 Hz, CHO), 7.40-7.21 (5H, m, Ph),
4.53 (2H, s, CH₂Ph), 3.50 (1H, dd, J = 10.5, 5.5 Hz, CH₃H₈OBn), 3.42 (1H, dd, J = 10.5, 5.0 Hz,
CH₃H₈OBn), 1.89-1.77 (2H, m, CH-cyclopropyl), 1.33 (1H, dt, J = 8.5, 5.0 Hz, cyclopropyl-CH₃H₈),
1.12-1.04 (1H, m, cyclopropyl-CH₃H₈); ¹³C NMR (90 MHz, CDCl₃) δ_C = 200.2, 138.0, 128.4, 127.7,
127.6, 72.8, 70.9, 28.1, 12.4; IR cm⁻¹ ν = 1708 (C=O); HRMS: m/z (ES) 213.0886, C₁₂H₁₄NaO₂
[M+Na]⁺ requires 213.0886; [α]25D = +80.0 (c = 0.45 g/100 mL in CHCl₃).
$N,N$-Dibenzyl-1-\{(1S,2S)-2-((benzyloxy)methyl)cyclopropyl\}methanamine, 546

![Diagram](image)

(15,2S)-2-((Benzyloxy)methyl)cyclopropanecarbaldehyde 545 (0.99 g, 5.22 mmol) and dibenzylamine (1.00 mL, 5.22 mmol) were dissolved in dichloroethane (35 mL) along with 4Å MS at room temperature under nitrogen. Sodium triacetoxyborohydride (1.77g, 8.35 mmol) was added and the resulting mixture was stirred for four hours. The reaction was quenched with saturated NaHCO₃ and the layers were separated. The aqueous layer was extracted with ethyl acetate, the combined organic extracts were combined, dried over MgSO₄ and concentrated to afford $N,N$-dibenzyl-1-\{(15,2S)-2-((benzyloxy)methyl)cyclopropyl\}methanamine 546 (1.20 g, 3.24 mmol) as a yellow oil which solidified on standing in 62% yield.

$^1$H NMR (400 MHz, CDCl₃) δₕ = 7.16-7.40 (15H, m, Ph), 4.47 (2H, s, OCH₂Ph), 3.65 (2H, d, J = 13.5 Hz, NCH₂Ph), 3.59 (2H, d, J = 13.5 Hz, NCH₂Ph), 3.26-3.32 (2H, m, CH₂NBn₂), 2.41 (1H, dd, J = 6.0, 13.0 Hz, CH₃H₂OBn), 2.27 (1H, dd, J = 7.0, 13.0 Hz, CH₃H₂OBn), 0.80-0.86 (2H, m, CH-cyclopropyl), 0.39 (1H, ddd, J = 5.0, 5.0, 10.5 Hz, cyclopropyl-CH₃H₆), 0.30 (1H, ddd, J = 5.0, 5.0, 10.5 Hz, cyclopropyl-CH₃H₆); $^{13}$C NMR (100 MHz, CDCl₃) δₙ = 140.0, 138.6, 128.7, 128.3, 128.1, 127.5, 127.4, 126.7, 73.9, 72.4, 58.1, 57.2, 17.9, 14.8, 9.5; HRMS: m/z (ES) 372.2349, C₂₆H₃₀NO [M+H]$^+$ requires 372.2322; $[\alpha]_{D}^{15}$ = +18.0 (c = 2.1 g/100 mL in CHCl₃).
Experimental

tert-Butyl-(((1S,2S)-2-(Hydroxymethyl)cyclopropyl)methyl)carbamate, 548

N,N-Dibenzyl-1-((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)methanamine 546 (1.20 g, 3.24 mmol) and a few drops of formic acid were dissolved in methanol (120 mL). Palladium on carbon (10%, 0.34 g, 0.32 mmol) was added in one portion and the reaction was stirred vigorously under a hydrogen atmosphere at room temperature for 16 hours. The resulting suspension was filtered through a pad of Celite® and concentrated. The crude product was redissolved in methanol (120 mL) and di-tert-butyl dicarbonate (0.71 g, 3.24 mmol) was added to the solution, followed by sodium hydroxide (0.13 g, 3.24 mmol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched with saturated NH₄Cl and was diluted with diethyl ether. The layers were separated, the organic layer was washed with brine, dried over MgSO₄ and concentrated to afford a 50:50 mixture of tert-butyl-benzyl(((1S,2S)-2-(hydroxymethyl)cyclopropyl)methyl)carbamate 547 and tert-butyl-(((1S,2S)-2-((benzyloxy)methyl)cyclopropyl)methyl)carbamate 548. The crude mixture was dissolved in THF (100 mL) and palladium hydroxide on carbon (20%, 60% wet, 0.90 g, 0.32 mmol) was added in one portion. The resulting suspension was stirred vigorously under a hydrogen atmosphere at room temperature for two and a half hours. The reaction was filtered through a pad of Celite® and concentrated to afford tert-butyl-(((1S,2S)-2-(hydroxymethyl)cyclopropyl)methyl)carbamate 548 (0.65 g, 3.24 mmol) as a colourless oil in quantitative yield. ¹H NMR (250 MHz, CDCl₃) δH = 3.57 (1H, dd, J = 4.5, 8.0 Hz, CH₂H₆OH), 3.28 (1H, dd, J = 5.0, 8.0 Hz, CH₂H₆OH), 3.09 (1H, dd, J = 4.5, 9.5 Hz, CH₆H₂NHBOc), 2.90 (1H, dd, J = 5.0, 9.5 Hz, CH₆H₂NHBOc), 1.42 (9H, s, (CH₃)₃C), 0.93-1.10 (1H, m, CH-cyclopropyl), 0.83-0.91 (1H, m, CH-cyclopropyl), 0.42 (2H, dd, J = 5.0, 5.0 Hz, CH₂-cyclopropyl); ¹³C NMR (60 MHz, CDCl₃) δC = 156.1, 79.2, 66.0, 44.5, 28.3, 19.9, 17.1, 8.2; IR cm⁻¹ ν = 3344 (OH), 1691 (C=O); HRMS: m/z (ES) 224.1254, C₁₀H₁₈NNaO₃ [M+Na]⁺ requires 224.1257; [α]D²⁰ = +7.1 (c = 0.50 g/100 mL in CHCl₃).
Experimental

(1S,2S)-2-(((tert-Butoxycarbonyl)amino)methyl)cyclopropanecarboxylic acid, 549

\[
\text{Boc-} \begin{array}{c}
\text{N} \\
\text{CH}_3 \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{OH} \\
\text{O}
\end{array}
\]

tert-Butyl (((1S,2S)-2-(hydroxymethyl)cyclopropyl)methyl)carbamate 548 (0.65 g, 3.24 mmol) was dissolved in acetone (60 mL) at 0 °C. Jones’ reagent (~2% CrO₃ basis) was added dropwise until the orange tint persisted in the reaction mixture. The solution was stirred at 0 °C for two hours followed by a further two hours at room temperature. The reaction was quenched with isopropyl alcohol, diluted with diethyl ether and extracted with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford (1S,2S)-2-(((tert-butoxycarbonyl)amino)methyl)cyclopropanecarboxylic acid 549 (0.44 g, 2.04 mmol) as a colourless oil in 63% yield. \(^1\)H NMR (360 MHz, CDCl₃) δ_H = 5.62 (1H, broad s, COOH), 4.72 (1H, broad s, NH), 3.16-3.30 (1H, m, CH₂H₆NHBOc), 2.95-3.15 (1H, m, CH₂H₆NHBOc), 1.60-1.74 (1H, m, CH-cyclopropyl), 1.57 (1H, ddd, J = 13.0, 4.5, 4.5 Hz, CH-cyclopropyl), 1.48 (9H, s, (CH₃)₃C), 1.23 (1H, ddd, J = 13.0, 4.5, 4.5 Hz, CH-cyclopropyl); HRMS: m/z (ES) 238.1049, C₁₀H₁₇NNaO₄ [M+Na]^+ requires 238.1050; [\(\alpha\)]D²⁰ = +51 (c = 0.30 g/100 mL in CHCl₃).
4.1.9 *Synthesis of Compounds for (+)-Prelactone B, E and V*

**(R)-4-Benzyl-5,5-dimethyloxazolidin-2-one**

Potassium tert-butoxide (3.0 g, 26.8 mmol) was added in one portion to a solution of (R)-tert-butyl(3-hydroxy-3-methyl-1-phenylbutan-2-yl)carbamate (5.0 g, 17.9 mmol) in THF (30 mL) at room temperature. The resulting orange solution was stirred for two hours and then THF was removed under reduced pressure. The residue was redissolved in diethyl ether and extracted with saturated ammonium chloride and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified *via* recrystallisation from diethyl ether and hexane to afford (R)-4-benzyl-5,5-dimethyloxazolidin-2-one (2.6 g, 12.8 mmol) as a yellow crystalline solid. ¹H NMR (300 MHz, CDCl₃) δ_H = 7.43-7.22 (5H, m, Ph), 5.27 (1H, broad s, NH), 3.76 (1H, ddd, J = 10.3, 4.2, 0.7 Hz, CHN), 2.90 (1H, dd, J = 13.4, 4.2 Hz, CH₃H₃Ph), 2.76 (1H, dd, J = 13.4, 10.5 Hz, CH₃H₃Ph), 1.52 (3H, s, C(CH₃)(CH₃)), 1.51 (3H, s, C(CH₃)(CH₃)); ¹³C NMR (75 MHz, CDCl₃) δ_C = 158.1, 137.0, 129.1, 128.9, 127.2, 83.3, 63.2, 37.2, 27.6, 22.0; IR cm⁻¹ ν = 3250 (N-H), 1717 (C=O); HRMS: m/z (ES) 228.1016, C₁₂H₁₅NNaO₂ [M+Na]⁺ requires 228.1000; [α]D²⁵ = +100.0 (c = 1.0 g/100 mL in CHCl₃).
Experimental

(R)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one, 550

n-BuLi (10.71 mL, 26.8 mmol, 2.5 M solution in hexane) was added to a solution of (R)-4-benzyl-5,5-dimethyloxazolidin-2-one (5.00 g, 24.3 mmol) in dry THF (150 mL) at -78 °C under nitrogen and was stirred for 30 minutes. Chloroacetyl chloride (2.07 mL, 26.8 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.50] to afford (R)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 550 (5.69 g, 20.1 mmol) as a colourless oil in 83% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.32-7.20 (5H, m, Ph), 4.76 (1H, d, J = 15.8 Hz, COCH₂H₂Cl), 4.64 (d, J = 15.8 Hz, COCH₂H₂Cl), 4.49 (1H, dd, J = 9.7, 3.9 Hz, CH₂N), 3.20 (1H, dd, J = 14.4, 3.8 Hz, CHH₂H₂Ph), 2.88 (1H, dd, J = 14.4, 9.8 Hz, CH₂H₂Ph), 1.38 (3H, s, C(CH₃)(CH₃)), 1.36 (3H, s, C(CH₃)(CH₃)); ¹³C NMR (75 MHz, CDCl₃) δC = 166.4, 152.4, 136.5, 129.1, 128.9, 127.1, 83.7, 64.1, 44.0, 35.0, 28.7, 22.4; IR cm⁻¹ ν = 1768 (C=O ox), 1708 (C=O); HRMS: m/z (ES) 304.0722, C₁₄H₁₈ClNNaO₃ [M+Na]⁺ requires 304.0716; [α]D²⁵ = +32.0 (c = 0.5 g/100 mL in CHCl₃).
(R)-4-Benzyl-3-((2R,3S,E)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 554

(R)-4-Benzyl-3-{(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 550 (1.65 g, 5.86 mmol) was dissolved in dry dichloromethane (10 mL) at 0 °C under nitrogen and was stirred for 30 minutes. Dibutylboron triflate (6.44 mL, 6.44 mmol, 1 M in dichloromethane) was added dropwise. After 30 minutes, N,N-diisopropylethylamine (1.33 mL, 7.61 mmol) was added and the resulting solution was stirred for 30 minutes. The reaction was cooled to -78 °C. Crotonaldehyde (0.63 mL, 7.61 mmol) was added in one portion and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution (Na₂PO₄/NaH₂PO₄) (4 mL) and was stirred for 10 minutes. Hydrogen peroxide (2 mL) and methanol (4 mL) were then added, the methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [15:85 EtOAc:Petroleum ether, Rf 0.27] to afford (R)-4-benzyl-3-{(2R,3S,E)-2-chloro-3-hydroxyhex-4-enoyl}-5,5-dimethyloxazolidin-2-one 554 (1.01 g, 2.87 mmol) as a yellow oil in 49% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.30-7.18 (5H, m, Ph), 5.88-5.71 (1H, m, CH=CHCH₃), 5.73 (1H, d, J = 5.9 Hz, CHCl), 5.52 (1H, ddd, J = 15.5, 6.8, 1.0 Hz, CH=CHCH₃), 4.53-4.46 (2H, m, CHOCH₃ and CHN), 3.34 (1H, broad s, OH), 3.10 (1H, dd, J = 14.4, 3.7 Hz, CH₂H₂Ph), 2.89 (1H, dd, J = 14.4, 9.4 Hz, CH₃H₂Ph), 1.68 (3H, d, J = 6.4 Hz, CH=CHCH₃), 1.36, (3H, s, C(CH₃)(CH₂)), 1.33 (3H, s, C(CH₃)(CH₂)); ¹³C NMR (75 MHz, CDCl₃) δc = 167.8, 151.8, 136.2, 130.9, 128.9, 128.6, 127.8, 126.7, 82.9, 72.9, 63.7, 58.9, 34.6, 28.1, 21.9, 17.7; IR cm⁻¹ ν = 3488 (OH), 1770 (C=O, ox), 1704 (C=O); HRMS: m/z (ES) 352.1289, C₁₈H₂₃NO₄Cl [M+H]^+ requires 352.1315; [α]D²⁵ = +26.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(R)-4-Benzyl-3-((2R,3S,E)-2-chloro-3-hydroxyhept-4-enoyl)-5,5-dimethyloxazolidin-2-one, 555

(R)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 550 (1.37 g, 4.86 mmol) was dissolved in dry dichloromethane (10 mL) at 0 °C under nitrogen and was stirred for 30 minutes. Dibutylboron triflate (5.35 mL, 5.35 mmol, 1 M in dichloromethane) was added dropwise. After 30 minutes, N,N-diisopropylethylamine (1.10 mL, 6.32 mmol) was added and the resulting solution was stirred for 30 minutes. The reaction was cooled to -78 °C. trans-2-Pentenal (0.62 mL, 6.32 mmol) was added in one portion and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution (Na₂PO₄/NaH₂PO₄) (4 mL) and was stirred for 10 minutes. Hydrogen peroxide (2 mL) and methanol (4 mL) were then added, the methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [15:85 EtOAc:Petroleum ether, Rₖ 0.29] to afford (R)-4-benzyl-3-((2R,3S,E)-2-chloro-3-hydroxyhept-4-enoyl)-5,5-dimethyloxazolidin-2-one 555 (0.81 g, 2.19 mmol) as a yellow oil in 45% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.30-7.20 (5H, m, Ph), 5.87 (1H, dt, J = 15.2, 6.0 Hz, CH=CHCH₂CH₃), 5.73 (1H, d, J = 5.7 Hz, CHCl), 5.50 (1H, dd, J = 15.7, 6.7 Hz, CH=CHCH₂CH₃), 4.56-4.47 (2H, m, CHOH and CHN), 3.45 (1H, broad s, OH), 3.11 (1H, dd, J = 14.5, 3.7 Hz, CH₃CH₂Ph), 2.89 (1H, dd, J = 14.1, 9.5 Hz, CH₃CH₂Ph), 2.08-1.99 (2H, m, CH₂CH₃), 1.36 (3H, s, C(CH₃)(CH₃)), 1.32 (3H, s, C(CH₃)(CH₂)), 0.96 (3H, t, J = 7.4 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δc = 167.7, 151.7, 137.2, 136.1, 128.8, 128.4, 126.6, 125.4, 82.8, 72.7, 63.5, 58.9, 34.4, 28.0, 24.9, 21.8, 12.8; IR cm⁻¹ ν = 3476 (OH), 1772 (C=O); HRMS: m/z (ES) 388.1368, C₁₉H₂₃NO₄ClNa [M+Na]⁺ requires 388.1292; [α]D⁺²⁵ = +24.0 (c = 0.5 g/100 mL in CHCl₃).
(R)-4-Benzyl-3-((2R,3S,E)-2-chloro-3-hydroxy-6-methylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one, 556

(R)-4-Benzyl-3-((2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 550 (5.00 g, 17.75 mmol) was dissolved in dry dichloromethane (30 mL) at 0 °C under nitrogen and was stirred for 30 minutes. 9-Borabicyclo[3.3.1]nonyl triflate (39.01 mL, 19.52 mmol, 0.5 M in hexane) was added dropwise. After 30 minutes, N,N-disopropylethylamine (4.01 mL, 23.07 mmol) was added and the resulting solution was stirred for 30 minutes. The reaction was cooled to -78 °C. 4-Methyl-2-pentenal (2.68 mL, 23.07 mmol) was added in one portion and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with pH 7 buffer solution (Na₂PO₄/NaH₂PO₄) (10 mL) and was stirred for 10 minutes. Hydrogen peroxide (4 mL) and methanol (8 mL) were then added, the methanol was evaporated, the solution diluted with dichloromethane and washed with saturated NaHCO₃ and brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.39] to afford (R)-4-benzyl-3-((2R,3S,E)-2-chloro-3-hydroxy-6-methylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one 556 (5.08 g, 13.38 mmol) as a yellow oil in 75% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.30-7.17 (5H, m, Ph), 5.81 (1H, ddd, J = 15.4, 6.4, 0.8 Hz, CH=CHCH(CH₃)(CH₃)), 5.67 (1H, d, J = 5.2 Hz, CHCl), 5.43 (1H, ddd, J = 15.6, 6.6, 1.4 Hz, CH=CHCH(CH₃)(CH₃)), 4.54 (1H, app. t, J = 5.9 Hz, CHOH), 4.47 (1H, dd, J = 9.5, 3.9 Hz, CHN), 3.13 (2H, dd, J = 14.5, 3.8 Hz, CH₃CPh and broad s, OH), 2.88 (1H, dd, J = 14.4, 9.5 Hz, CH₃CPh), 2.27 (1H, app. sex., J = 6.8 Hz, CH=CHCH(CH₃)(CH₃)), 1.37 (3H, s, (CH₃)C(CH₃)), 1.33 (3H, s, (CH₃)C(CH₃)), 0.97 (6H, dd, J = 6.8, 1.8 Hz, CH=CHCH(CH₃)(CH₃)); ¹³C NMR (75 MHz, CDCl₃) δc = 168.1, 151.9, 143.0, 136.4, 129.1, 128.8, 127.0, 123.6, 83.1, 72.8, 64.0, 59.4, 34.8, 30.8, 28.5, 22.2, 22.0, 21.9; IR cm⁻¹ v = 3499 (OH), 1772 (C=O), 1702 (C=O); HRMS: m/z (ES) 402.1462, C₂₀H₂₆NO₄ClNa [M+Na]⁺ requires 402.1448; [α]D²⁵ = +10.0 (c = 0.5 g/100 mL in CHCl₃).
**Experimental**

(R)-4-Benzyl-3-((2R,3S)-2-chloro-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl-oxazolidin-2-one, 557

(R)-4-Benzyl-3-((2R,3S)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 554

(0.914 g, 2.60 mmol) was dissolved in dichloromethane (30 mL) and stirred at 0 °C under nitrogen. Diethylzinc (12.98 mL, 12.98 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (1.05 mL, 12.98 mmol). The reaction was stirred for two hours in the absence of light. The reaction was quenched with saturated sodium sulphite (10 mL) and stirred for 10 minutes before sufficient 1 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 product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rₜ 0.34] to afford (R)-4-benzyl-3-((2R,3S)-2-chloro-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl-oxazolidin-2-one 557, (0.80 g, 2.21 mmol) as a colourless oil in 85% yield. $^1$H NMR (300 MHz, CDCl₃) δ_H = 7.31-7.18 (5H, m, Ph), 5.76 (1H, d, J = 4.2 Hz, CHCl), 4.48 (1H, dd, J = 9.8, 3.5 Hz, CHN), 3.41 (1H, dd, J = 7.8, 4.0 Hz, CHO), 3.18 (1H, dd, J = 14.4, 3.4 Hz, CH₃H₂Ph), 2.87 (1H, dd, J = 14.5, 9.8 Hz, CH₃H₂Ph), 2.52 (1H, broad s, OH), 1.36 (3H, s, C(CH₃)(CH₂)), 1.33 (3H, s, C(CH₃)(CH₂)), 1.00 (3H, d, J = 5.8 Hz, CHCH₃), 0.89-0.74 (2H, m, CHOHCH-cyclopropyl and cyclopropyl-CH), 0.64-0.58 (1H, m, cyclopropyl-CH), 0.39-0.33 (1H, m, cyclopropyl-CH); $^{13}$C NMR (75 MHz, CDCl₃) δ_C = 168.1, 151.9, 136.4, 128.9, 128.6, 126.8, 83.0, 74.9, 63.1, 60.1, 34.5, 28.4, 22.5, 22.1, 18.1, 11.6, 10.9; IR cm⁻¹ ν = 3505 (OH), 1786 (C=O), 1711 (C=O); HRMS: m/z (ES) 388.1278, C₁₉H₂₄ClNNaO₄ [M+Na]⁺ requires 388.1291; [α]$_D^{25}$ = +12.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(R)-4-Benzyl-3-((2R,3S)-2-chloro-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one, 558

(R)-4-Benzyl-3-((2R,3S,E)-2-chloro-3-hydroxyhept-4-enoyl)-5,5-dimethyloxazolidin-2-one 555 (0.81 g, 2.21 mmol) was dissolved in dichloromethane (25 mL) and stirred at 0 °C under nitrogen. Diethylzinc (11.06 mL, 11.07 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (0.89 mL, 11.07 mmol). The reaction was stirred for two hours in the absence of light. The reaction was quenched with saturated sodium sulphite (20 mL) and stirred for 10 minutes before sufficient 1 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 product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.32] to afford (R)-4-benzyl-3-((2R,3S)-2-chloro-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one 558 (0.58 g, 1.53 mmol) as a colourless oil in 69% yield. 

$^1$H NMR (300 MHz, CDCl₃) δ H = 7.30-7.18 (5H, m, Ph), 5.79 (1H, d, J = 3.7 Hz, CHCl), 4.49 (1H, dd, J = 9.8, 3.4 Hz, CHN), 3.41 (1H, dd, J = 8.2, 3.6 Hz, CHOH), 3.19 (1H, dd, J = 14.6, 3.4 Hz, CHA₂H₈Ph), 2.87 (2H, dd and broad s, J = 14.4, 9.8 Hz, CHA₂H₈Ph and OH), 1.36 (3H, s, C(CH₃)(CH₃)), 1.33 (3H, s, C(CH₂)(CH₂)), 1.36-1.08 (2H, m, CH₂CH₃), 0.94 (3H, t, J = 7.3 Hz, CH₂CH₃), 0.93-0.73 (2H, m, CHOCH-cyclopropyl and cyclopropyl-CH), 0.64-0.58 (1H, m, cyclopropyl-CH), 0.43-0.37 (1H, m, cyclopropyl-CH); $^{13}$C NMR (75 MHz, CDCl₃) δC = 168.3, 151.9, 136.5, 129.0, 128.8, 126.9, 83.1, 75.1, 64.1, 60.5, 34.6, 28.6, 26.4, 22.3, 21.6, 18.5, 13.5, 10.7; IR cm⁻¹ ν = 3494 (OH), 1770 (C=Oω), 1707 (C=O); HRMS: m/z (ES) 402.1469, C₂₀H₂₆ClNNaO₄ [M+Na]⁺ requires 402.1448; [α]$_D^{25}$ = +12.0 (c = 0.5 g/100 mL in CHCl₃).
(R)-4-Benzyl-3-((2R,3S)-2-chloro-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyl-oxazolidin-2-one, 559

(R)-4-Benzyl-3-((2R,3S,E)-2-chloro-3-hydroxy-6-methylhept-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 556 (1.85 g, 4.87 mmol) was dissolved in dichloromethane (90 mL) and stirred at 0 °C under nitrogen. Diethylzinc (24.35 mL, 24.35 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (1.96 mL, 24.35 mmol). The reaction was stirred for two hours in the absence of light. The reaction was quenched with saturated sodium sulphite (20 mL) and stirred for 10 minutes before sufficient 1 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 product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.13] to afford (R)-4-benzyl-3-((2R,3S)-2-chloro-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyl-oxazolidin-2-one 559 (1.44 g, 3.66 mmol) as a colourless oil in 76% yield. ¹H NMR (300 MHz, CDCl₃) δ H = 7.30-7.20 (5H, m, Ph), 5.78 (1H, d, J = 3.0 Hz, CHCl), 4.47 (1H, dd, J = 10.0, 3.3 Hz, CHN), 3.35 (1H, dd, J = 8.4, 3.0 Hz, CHOH), 3.19 (1H, dd, J = 14.5, 3.2 Hz, CH₃H₈Ph), 2.86 (1H, dd, J = 10.0, 14.5 Hz, CH₃H₈Ph), 2.63 (1H, broad s, OH), 1.35 (3H, s, C(CH₃)(CH₃)), 1.32 (3H, s, C(CH₃)(CH₃)), 0.96-0.93 (9H, m, CH(CH₃)(CH₃) and CHOCH-Cyclopropyl and cyclopropyl-CH(CH₃)(CH₃)), 0.60-0.56 (1H, m, cyclopropyl-CH₃H₈), 0.46-0.44 (1H, m, cyclopropyl-CH₃H₈); ¹³C NMR (75 MHz, CDCl₃) δC = 168.4, 152.0, 136.5, 129.1, 128.7, 127.0, 83.2, 75.3, 64.2, 60.8, 34.6, 32.5, 28.7, 24.7, 22.4, 22.1, 22.0, 21.3, 10.5; IR cm⁻¹ ν = 3500 (OH), 1773 (C=O,CH), 1709 (C=O); HRMS: m/z (ES) 416.1599, C₂₁H₂₉ClINaO₄ [M+Na]⁺ requires 416.1596; [α] D²⁵ = +10.0 (c = 0.5 g/100 mL in CHCl₃).
(R)-4-Benzyl-3-((R)-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one, 560

(R)-4-Benzyl-3-((2R,3S)-2-chloro-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one 557, (0.80 g, 2.21 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.57 g, 8.78 mmol) was added in one portion followed by ammonium chloride (0.47 g, 8.78 mmol). The resulting suspension was stirred at room temperature for one hour. The reaction was diluted with diethyl ether, filtered through a pad of Celite® and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R$_f$ 0.25] to afford (R)-4-benzyl-3-((R)-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one 560 (0.50 g, 1.52 mmol) as a yellow gum in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.33-7.19 (5H, m, Ph), 4.51 (1H, dd, $J = 9.0, 4.5$ Hz, CHN), 3.40 (1H, dd, $J = 13.6, 6.1$ Hz, CHOH), 3.20 (2H, d, $J = 5.9$ Hz, COCH$_2$CHOH), 3.13 (1H, dd, $J = 14.4, 4.5$ Hz, CH$_3$H$_3$Ph), 2.89 (1H, dd, $J = 14.3, 9.0$ Hz, CH$_3$H$_3$Ph), 2.51 (1H, broad s, OH), 1.39 (3H, s, C(CH$_3$)(CH$_3$)), 1.37 (3H, s, C(CH$_3$)(CH$_3$)), 1.03 (3H, d, $J = 5.6$ Hz, cyclopropyl-CH$_3$), 0.74-0.53 (3H, m, CHOCH$_2$-cyclopropyl and cyclopropyl-H), 0.34-0.29 (1H, m, cyclopropyl-H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 172.3, 152.5, 136.7, 128.9, 128.5, 126.6, 82.3, 71.5, 63.2, 43.0, 35.1, 28.3, 25.3, 22.0, 18.2, 11.5, 10.3; IR cm$^{-1}$ $\nu$ = 3519 (OH), 1773 (C=O); HRMS: $m/z$ (ES) 354.1779, C$_{19}$H$_{25}$NNaO$_4$ [M+Na]$^+$ requires 354.1681; $[\alpha]_{D}^{25} = +46.0$ (c = 0.5 g/100 mL in CHCl$_3$).
(R)-4-Benzyl-3-(((R)-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyl oxazolidin-2-one, 561

( R )-4-Benzyl-3-((R)-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyl oxazolidin-2-one 558 (0.58 g, 1.53 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.39 g, 6.1 mmol) was added in one portion followed by ammonium chloride (0.33 g, 6.1 mmol). The resulting suspension was stirred at room temperature for one hour. The reaction was diluted with diethyl ether, filtered through a pad of Celite® and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.24] to afford (R)-4-benzyl-3-((R)-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyl oxazolidin-2-one 561 (0.37 g, 1.07 mmol) as a yellow oil in 70% yield. 1H NMR (300 MHz, CDCl3) δH = 7.33-7.19 (5H, m, Ph), 4.51 (1H, dd, J = 9.0, 4.5 Hz, CHN), 3.41-3.34 (1H, m, CHOH), 3.22-3.20 (2H, m, COCH2CHOH), 3.13 (1H, dd, J = 14.4, 4.5 Hz, CH3Ph), 2.89 (1H, dd, J = 14.2, 9.0 Hz, CH3Ph), 2.62 (1H, broad s, OH), 1.42-1.13 (2H, m, CH2CH3), 1.38 (3H, s, C(CH3)(CH3)), 1.37 (3H, s, C(CH3)(CH3)), 0.94 (3H, app. t, J = 7.3 Hz, cyclopropyl-CH2CH3), 0.77-0.68 (1H, m, cyclopropyl-H), 0.60-0.52 (2H, m, CHOHCH-cyclopropyl and cyclopropyl-H), 0.39-0.33 (1H, m, cyclopropyl-H); 13C NMR (75 MHz, CDCl3) δC = 172.4, 152.5, 136.8, 128.9, 128.6, 126.7, 82.3, 71.8, 63.3, 42.9, 35.2, 28.3, 26.4, 24.2, 22.1, 18.2, 13.6, 10.4; IR cm⁻¹ ν = 3501 (OH), 1772 (C=O), 1694 (C=O); HRMS: m/z (ES) 368.1946, C20H27NNaO4 [M+Na]+ requires 368.1838; [α]D²⁵ = +44.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(R)-4-Benzyl-3-((R)-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one, 562

(R)-4-Benzyl-3-((R)-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one 559 (1.40 g, 3.55 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.93 g, 14.22 mmol) was added in one portion followed by ammonium chloride (0.76 g, 14.22 mmol). The resulting suspension was stirred at room temperature for one hour. The reaction was diluted with diethyl ether, filtered through a pad of Celite® and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.13] to afford (R)-4-benzyl-3-((R)-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one 562 (0.72 g, 2.00 mmol) as a colourless oil in 56% yield. 

1H NMR (300 MHz, CDCl₃) δH = 7.30-7.17 (5H, m, Ph), 4.51 (1H, dd, J = 9.2, 4.5 Hz, CHN), 3.35 (1H, td, J = 4.0, 8.0 Hz, CHOH), 3.22-3.19 (2H, m, COCH₂CH₂OH), 3.12 (1H, dd, J = 14.2, 4.2 Hz, CH₂H₃Ph), 2.87 (2H, dd, J = 14.2, 9.0 Hz, CH₂H₃Ph and broad s, OH), 1.35 (3H, s, C(CH₃)(CH₃)), 1.34 (3H, s, C(CH₃)(CH₃)), 0.94 (7H, m, CH(CH₃)(CH₃)), 0.80-0.71 (1H, m, CHOHC₃-cyclopropyl), 0.56-0.50 (2H, m, cyclopropyl-CHCH(CH₃)(CH₃)), and cyclopropyl-CH₂H₃); 13C NMR (75 MHz, CDCl₃) δC = 172.4, 152.5, 136.8, 128.9, 128.5, 128.4, 126.6, 82.2, 71.8, 63.2, 42.8, 35.2, 32.2, 28.3, 24.6, 23.6, 22.0, 21.8, 9.8; IR cm⁻¹ ν = 3526 (OH), 1775 (C=Oₘₙ), 1696 (C=O); HRMS: m/z (ES) 382.2026, C₂₁H₂₉NNaO₄ [M+Na]+ requires 382.1989; [α]₂₅°D = +50.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(R)-Methyl 3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoate, 563

(R)-4-Benzyl-3-((R)-3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one 560 (0.50 g, 1.51 mmol) was dissolved in dichloromethane (15 mL) at room temperature under nitrogen. A solution of sodium methoxide (3.02 mL, 1.51 mmol, 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO4 and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.22] to afford (R)-methyl 3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoate 563 (0.15 g, 0.94 mmol) as a colourless oil in 62% yield. 1H NMR (300 MHz, CDCl3) δH = 3.60 (3H, s, OCH3), 3.30-3.23 (1H, m, CHOH), 2.90 (1H, broad s, OH), 2.51 (2H, d, J = 6.4 Hz, COCH2CHOH), 0.91 (3H, d, J = 5.4 Hz, cyclopropyl-CH3), 0.59-0.51 (2H, m, CHOHC-CH2- and cyclopropyl-H), 0.22-0.17 (1H, m, cyclopropyl-H); 13C NMR (75 MHz, CDCl3) δC = 172.8, 72.1, 51.6, 41.7, 25.6, 18.2, 11.4, 10.5; IR cm⁻¹ ν = 3438 (OH), 1725 (C=O); HRMS: m/z (ES) 181.0859, C₈H₁₄NaO₃ [M+Na]+ requires 181.0840; [α]D₂⁵ = -16.0 (c = 0.5 g/100 mL in CHCl₃).
Experimental

(R)-Methyl 3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoate, 564

(R)-4-benzyl-3-((R)-3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethylloxazolidin-2-one 561 (0.37 g, 1.07 mmol) was dissolved in dichloromethane (12 mL) at room temperature under nitrogen. A solution of sodium methoxide (2.14 mL, 1.07 mmol, 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.21] to afford (R)-methyl 3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoate 564 (0.14 g, 0.78 mmol) as a colourless oil in 72% yield. ¹H NMR (300 MHz, CDCl₃) δH = 3.62 (3H, s, OCH₃), 3.26 (1H, ddd, J = 15.5, 8.3, 5.3 Hz, CHOH), 2.83 (1H, broad s, OH), 2.53 (2H, d, J = 2.3 Hz, CH₂CHOH), 1.31-1.16 (1H, m, CH₃CH₃), 1.13-0.99 (1H, m, CH₃H₆CH₃), 0.85 (3H, t, J = 7.3 Hz, cyclopropyl-CH₂CH₃), 0.63-0.42 (3H, m, CHOHCH-cyclopropyl and cyclopropyl-H); ¹³C NMR (75 MHz, CDCl₃) δC = 172.9, 72.3, 51.6, 41.5, 26.5, 24.4, 18.4, 13.5, 10.4; IR cm⁻¹ ν = 3428 (OH), 1732 (C=O); HRMS: m/z (ES) 195.0952, [M+Na]⁺ requires 195.0997; [α]D²⁰ = -6.0 (c = 0.5 g/100 mL in CHCl₃).
**Experimental**

(R)-Methyl 3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoate, 565

![Chemical Structure](attachment:structure.png)

(R)-4-Benzyl-3-((R)-3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethylloxazolidin-2-one 562 (0.71 g, 1.99 mmol) was dissolved in dichloromethane (20 mL) at room temperature under nitrogen. A solution of sodium methoxide (3.97 mL, 1.99 mmol, 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, RF 0.27] to afford (R)-methyl 3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoate 565 (0.23 g, 1.25 mmol) as a colourless oil in 63% yield. $^1$H NMR (300 MHz, CDCl₃) δH = 3.62 (3H, s, OCH₃), 3.23 (1H, m, CHOH), 2.89 (1H, broad s, OH), 2.53 (2H, m, CH₂CHOH), 0.91-0.86 (7H, m, CH(CH₃)(CH₃)), 0.68-0.59 (1H, m, CHOHC₃-cyclopropyl), 0.47-0.42 (1H, m, cyclopropyl-CHCH₃), 0.38-0.27 (2H, m, cyclopropyl-CH₂H₆ and cyclopropyl-CH₃H₆); $^{13}$C NMR (75 MHz, CDCl₃) δC = 172.9, 72.3, 51.6, 41.4, 32.4, 24.9, 23.8, 22.0, 21.9, 9.9; IR cm⁻¹ ν = 3467 (OH), 1735 (C=O); HRMS: m/z (ES) 209.1151, C₁₀H₁₈NaO₃ [M+Na]$^+$ requires 209.1148; $\alpha_{25}^{D} = +16.0$ (c = 0.5 g/100 mL in CHCl₃).
Mercury trifluoroacetate (0.99 g, 2.32 mmol) was added in one portion to a stirred solution of 
(R)-methyl 3-hydroxy-3-((1R,2R)-2-methylcyclopropyl)propanoate 563 (0.147 g, 0.93 mmol) in 
dichloromethane (10 mL). The resulting yellow solution was stirred at ambient temperature for 
24 hours under nitrogen, before being quenched with brine (10 mL) and stirred for a further one hour. The organic layer was extracted with brine and the aqueous layer was extracted further with ethyl acetate. The organic layers were combined, dried over MgSO_{4} and 
concentrated to afford the corresponding organomercurial δ-lactone. This was subsequently 
dissolved in methanol (5 mL) and cooled to 0 °C under nitrogen. Sodium borohydride (0.105 g, 2.79 mmol) was dissolved in 3.5 M sodium hydroxide (4 mL) and was added in one portion to the solution of organomercurial δ-lactone. The resulting dark grey solution was stirred for two minutes at 0 °C and was then quenched with 1 M HCl solution to pH 2. The methanol was evaporated, the aqueous layer was saturated with NaCl and the resulting brine solution was extracted with three portions of ethyl acetate. The organic extracts were combined, dried over MgSO_{4} and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:1 EtOAc:Petroleum ether, R_{f} 0.22] to afford (4R,5S,6R)-4-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-one 566 (0.087 g, 0.60 mmol) as a gummy solid in 65% yield. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} = 3.98 (1H, dq, J = 10.4, 6.4 Hz, COOC\textsubscript{H}\textsubscript{3}CH\textsubscript{3}), 3.76 (1H, td, J = 8.0, 5.9 Hz, CHO)H), 2.91 (1H, dd, J = 17.3, 5.9 Hz, COCH\textsubscript{2}H\textsubscript{2}CHOH), 2.50 (1H, dd, J = 17.3, 8.1 Hz, COCH\textsubscript{2}H\textsubscript{2}CHOH), 2.21 (1H, broad s, OH), 1.66-1.53 (1H, m, CHOHC\textsubscript{H}\textsubscript{2}CH\textsubscript{2}O), 1.40 (3H, d, J = 6.4 Hz, COOC\textsubscript{H}\textsubscript{3}CH\textsubscript{3}), 1.08 (3H, d, J = 6.7 Hz, CHO\textsubscript{H}CH\textsubscript{2}CH\textsubscript{2}O); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ\textsubscript{C} = 170.9, 79.2, 69.7, 43.4, 39.2, 19.7, 13.9; IR cm\textsuperscript{-1} v = 3413 (OH), 1718 (C=O); HRMS: m/z (ES) 145.0866, C\textsubscript{7}H\textsubscript{13}O\textsubscript{3} [M+H]\textsuperscript{+} requires 145.0864; [\alpha\textsubscript{D}\textsuperscript{25}] = +8.0 (c = 0.5 g/100 mL in CHCl\textsubscript{3}).
Mercury trifluoroacetate (0.84 g, 1.96 mmol) was added in one portion to a stirred solution of (R)-methyl 3-((1R,2R)-2-ethylcyclopropyl)-3-hydroxypropanoate 564 (0.14 g, 0.78 mmol) in dichloromethane (10 mL). The resulting yellow solution was stirred at ambient temperature for 24 hours under nitrogen, before being quenched with brine (10 mL) and stirred for a further one hour. The organic layer was extracted with brine and the aqueous layer was extracted further with ethyl acetate. The organic layers were combined, dried over MgSO₄ and concentrated to afford the corresponding organomercurial δ-lactone. This was subsequently dissolved in methanol (5 mL) and cooled to 0 °C under nitrogen. Sodium borohydride (0.089 g, 2.35 mmol) was dissolved in 3.5 M sodium hydroxide (4 mL) and was added in one portion to the solution of organomercurial δ-lactone. The resulting dark grey solution was stirred for two minutes at 0 °C and was then quenched with 1 M HCl solution to pH 2. The methanol was evaporated, the aqueous layer was saturated with NaCl and the resulting brine solution was extracted with three portions of ethyl acetate. The organic extracts were combined, dried over MgSO₄ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:1 EtOAc:Petroleum ether, Rf 0.21] to afford (4R,5S,6R)-6-ethyl-4-hydroxy-5-methyltetrahydro-2H-pyran-2-one, 567 (0.064 g, 0.41 mmol) as a gummy solid in 52% yield. ¹H NMR (300 MHz, CDCl₃) δ_H = 3.82 and 3.76 (1H, ddd, J = 10.4, 7.4, 3.0 Hz and 1H, ddd, J = 13.7, 7.8, 5.9 Hz, CHOH and CHCH₂CH₃), 2.89 (1H, dd, J = 17.1, 5.9 Hz, COCH₃H₃), 2.48 (1H, dd, J = 17.1, 7.8 Hz, COCH₃H₃), 2.51 (1H, broad s, OH), 1.82 and 1.74-1.48 (1H, app. sex. of doublets, J = 7.5, 3.0 Hz and 2H, m, CHCH₃ and CH₂CH₃), 1.06 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ_C = 172.0, 83.8, 69.4, 40.4, 39.0, 25.7, 13.9, 8.8; IR cm⁻¹ ν = 3415 (OH), 1716 (C=O); HRMS: m/z (ES) 159.1015, C₈H₁₅O₃ [M+H]⁺ requires 159.1021; [α]D²⁵ = +36.0 (c = 0.5 g/100 mL in CHCl₃).
Mercury trifluoroacetate (0.68 g, 1.60 mmol) was added in one portion to a stirred solution of (R)-methyl 3-hydroxy-3-((1R,2S)-2-isopropylcyclopropyl)propanoate 565 (0.12 g, 0.64 mmol) in dichloromethane (10 mL). The resulting yellow solution was stirred at ambient temperature for 24 hours under nitrogen, before being quenched with brine (10 mL) and stirred for a further one hour. The organic layer was extracted with brine and the aqueous layer was extracted further with ethyl acetate. The organic layers were combined, dried over MgSO₄ and concentrated to afford the corresponding organomercurial δ-lactone. This was subsequently dissolved in methanol (4 mL) and cooled to 0 °C under nitrogen. Sodium borohydride (0.073 g, 1.92 mmol) was dissolved in 3.5 M sodium hydroxide (3.5 mL) and was added in one portion to the solution of organomercurial δ-lactone. The resulting dark grey solution was stirred for two minutes at 0 °C and was then quenched with 1 M HCl solution to pH 2. The methanol was evaporated, the aqueous layer was saturated with NaCl and the resulting brine solution was extracted with three portions of ethyl acetate. The organic extracts were combined, dried over MgSO₄ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, Rₘ 0.10] to afford (4R,5S,6R)-4-hydroxy-6-isopropyl-5-methyltetrahydro-2H-pyran-2-one 568 (0.10 g, 0.60 mmol) as a gummy solid in 94% yield. 1H NMR (300 MHz, CDCl₃) δH = 3.73 (2H, m, COOC₂H₃CH(CH₃)(CH₃) and C₂H₅OH), 3.41 (1H, broad s, OH), 2.85 (1H, dd, J = 17.1, 5.9 Hz, COCH₂CH₂CHOH), 2.43 (1H, dd, J = 17.1, 7.7 Hz, COCH₃CH₂CHOH), 1.94 (1H, d, J = 6.9, 2.1 Hz, COOCH₂CH₂(CH₃)(CH₃)), 1.70 (1H, m, CHCH₃), 1.03 (6H, m, COOCH₂CH₂(CH₃)(CH₃) and CHCH₃), 0.87 (3H, d, J = 6.8 Hz, COOCH₂CH₂(CH₃)(CH₃)); 13C NMR (75 MHz, CDCl₃) δC = 172.11, 86.6, 69.5, 39.0, 38.9, 28.9, 20.1, 14.1, 13.7; IR cm⁻¹ ν = 3467 (OH), 1712 (C=O); HRMS: m/z (ES) 195.0986, C₉H₁₆NaO₃ [M+Na]⁺ requires 195.0997; [α]D₂⁰ = +28.0 (c = 0.5 g/100 mL in CHCl₃).
4.2 Compounds from Chapter 3

4.2.1 Synthesis of Non-Commercially Available Aldehydes

4-(Benzyloxy)butan-1-ol

NaH (0.98 g, 24.41 mmol, 60% dispersion in mineral oil) was added portionwise to THF (20 mL) at 0 °C. Butane-1,4-diol (2.0 g, 22.19 mmol) was added dropwise followed by benzyl bromide (3.17 mL, 26.63 mmol). The resulting suspension was stirred at room temperature for five hours before being quenched with water (20 mL). The THF was evaporated under reduced pressure, the resulting oil was redissolved in ethyl acetate and extracted with brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc: Petroleum ether, Rₚ 0.21] to afford 4-(benzyloxy)butan-1-ol (1.57 g, 8.65 mmol) as a colourless oil in 39% yield.

¹H NMR (300 MHz, CDCl₃) δH = 7.27-7.18 (5H, m, Ph), 4.43 (2H, s, OCH₃Ph), 3.50 (2H, t, J = 6.1 Hz, HOCH₂), 5.82 (2H, t, J = 5.8 Hz, CH₂OBn), 3.10 (1H, broad s, OH), 1.67-1.50 (4H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δC = 138.2, 128.3, 127.6, 127.5, 72.9, 70.2, 62.2, 29.7, 26.4; IR cm⁻¹ ν = 3367 (OH); HRMS: m/z (ES) 181.1215, C₁₁H₁₇O₂ [M+H]⁺ requires 181.1228.
**Experimental**

4-(Benzyloxy)butanal, 603

Oxalyl chloride (1.03 mL, 12.20 mmol) was dissolved in dry dichloromethane (50 mL) at -55 °C under nitrogen. Dimethylsulphoxide (1.58 mL, 22.20 mmol) was added and the resulting solution was stirred for two minutes. 4-(Benzyloxy)butan-1-ol (2.00 g, 11.10 mmol) in dichloromethane (5 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for 15 minutes at -55 °C. Triethylamine (7.73 mL, 55.50 mmol) was then added and the resulting solution was stirred for a further 15 minutes at -55 °C. The thick white slurry was warmed to room temperature and was quenched with the addition of water (50 mL). The layers were separated and the aqueous layer was extracted three times with dichloromethane (50 mL). The combined organic layers were washed with 1 M HCl (10 mL) and saturated NaHCO₃ before being dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rₚ 0.63] to afford 4-(benzyloxy)butanal 603 (1.48 g, 8.30 mmol) as a colourless liquid in 75% yield. ¹H NMR (300 MHz, CDCl₃) δ_H = 9.68 (1H, s, CHO), 7.30-7.18 (5H, m, Ph), 4.41 (2H, s, OCH₂Ph), 3.43 (2H, t, J = 6.1 Hz, CH₂OBn), 2.45 (2H, t, J = 7.1 Hz, CHOCH₂), 1.87 (2H, app. quintet, J = 6.6 Hz, CH₂CH₂CH₂OBn); ¹³C NMR (75 MHz, CDCl₃) δ_C 202.1, 138.3, 128.3, 127.5, 72.8, 69.0, 40.8, 22.5; IR cm⁻¹ ν = 1721 (C=O); HRMS: m/z (ES) 201.0894, C₁₁H₁₄NaO₂, [M+Na]^+ requires 201.0891.
Experimental

4-(Benzyloxy)-2-methylenebutanal, 604

4-(Benzyloxy)butanal 603 (0.50 g, 2.80 mmol) was dissolved in 37% aqueous formaldehyde solution (0.27 mL, 3.70 mmol). Dimethylamine hydrochloride (0.30 g, 3.70 mmol) was added and the mixture was heated at 70 °C for 24 hours. The reaction was cooled to room temperature, quenched with saturated NaHCO₃, extracted into hexane and the combined organic fractions were washed with water, dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.31] to afford 4-(benzyloxy)-2-methylenebutanal 604 (0.41 g, 2.20 mmol) as a colourless liquid in 78% yield. ¹H NMR (300 MHz, CDCl₃) δH = 9.46 (1H, s, CHO), 7.30-7.19 (5H, m, Ph), 6.31 (1H, s, C=CH₂H₆), 6.00 (1H, s, C=CH₂H₆), 4.43 (2H, s, OCH₂Ph), 3.53 (2H, t, J = 6.4 Hz, CH₂OBn), 2.51 (2H, t, J = 6.4 Hz, CH₂=CH₂); ¹³C NMR (75 MHz, CDCl₃) δC 194.4, 146.9, 138.2, 135.7, 128.4, 127.6, 127.5, 72.8, 67.9, 28.2; IR cm⁻¹ ν = 1686 (C=O); HRMS: m/z (ES) 213.0912, C₁₂H₁₄NaO₂, [M+Na]⁺ requires 213.0886.
2-(Benzyloxy)acetaldehyde, 606

Oxalyl chloride (0.18 mL, 2.17 mmol) was dissolved in dry dichloromethane (7 mL) at -55 °C under nitrogen. Dimethylsulfoxide (0.28 mL, 3.94 mmol) was added and the resulting solution was stirred for two minutes. 2-(Benzyloxy)ethanol (0.30 g, 1.97 mmol) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for 15 minutes at -55 °C. Triethylamine (1.37 mL, 9.86 mmol) was then added and the resulting solution was stirred for a further 15 minutes at -55 °C. The thick white slurry was warmed to room temperature and was quenched with the addition of water (10 mL). The layers were separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were washed with 1 M HCl and saturated NaHCO₃ before being dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.10] to afford 2-(benzyloxy)acetaldehyde 606 (0.27 g, 1.79 mmol) as a colourless liquid in 91% yield. §H NMR (300 MHz, CDCl₃) δ_H = 9.57 (1H, s, C=H), 7.27-7.19 (5H, m, Ph), 4.50 (2H, s, OCH₂Ph), 3.97 (2H, d, J = 0.7 Hz, CHOCH₂); §C NMR (75 MHz, CDCl₃) δ_C = 200.3, 136.8, 128.5, 128.1, 127.9, 75.2, 73.5; IR cm⁻¹ ν = 3411 (OH), 1735 (C=O); HRMS: m/z (ES) 173.0601, C₉H₁₀NaO₂ [M+Na]⁺ requires 173.0578.
**Experimental**

(E)-**Ethyl 4-(benzyloxy)-2-methylbut-2-enoate, 608**

![Chemical Structure](attachment:image.png)

(Carbethoxyethylidene)triphenylphosphorane (0.65 g, 1.80 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0 °C. 2-(Benzyloxy)acetaldehyde 606 (0.24 g, 1.60 mmol) in dichloromethane (1 mL) was added dropwise and the resulting solution was stirred for 30 minutes. The dichloromethane was removed under reduced pressure and the crude product was purified using flash silica chromatography [1:99 EtOAc:Petroleum ether, Rf 0.31] to afford (E)-ethyl 4-(benzyloxy)-2-methylbut-2-enoate 608 (0.24 g, 1.04 mmol) as a colourless liquid in 65% yield.

**1H NMR (300 MHz, CDCl₃)** \(\delta_H = 7.27-7.18 \text{ (5H, m, Ph)}, 6.80 \text{ (1H, td, } J = 5.8, 1.1 \text{ Hz, } \text{CH}_3\text{C=CH}), 4.45 \text{ (2H, s, OCH}_2\text{Ph)}, 4.11 \text{ (4H, app. quartet, } J = 7.1 \text{ Hz, C=CH}_2\text{ and CH}_3\text{CH}_2\text{OC=O}), 1.74 \text{ (3H, s, CH}_3\text{C=CCH)}, 1.20 \text{ (3H, t, } J = 7.0 \text{ Hz, CH}_3\text{CH}_2\text{OC=O}); **13C NMR (75 MHz, CDCl₃) \(\delta_C = 167.4, 137.9, 137.8, 129.4, 128.4, 127.7, 72.7, 66.8, 60.6, 14.9, 12.8; IR cm⁻¹ ν = 1709 (C=O); HRMS: m/z (ES) 257.1139, C₁₄H₁₈NaO₃ [M+Na]⁺ requires 257.1153.
(E)-4-(Benzylxy)-2-methylbut-2-en-1-ol, 609

(E)-4-(benzylxy)-2-methylbut-2-enoate 608 (0.24 g, 1.04 mmol) was dissolved in dry diethyl ether (5 mL) at -78 °C. DIBAL (1.25 mL, 1.24 mmol, 1M in hexane) was added dropwise and the resulting solution was stirred for one hour at -78 °C followed by one hour at 0 °C. The reaction was quenched with saturated ammonium chloride and the layers were separated. The organic layer was washed with 1 M HCl and saturated NaHCO₃ before being dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.19] to afford (E)-4-(benzylxy)-2-methylbut-2-en-1-ol 609 (0.08 g, 0.43 mmol) as a colourless liquid in 41% yield. ¹H NMR (300 MHz, CDCl₃) δ_H = 7.27-7.18 (5H, m, Ph), 5.57 (1H, tq, J = 6.6, 1.3 Hz, CH₂C=CH), 4.43 (2H, s, CH₂OPh), 3.99 (2H, d, J = 6.6 Hz, CH₂OBn), 3.90 (2H, s, CH₂OH), 2.27 (1H, broad s, OH), 1.57 (3H, s, CH₃C=CH); ¹³C NMR (75 MHz, CDCl₃) δ_C = 139.5, 138.3, 128.4, 127.9, 127.7, 121.2, 72.4, 67.8, 66.3, 13.9; IR cm⁻¹ ν = 3399 (OH); HRMS: m/z (ES) 215.1096, C₁₂H₁₅NaO₂ [M+Na]^+ requires 215.1048.
**Experimental**

**(E)-4-(Benzyloxy)-2-methylbut-2-enal, 610**

![Chemical structure](image)

Oxalyl chloride (0.15 mL, 1.74 mmol) was dissolved in dry dichloromethane (6 mL) at -55 °C under nitrogen. Dimethylsulfoxide (0.22 mL, 3.16 mmol) was added and the resulting solution was stirred for two minutes. (E)-4-(Benzyloxy)-2-methylbut-2-en-1-ol **609** (0.30 g, 1.58 mmol) in dichloromethane (1 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for 15 minutes at -55 °C. Triethylamine (1.10 mL, 7.91 mmol) was then added and the resulting solution was stirred for a further 15 minutes at -55 °C. The thick white slurry was warmed to room temperature and was quenched with the addition of water (10 mL). The layers were separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were washed with 1 M HCl and saturated NaHCO₃ before being dried over MgSO₄ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.63] to afford (E)-4-(benzyloxy)-2-methylbut-2-enal **610** (0.27 g, 1.45 mmol) as a colourless liquid in 92% yield. ³¹H NMR (300 MHz, CDCl₃) δH = 9.33 (1H, s, CHO), 7.30-7.16 (5H, m, Ph), 6.50 (1H, tq, J = 5.6, 1.3 Hz, (CH₃C=CH)), 4.48 (2H, s, OCH₂Ph), 4.25 (2H, dd, J = 5.6, 1.1 Hz, CH₂OBn), 1.63 (3H, app. quartet, J = 1.1 Hz, CH₃C=CH); ¹³C NMR (75 MHz, CDCl₃) δC = 194.4, 149.5, 139.5, 137.6, 128.6, 128.0, 127.9, 73.2, 66.8, 9.6; IR cm⁻¹ ν = 1687 (C=O); HRMS: m/z (ES) 213.0883, C₁₂H₁₄NaO₂ [M+Na]⁺ requires 213.0891.
Experimental

4.2.2 Synthesis of syn-Aldol Products 613, 614, 615

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 613

The title compound was prepared according to General Procedure 1 from 9-BBN-OTf (3.78 mL, 1.90 mmol), (S)-4-benzyl-5,5-dimethyl-3-propionoyloxazolidin-2-one 95 (0.40 g, 1.70 mmol), N,N-diisopropylethylamine (0.43 ml, 2.50 mmol) and acrolein (0.16 mL, 2.50 mmol) in dichloromethane (90 mL). The crude product was purified using flash silica chromatography to afford (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one 613 (0.26 g, 0.90 mmol) as a colourless oil in 53% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H = 7.26$-7.12 (5H, m, Ph), 5.83-5.70 (1H, ddd, $J = 10.5, 5.5, 5.3$ Hz, CH=CH$_2$), 5.25 (1H, dt, $J = 1.5$ Hz, CH$_{cis}$H$_{trans}$=C), 5.13 (1H, dt, $J = 10.5, 1.5$ Hz, CH$_{cis}$H$_{trans}$=C), 4.99 (1H, dd, J = 9.0, 4.5 Hz, CHN), 4.38 (1H, m, CH$_{OH}$), 3.85 (1H, dq, J = 7.0, 4.0 Hz, CHCH$_3$), 3.0 (1H, dd, J = 14.5, 4.5 Hz, CH$_3$H$_{trans}$=C), 2.85 (1H, dd, J = 14.5, 9.0 Hz, CH$_3$H$_{trans}$=C), 2.65 (1H, broad s, OH), 1.33 (3H, s, (CH$_3$)$_2$C(CH$_3$)$_2$), 1.13 (3H, s, (CH$_3$)$_2$C(CH$_3$)$_2$), 1.10 (3H, d, J = 7.0 Hz, CH$_3$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C = 176.9$ 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 cm$^{-1}$ ν = 3501 (broad OH), 1754 (C=O), 1702 (C=O$_{en}$); HRMS: m/z (ES) 340.1577, C$_{18}$H$_{23}$NNaO$_4$ [M+Na]$^+$ requires 340.1519; $[\alpha]D^{22} = -26.0$ (c = 0.60 g/100 mL in CHCl$_3$).
(S)-4-Benzyl-3-((2S,3S)-6-(benzyloxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyl-oxazolidin-2-one, 614

The title compound was prepared according to General Procedure 1 from diisobutylboron triflate (1.78 mL, 1.80 mmol), (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.42 g, 1.60 mmol), N,N-diisopropylethylamine (0.36 mL, 2.10 mmol) and 4-(benzyloxy)-2-methylenebutanal 604 (0.40 g, 2.10 mmol) in dichloromethane (5 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.27] to afford (S)-4-benzyl-3-((2S,3S)-6-(benzyloxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyl-oxazolidin-2-one 614 (0.57 g, 1.30 mmol) as a colourless oil in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.27-7.16 (10H, m, Ph and Ph$_{\text{ox}}$), 5.11 (1H, s, C=CH$_A$H$_B$), 4.95 (1H, s, C=CH$_A$H$_B$), 4.45-4.40 (3H, m, OCH$_2$Ph, CHN), 4.32 (1H, broad d, $J$ = 5.8 Hz, CHO$_{\text{OH}}$), 4.00 (1H, app. quintet, $J$ = 6.6 Hz, CHCH$_3$), 3.62-3.48 (2H, m, CH$_2$OBn), 3.18 (1H, broad s, OH), 2.99 (1H, dd, $J$ = 14.4, 4.3 Hz, CH$_A$H$_B$Ph), 2.83 (1H, dd, $J$ = 14.1, 8.7 Hz, CH$_A$H$_B$Ph), 2.44-2.35 (1H, m, CH$_A$H$_B$OBn), 2.29-2.21 (1H, m, CH$_A$H$_B$OBn), 1.31 (3H, s, C(CH$_3$)(CH$_3$)), 1.26 (3H, s, C(CH$_3$)(CH$_3$)), 1.12 (3H, d, $J$ = 6.9 Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 176.3, 152.2, 146.8, 137.9, 136.7, 129.1, 128.6, 128.4, 127.7, 127.6, 126.8, 113.3, 82.2, 74.5, 73.0, 70.0, 63.3, 41.5, 35.3, 32.7, 28.2, 22.1, 12.0; IR cm$^{-1}$ v = 3467 (OH), 1770 (C=O$_{\text{ox}}$), 1694 (C=O); HRMS: m/z [ES] 452.2458, C$_{27}$H$_{34}$NO$_5$ [M+H]$^+$ requires 452.2436; [a]$_D^{17}$ = -30.0 ($c$ = 0.50 g/100 mL in CHCl$_3$).
The title compound was prepared according to General Procedure 1 from dibutylboron triflate (1.50 mL, 1.50 mmol), (S)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 95 (0.36 g, 1.40 mmol), N,N-diisopropylethylamine (0.31 mL, 1.80 mmol) and (E)-4-(benzylxoy)-2-methylbut-2-enal 610 (0.34 g, 1.80 mmol) in dichloromethane (3 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.24] to afford (S)-4-benzyl-3-((2S,3S,E)-6-(benzyloxy)-3-hydroxy-2,4-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 615 (0.28 g, 0.60 mmol) as a colourless oil in 46% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta_H = 7.27$-$7.15$ (10H, m, Ph and Ph$_{ox}$), 5.71 (1H, broad t, $J = 6.3$ Hz, C=CH), 4.46-$4.43$ (3H, m, OCH$_2$Ph and CHN), 4.28 (1H, d, $J = 3.7$ Hz, CHO), 4.02 (2H, d, $J = 6.6$ Hz, CH$_2$OBn), 3.96-$3.91$ (1H, m, CHCH$_3$), 3.01 (1H, dd, $J = 14.3$, 4.0 Hz, CH$_2$H$_2$Ph), 2.82 (2H, dd, broad s, $J = 14.3$, 9.1 Hz, CH$_2$H$_2$Ph and OH), 1.57 (3H, s, CH$_3$C=CH), 1.30 (3H, s, C(CH$_3$)(CH$_3$)), 1.26 (3H, s, C(CH$_3$)(CH$_3$)), 1.05 (3H, d, $J = 7.4$ Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_C = 176.6$, 152.3, 138.3, 138.1, 136.7, 129.1, 128.6, 128.4, 127.8, 127.6, 126.9, 122.9, 82.4, 75.2, 72.1, 66.2, 63.5, 40.6, 35.3, 28.3, 22.1, 13.6, 10.9; IR cm$^{-1}$ $\nu = 3481$ (OH), 1771 (C=O$_{ox}$), 1698 (C=O); HRMS: $m/z$ (ES) 452.2446, C$_{27}$H$_{34}$NO$_5$ [M+H]$^+$ requires 452.2436; $[\alpha]_D^{20} = -42.0$ (c = 0.50 g/100 mL in CHCl$_3$).
Experimental

4.2.3  **Upjohn Dihydroxylation for the Synthesis of Hydroxy-γ-Butyrolactones 632-637**

**Upjohn Dihydroxylation: Synthesis of Hydroxy-γ-Butyrolactones - General Procedure 5**

Osmium tetroxide (OsO₄) (0.1 equiv.) was added in one portion to a stirring solution of the appropriate β-alkenyl-β-hydroxy-N-acyloxazolidin-2-one 613-616, 536, 538 (1.0 equiv.) in acetone/water (8:1 ratio) under nitrogen. After five minutes, NMO (N-methylmorpholine N-oxide, 60% by weight in water, 1.1 equiv.) was added in one portion and the solution was stirred for 24 hours. The resulting reaction mixture was concentrated under reduced pressure and immediately purified via column chromatography.
(3S,4S,5R)-5-Ethyl-4-hydroxy-5-(hydroxymethyl)-3-methylidihydrofuran-2(3H)-one, 599

![Structural diagram]

OsO₄ (0.022 g, 0.09 mmol) was added to a solution of (S)-4-benzyl-3-((2S,3S)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one 592 (0.31 g, 0.88 mmol) in acetone/water (8:1, 3 mL) followed by addition of NMO (60% by weight in water, 0.16 mL, 0.97 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methylidihydrofuran-2(3H)-one 599 (0.12 g, 0.61 mmol) as a colourless oil in 69 % yield and 49:1 dr. ¹H NMR (500 MHz, MeOD) δH = 4.24 (1H, d, J = 9.4 Hz, CHOH), 3.74 (1H, d, J = 12.1 Hz, CH₂H₂OH), 3.52 (1H, d, J = 12.2 Hz, CH₂H₂OH), 2.68 (1H, qd, J = 9.4, 7.1 Hz, CHCO), 1.81 (1H, dq, J = 15.0, 7.5 Hz, CH₃H₂CH₃), 1.71 (1H, dq, J = 15.0, 7.5 Hz, CH₃H₂CH₃), 1.28 (3H, d, J = 7.5 Hz, CH₃), 1.01 (3H, t, J = 7.5 Hz, CH₃CH₃); ¹³C NMR (75 MHz, MeOD) δC = 179.6, 90.2, 76.5, 64.7, 44.2, 25.0, 13.9, 8.6; IR cm⁻¹ ν = 3368 (broad OH), 1751 (C=O); HRMS: m/z (ES) 175.0957, [M+H]+ requires 175.0970; [α]D²⁴ = - 3.4 (c = 0.88 g/100 mL in CHCl₃).
OsO₄ (0.015 g, 0.06 mmol) was added to a solution of (S)-4-benzyl-3-((25,3R)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one 613 (0.15 g, 0.52 mmol) in acetone/water (8:1, 5 mL) followed by addition of NMO (60% by weight in water, 0.09 mL, 0.52 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one 632 (0.06 g, 0.41 mmol) as a colourless oil in 79% yield and 3:1 dr. The two diastereoisomers were analysed as a mixture. (3S,4S,5R)-major: ¹H NMR (500 MHz, MeOD) δ_H = 4.19-4.17 (1H, m, CHCH₂OH), 4.02 – 3.99 (1H, m, CHOH), 3.94 (1H, dd, J = 12.8, 2.5 Hz, CH₃CH₂OH), 3.72 (1H, dd, J = 12.8, 4.8 Hz, CH₃CH₂OH), 2.66 (1H, dq, J = 8.9, 7.1 Hz, CHCH₃), 1.30 (3H, d, J = 7.3 Hz, CH₃); ¹³C NMR (75 MHz, MeOD) δ_C = 180.0, 86.8, 75.6, 62.0, 45.7, 13.6; (3S,4S,5S)-minor: ¹H NMR (500 MHz, CDCl₃) δ_H = 4.57 (1H, dt, J = 5.8, 3.7 Hz, CH₂CH₂OH), 4.27 (1H, t, J = 6.0 Hz, CHOH), 3.90 (2H, d, J = 3.7 Hz, CH₂CH₂OH), 2.71 (1H, dt, J = 13.6, 7.6 Hz, CHCH₃), 1.29 (3H, d, J = 7.5 Hz, CH₃); ¹³C NMR (75 MHz, MeOD) δ_C = 181.6, 84.1, 76.2, 62.2, 45.5, 14.4; IR cm⁻¹ ν = 3377 (broad OH), 2934 (broad OH), 1763 (C=O); HRMS: m/z (ES) 147.0650, C₆H₁₁O₄ [M+H]+ requires 147.0657; [α]D²⁴ = +4.0 (c = 0.50 g/100 mL in MeOH).
OsO₄ (0.008 g, 0.03 mmol) was added to a solution of (S)-4-benzyl-3-((2S,3S)-6-(benzyl)oxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one 614 (0.14 g, 0.31 mmol) in acetone/water (8:1, 1.5 mL) followed by addition of NMO (60% by weight in water, 0.07 mL, 0.34 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5R)-5-(2-(benzyl)oxyethyl)-4-hydroxy-5-(hydroxymethyl)-3-methylidihydrofuran-2(3H)-one 633 (0.08 g, 0.28 mmol) as a colourless oil in 93% yield and 10:1 dr. ¹H NMR (300 MHz, CDCl₃) δH = 7.31-7.18 (5H, m, Ph), 4.43 (2H, s, OCH₂Ph), 4.12 (1H, broad s, OH), 3.96 (1H, d, J = 8.4 Hz, CH₂OH), 3.59-3.49 (4H, m, CH₂OBn, CH₂OH), 2.80 (1H, broad s, OH), 2.49 (1H, app. quintet, J = 7.4 Hz, CHCH₃), 2.07-1.91 (2H, m, CH₂CH₂OBn), 1.20 (3H, d, J = 7.4 Hz, CHCH₃); ¹³C NMR (75 MHz, CDCl₃) δC = 177.4, 136.5, 128.8, 128.5, 128.3, 87.8, 76.5, 73.9, 66.4, 64.8, 42.9, 30.3, 13.7; IR cm⁻¹ ν = 3402 (OH), 1754 (C=O); HRMS: m/z (ES) 303.1210, C₁₅H₂₀NaO₅, [M+Na]⁺ requires 303.1208; [α]D²⁴ = +18.0 (c = 0.50 g/100 mL in CHCl₃).
**Experimental**

(3S,4S,5S)-5-{(S)-2-(Benzyloxy)-1-hydroxyethyl}-4-hydroxy-3-methylidihydrofuran-2(3H)-one, 634

OsO_4 (0.006 g, 0.02 mmol) was added to a solution of (S)-4-benzyl-3-{((2S,3R,E)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 538 (0.10 g, 0.22 mmol) in acetone/water (8:1, 1.2 mL) followed by addition of NMO (60% by weight in water, 0.04 mL, 0.25 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5S)-5-{(S)-2-(benzyloxy)-1-hydroxyethyl}-4-hydroxy-3-methylidihydrofuran-2(3H)-one 634 (0.047 g, 0.17 mmol) as a colourless oil in 77% yield and 4:1 dr. $^1$H NMR (300 MHz, CDCl$_3$) δ_H = 7.33-7.20 (5H, m, Ph), 4.50 (2H, s, OCH$_2$Ph), 4.04-3.90 (3H, m, CH$_3$CHCOH, COOCH, OCH$_2$CHOH), 3.63-3.52 (3H, m, CH$_2$OBn, OH), 2.95 (1H, d, J = 4.3 Hz, OH), 2.61-2.51 (1H, m, CHCH$_3$), 1.22 (3H, d, J = 7.0 Hz, CHCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ_C = 176.6, 137.1, 128.8, 128.4, 128.1, 84.3, 74.6, 74.0, 71.1, 69.3, 43.2, 12.4; IR cm$^{-1}$ ν = 3396 (OH), 1760 (C=O); HRMS: m/z (ES) 289.1041, C$_{14}$H$_{18}$NaO$_5$ [M+Na]$^+$ requires 289.1051; [α]$_D^{24}$ = +4.0 (c = 0.50 g/100 mL in CHCl$_3$).
**Experimental**

(3S,4S,5S)-5-[(R)-2-(Benzyloxy)-1-hydroxyethyl]-4-hydroxy-3-methyldihydrofuran-2(3H)-one, 635

OsO₄ (0.006 g, 0.02 mmol) was added to a solution of (S)-4-benzyl-3-[(25,3R,2)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl]-5,5-dimethyloxazolidin-2-one 536 (0.10 g, 0.22 mmol) in acetone/water (8:1, 1.2 mL) followed by addition of NMO (60% by weight in water, 0.04 mL, 0.25 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether 2:1 (v/v)] to afford (3S,4S,5S)-5-[(R)-2-(benzyloxy)-1-hydroxyethyl]-4-hydroxy-3-methyldihydrofuran-2(3H)-one 635 as a colourless oil as a separable diastereomeric mixture in overall 74% yield and 2:1 dr. The diastereomers were separated using flash column chromatography and analysed separately; 635 major (0.028 g, 0.11 mmol, 45% yield), 658 minor (0.013 g, 0.05 mmol, 21% yield) and a mixture of 635 major and 658 minor (0.004 g, 0.15 mmol, 7% yield). (3S,4S,5S)-5-(S)-major: $^1$H NMR (300 MHz, 50:50 CDCl₃:CD₃OD) $\delta$H = 7.32-21 (5H, m, Ph), 4.43 (1H, d, $J = 11.6 \text{ Hz}, OC\text{H}_2\text{H}_2\text{Ph})$, 4.36 (1H, d, $J = 11.6 \text{ Hz}, OC\text{H}_2\text{H}_2\text{Ph})$, 4.03 (1H, dd, $J = 9.9, 7.3 \text{ Hz}, CH_3\text{CHCHOH}$), 3.85 (1H, dd, $J = 7.3, 5.1 \text{ Hz}, COOC\text{H}_2\text{H}_2\text{Ph}$), 3.79-3.75 (1H, m, OCH₂CHOH), 3.51 (1H, dd, $J = 10.3, 3.3 \text{ Hz}, CH_2\text{H}_2\text{OBn}$), 3.46 (1H, dd, 10.3, 4.2 Hz, CH₂H₂OBn), 3.21 (1H, broad s, OH), 2.59 (1H, broad s, OH), 2.50 (1H, dq, $J = 9.9, 7.1 \text{ Hz}, CHCH_3$), 1.25 (3H, d, $J = 7.1 \text{ Hz}, CHCH_3$); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$C = 176.5, 136.9, 128.8, 128.5, 128.2, 83.1, 74.5, 74.3, 70.9, 70.4, 42.7, 12.6; IR cm$^{-1}$ ν = 3419 (OH), 1760 (C=O); HRMS: m/z (ES) 289.1042, C_{14}H_{12}NaO_{5}, [M+Na]$^+$ requires 289.1051; $[\alpha]_{D}^{226}$ = -2.0 ($c = 0.50 \text{ g/100 mL in CHCl}_3$). (3S,4S,5S)-5-(R)-minor: $^1$H NMR (300 MHz, CDCl₃) $\delta$H = 7.40-7.30 (5H, m, Ph), 4.59 (2H, s, OCH₂Ph), 4.43 (1H, dd, $J = 8.0, 4.7 \text{ Hz}, COOCH$), 4.32 (1H, dd, $J = 4.7, 2.6 \text{ Hz}, CH_3\text{CHCHOH}$), 4.18-4.13 (1H, m, OCH₂CHOH), 3.79 (1H, dd, $J = 9.9, 3.3 \text{ Hz}, CH_2\text{H}_2\text{OBn}$), 3.69 (1H, dd, $J = 9.9, 5.0 \text{ Hz}, CH_2\text{H}_2\text{OBn}$), 3.11 (1H, broad s, OH), 2.87 (1H, broad s, OH), 2.68 (1H, qd, $J = 7.8, 2.5 \text{ Hz}, CHCH_3$), 1.30 (3H, d, $J = 7.8 \text{ Hz}, CHCH_3$); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$C = 178.4, 137.3, 128.8, 128.3, 128.1, 79.2, 75.0, 73.9, 71.0, 69.1, 43.8, 13.8; IR cm$^{-1}$ ν = 3421 (OH), 1774 (C=O); HRMS: m/z (ES) 289.1032, C₁₆H₁₄NaO₅, [M+Na]$^+$ requires 289.1051; $[\alpha]_{D}^{226}$ = -6.0 ($c = 0.50 \text{ g/100 mL in CHCl}_3$).
(3S,4S,5S)-5-((S)-2-(Benzyloxy)-1-hydroxyethyl)-4-hydroxy-3,5-dimethyldihydrofuran-2(3H)-one, 636

OsO₄ (0.004 g, 0.02 mmol) was added to a solution of (S)-4-benzyl-3-((2S,3S,E)-6-(benzyloxy)-3-hydroxy-2,4-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 615 (0.075 g, 0.17 mmol) in acetone/water (8:1, 0.7 mL) followed by addition of NMO (60% by weight in water, 0.03 mL, 0.18 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5S)-5-((S)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3,5-dimethyldihydrofuran-2(3H)-one 636 (0.043 g, 0.15 mmol) as a colourless oil in 93% yield and >49:1 dr. ¹H NMR (300 MHz, CDCl₃) δ = 7.31-7.17 (5H, m, Ph), 4.49 (1H, d, J = 11.6 Hz, OCH₂H₆Ph), 4.43 (1H, d, J = 11.6 Hz, OCH₃H₆Ph), 3.86 (1H, d, J = 10.5 Hz, CHCH₂CHOH), 3.77 (1H, dd, J = 7.6, 6.2 Hz, CHOHCH₂OBn), 3.54 (1H, dd, J = 10.0, 6.2 Hz, CH₃H₆OBn), 3.47 (1H, dd, J = 9.8, 7.8 Hz, CH₃H₆OBn), 3.42 (1H, broad s, OH), 2.90 (1H, broad s, OH), 2.65-2.53 (1H, m, CHCH₃), 1.20-1.16 (6H, m, CHCH₃, CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ = 175.9, 136.6, 128.9, 128.6, 128.3, 87.7, 76.8, 74.3, 74.0, 70.0, 40.6, 13.9, 12.7; IR cm⁻¹ ν = 3420 (OH), 1761 (C=O); HRMS: m/z (ES) 281.1368, C₁₅H₂₂O₅, [M+H]⁺ requires 281.1388; [α]D²³ = -12.0 (c = 0.50 g/100 mL in CHCl₃).
Experimental

(3S,4S,5R)-4-Hydroxy-5-(2-hydroxypropan-2-yl)-3-methyldihydrofuran-2(3H)-one, 637

OsO₄ (0.014 g, 0.05 mmol) was added to a solution of (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethylloxazolidin-2-one 616 (0.18 g, 0.53 mmol) in acetone/water (8:1, 3 mL) followed by addition of NMO (60% by weight in water, 0.10 mL, 0.59 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3S,4S,5R)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyldihydrofuran-2(3H)-one 637 (0.038 g, 0.22 mmol) as a colourless oil in 41% yield and 5:1 dr. ¹H NMR (300 MHz, CDCl₃) δH = 4.94 (1H, d, J = 4.1 Hz, OH), 4.26 (1H, app. dt, J = 3.9, 1.5 Hz, CHOH), 4.09 (1H, d, J = 4.1 Hz, CHOCO), 2.96 (1H, broad s, OH), 2.68 (1H, qd, J = 7.8, 1.5 Hz, CH(CH₃)₂OH), 1.38 (3H, s, (CH₃)C(CH₃)), 1.36 (3H, s, (CH₃)C(CH₃)), 1.19 (3H, d, J = 7.8 Hz, CH₂CH); ¹³C NMR (75 MHz, CDCl₃) δC = 179.5, 84.0, 76.3, 73.0, 46.9, 28.7, 25.0, 13.5; IR cm⁻¹ ν = 3295 (broad OH), 1754 (C=O); HRMS: m/z (ES) 175.0970, C₈H₁₅O₄ [M+H]⁺ requires 175.0970; [α]D²³ = -55.6 (c = 0.99 g/100 mL in CHCl₃).
Experimental

Sharpless Asymmetric Dihydroxylations

\((3S,4S,5S)-5-((R)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-2(3H)\)-one, 635

AD-mix-β (0.25 g, 1.4 g/mmol of allylic alcohol) was dissolved in a 1:1 mixture of \(^1\)BuOH and water (1.8 mL, 10 mL/mmol of allylic alcohol). MeSO₂NH₂ (0.017 g, 0.18 mmol) was added and the biphasic suspension was cooled to 0 °C. \((S)-4\)-Benzy1-3-\((2S,3R,Z)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl\)-5,5-dimethyloxazolidin-2-one 536 (0.08 g, 0.18 mmol) dissolved in dichloromethane (1 mL) was added dropwise via syringe to the stirring suspension followed by OsO₄ (0.004 g, 0.18 mmol). The suspension was stirred vigorously whilst slowly warming to room temperature. After 48 hours, the reaction was quenched with solid sodium sulfite (0.10 g) at room temperature. The suspension was filtered through a pad of Celite*/Florisil®, eluting with ethyl acetate before the solution was dried over MgSO₄ and concentrated. The crude product was purified using flash column chromatography [1:1 EtOAc:Petroleum ether, \(R_f\) 0.15] to afford \((3S,4S,5S)-5-((R)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-2(3H)\)-one 635 (0.046 g, 0.17 mmol) as a white oil in 95% yield and 17:1 dr. Analytical data identical to that previously described.
AD-mix-α (0.25 g, 1.4 g/mmol of allylic alcohol) was dissolved in a 1:1 mixture of 1BuOH and water (1.8 mL, 10 mL/mmol of allylic alcohol). MeSO₂NH₂ (0.017 g, 0.18 mmol) was added and the biphasic suspension was cooled to 0 °C. (S)-4-Benzyl-3-((2S,3R,Z)-6-(benzylkoxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one 536 (0.08 g, 0.18 mmol) dissolved in dichloromethane (1 mL) was added dropwise via syringe to the stirring suspension followed by OsO₄ (0.005 g, 0.18 mmol). The suspension was stirred vigorously whilst slowly warming to room temperature. After 48 hours, the reaction was quenched with solid sodium sulfite (0.10 g) at room temperature. The suspension was filtered through a pad of Celite®/Florisil®, eluting with ethyl acetate before the solution was dried over MgSO₄ and concentrated. The crude product was purified using flash column chromatography [1:1 EtOAc:Petroleum ether, Rf 0.15] to afford (3S,4S,5R)-5-((S)-2-(benzylkoxy)-1-hydroxyethyl)-4-hydroxy-3-methylidihydrofuran-2(3H)-one 658 (0.046 g, 0.17 mmol) as a white oil in 95% yield and 4:1 dr. Analytical data identical to that previously described.
4.2.4 **Synthesis of Compounds for 2-Deoxy-D-Ribonolactone**

**(S)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethylloxazolidin-2-one, 660**

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{O-Cl} \\
\text{Ph} & 
\end{align*}
\]

*n*-BuLi (10.71 mL, 26.8 mmol, 2.5 M solution in hexane) was added to a solution of *(S)-4-benzyl-5,5-dimethylloxazolidin-2-one (5.00 g, 24.3 mmol) in dry THF (150 mL) at -78 °C under nitrogen and was stirred for 30 minutes. Chloroacetyl chloride (2.07 mL, 26.8 mmol) was added in one portion and the resulting solution was stirred for a further two hours. The reaction was quenched with saturated ammonium chloride and allowed to warm to ambient temperature. The THF was evaporated under reduced pressure, the resulting oil was redissolved in dichloromethane and extracted with brine. The combined organic extracts were dried over MgSO₄ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, Rf 0.50] to afford *(R)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethylloxazolidin-2-one 660 (5.69 g, 20.1 mmol) as a colourless oil in 83% yield. ¹H NMR (300 MHz, CDCl₃) δH = 7.32-7.20 (5H, m, Ph), 4.76 (1H, d, J = 15.8 Hz, COCH₂H₂Cl), 4.64 (d, J = 15.8 Hz, COCH₂H₂Cl), 4.49 (1H, dd, J = 9.7, 3.9 Hz, CHN), 3.20 (1H, dd, J = 14.4, 3.8 Hz, CHH₃H₈Ph), 2.88 (1H, dd, J = 14.4, 9.8 Hz, CH₂H₈Ph), 1.38 (3H, s, C(CH₃)(CH₃)), 1.36 (3H, s, C(CH₃)(CH₃)); ¹³C NMR (75 MHz, CDCl₃) δC = 166.4, 152.4, 136.5, 129.1, 128.9, 127.1, 83.7, 64.1, 44.0, 35.0, 28.7, 22.4; IR cm⁻¹ ν = 1769 (C=O ox), 1709 (C=O); HRMS: m/z (ES) 304.0722, C₁₅H₂₆ClNNaO₃ [M+Na]⁺ requires 304.0716; [α]D²⁵ = -32.0 (c = 0.50 g/100 mL in CHCl₃).
Experimental

(S)-4-Benzyl-3-((2S,3R)-2-chloro-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 661

The title compound was prepared according to General Procedure 1 from dibutylboron triflate (7.70 mL, 7.70 mmol), (S)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 660 (1.97 g, 7.00 mmol), N,N-diisopropylethylamine (1.58 mL, 9.10 mmol) and acrolein (0.61 mL, 9.10 mmol) in dichloromethane (15 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.27] to afford (S)-4-benzyl-3-((2S,3R)-2-chloro-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-2-one 661 (1.07 g, 3.20 mmol) as a colourless oil in 45% yield. 

$^1$H NMR (300 MHz, CDCl$_3$) $\delta_h$ = 7.31-7.17 (5H, m, Ph), 5.88 (1H, ddd, $J = 17.3, 10.5, 5.8$ Hz, CH=CH$_2$), 5.72 (1H, d, $J = 5.1$ Hz, CHCl), 5.40 (1H, dt, $J = 17.3, 1.3$ Hz, CH=CH$_2$), 5.28 (1H, dt, $J = 10.5, 1.2$ Hz, CH$_2$H$_2$), 5.28 (1H, dt, $J = 10.5, 1.2$ Hz, CH$_2$H$_2$), 4.59 (1H, app. t, $J = 5.5$ Hz, CHO), 4.48 (1H, dd, $J = 9.5, 3.8$ Hz, CH$_3$), 3.14 (1H, dd, $J = 14.4, 3.8$ Hz CH$_2$H$_2$Ph), 3.00 (1H, broad s, OH), 2.88 (1H, dd, $J = 14.4, 9.5$ Hz, CH$_2$H$_2$Ph), 1.36 (3H, s, C(CH$_3$)(CH$_3$)), 1.33 (3H, s, C(CH$_3$)(CH$_3$)); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_c$ = 167.9, 152.0, 136.4, 135.0, 129.1, 128.9, 127.8, 127.0, 118.9, 83.3, 72.9, 64.0, 59.1, 34.9, 28.5, 22.2; IR cm$^{-1}$ $\nu$ = 3496 (OH), 1771 (C=O$\alpha$), 1703 (C=O); HRMS: m/z (ES) 338.1149, C$_{17}$H$_{21}$ClNO$_{4}$ [M+H]$^+$ requires 338.1159; $[\alpha]_{D}^{24}$ = -12.0 ($c = 1.00$ g/100 mL in CHCl$_3$).
**Experimental**

(S)-4-Benzyl-3-((S)-3-hydroxypent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 662

(S)-4-Benzyl-3-((2S,3R)-2-chloro-3-hydroxypent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 661 (1.08 g, 3.20 mmol) was dissolved in dry methanol (12 mL) under nitrogen. Zinc dust (0.83 g, 12.80 mmol) and ammonium chloride (0.69 g, 12.80 mmol) were added and the reaction was stirred for one hour. The suspension was filtered through Celite® and concentrated to afford the crude product as a yellow oil. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, Rf 0.18] to afford (S)-4-benzyl-3-((S)-3-hydroxypent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 662 (0.79 g, 2.60 mmol) as a colourless oil in 82% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H = 7.33-7.24 (5H, m, Ph), 5.89 (1H, ddd, $J$ = 17.3, 10.5, 5.4 Hz, CH=CH$_2$), 5.32 (1H, d, $J$ = 17.3 Hz, CH=CH$_2$H$_a$), 5.15 (1H, d, $J$ = 10.5 Hz, CH=CH$_2$H$_b$), 4.58-4.50 (2H, m, CH$_2$OH, CH$_2$N), 3.16-3.09 (3H, m, CH$_2$CH$_2$Ph, CH$_2$CHOH), 2.93-2.85 (2H, m, CH$_2$CH$_2$Ph, CH$_2$OH), 1.39 (3H, s, C(CH$_3$)$_2$(CH$_3$)), 1.37 (3H, s, C(CH$_3$)$_2$(CH$_3$)); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C = 172.3, 152.7, 138.8, 136.8, 129.1, 128.9, 127.0, 115.5, 82.7, 68.9, 63.5, 42.6, 35.6, 28.6, 22.3; IR cm$^{-1}$v = 3483 (OH), 1771 (C=O), 1694 (C=O$_{=}$); HRMS: m/z (ES) 304.1511, C$_{17}$H$_{22}$NO$_4$, [M+H]$^+$ requires 304.1548; $[\alpha]^{20}_{D}$ = -52.0 (c = 0.50 g/100 mL in CHCl$_3$).
Experimental

2-Deoxy-D-ribonolactone - (4S,5R)-4-Hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one, 663

OsO₄ (0.016 g, 0.06 mmol) was added to a solution of (S)-4-benzyl-3-((S)-3-hydroxypent-4-enoyl)-5,5-dimethylloxazolidin-2-one 662 (0.20 g, 0.66 mmol) in acetone/water (8:1, 2.5 mL) followed by addition of NMO (60% by weight in water, 0.12 mL, 0.73 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (4S,5R)-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one 663 (0.076 g, 0.57 mmol) as a colourless oil in 87% yield and 9:1 dr. (4S,5R)-major: 1H NMR (500 MHz, MeOD) δ_H = 4.46 (1H, dt, J = 6.7, 2.3 Hz, CHO), 4.40–4.39 (1H, m, CHCH₂OH), 3.79 (1H, dd, J = 12.4, 3.3 Hz, CH₃CHO), 3.72 (1H, dd, J = 12.4, 3.7 Hz, CH₃H₂OH), 2.94 (1H, dt, J = 17.9, 6.8 Hz, CH₃H₃C=O), 2.40 (1H, dd, J = 17.9, 2.5 Hz, CH₃H₃C=O); 13C NMR (75 MHz, MeOD) δ_C = 179.5, 91.0, 70.6, 63.4, 40.0; (4S,5S)-minor: 1H NMR (500 MHz, MeOD) δ_H = 4.63-4.50 (2H, m, CHO & CHCH₂OH), 3.90 (2H, dd, J = 5.4, 1.6 Hz, CH₂OH), 2.93 (1H, dd, J = 17.6, 5.9 Hz, CH₃H₃C=O), 2.45 (1H, dd, J = 17.7, 1.6 Hz, CH₂CH₃C=O); 13C NMR (75 MHz, MeOD) δ_C = 179.5, 87.4, 69.8, 62.1, 40.9; IR cm⁻¹ ν = 3356 (OH), 1749 (C=O); HRMS: m/z (ES) 155.0333, C₅H₈NaO₄, [M+Na]+ requires 155.0320; [α]D²⁵ = +4.0 (c = 0.50 g/100 mL in MeOH) [lit: [α]D²⁵ = +2.17 (c = 0.6 g/100 mL in MeOH)].
5 References


References


References


(76) Simpura, I.; Nevalainen, V. Tetrahedron 2003, 59, 7535-7546.


References


(110) *Catalytic Antibodies*; Wiley-VCH, **2005**.


References


References


Krishna, P. R.; Reddy, V. V. R.; Sharma, G. V. M. Synthesis 2004, 2107-2114.


References


(223) Xu, Q.; Rozners, E. *Org. Lett.* 2005, 7, 2821-2824.


References


(243) Davies, I. R., Chiral Auxiliaries and Substrate Directable Reactions to Access Highly Functionalised Chiral Lactones, University of Bath, 2009.


References


References


Appendix

6 Appendix

X-Ray Crystal Structure Data for δ-Lactone 527

Figure i X-Ray crystal structure for (3S,4R,5R,6R)-4-hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one
Appendix

**Table i  Crystal data and structure refinement for δ-lactone 527**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{13}H_{16}O_{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>220.26</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a = 7.8508(3) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 6.9320(3) Å</td>
<td>β = 90.905(3)°</td>
</tr>
<tr>
<td>c = 10.6342(4) Å</td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>578.66(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.264 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.089 mm⁻³</td>
</tr>
<tr>
<td>F(000)</td>
<td>236</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.50 × 0.25 × 0.15 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>4.35 to 27.48 °</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-10 ≤ h ≤ 10, -8 ≤ k ≤ 8, -13 ≤ l ≤ 13</td>
</tr>
<tr>
<td>Reflections collected/unique</td>
<td>12446 / 2642 [R(int) = 0.0781]</td>
</tr>
<tr>
<td>Completeness to theta= 27.48</td>
<td>99.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. Transmission</td>
<td>0.9868 and 0.9569</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2642/1/151</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.055</td>
</tr>
<tr>
<td>Final R indices [&gt;2sigma(I)]</td>
<td>R1 = 0.0392, wR2 = 0.0911</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0516, wR2 = 0.0975</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>-0.3(9)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.155 and -0.218 e. Å³</td>
</tr>
</tbody>
</table>
Table ii

Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 ×10^3) for δ-lactone 527. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>6413(2)</td>
<td>13800(2)</td>
<td>10229(1)</td>
<td>35(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>7816(2)</td>
<td>7270(2)</td>
<td>11124(1)</td>
<td>36(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>7954(1)</td>
<td>8262(1)</td>
<td>9184(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>7480(2)</td>
<td>12228(2)</td>
<td>9874(2)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>7223(2)</td>
<td>10630(2)</td>
<td>10839(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>8096(2)</td>
<td>11097(2)</td>
<td>12096(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>7706(2)</td>
<td>8626(2)</td>
<td>10404(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>8088(2)</td>
<td>9802(2)</td>
<td>8239(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>7652(2)</td>
<td>8872(2)</td>
<td>6995(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>6043(2)</td>
<td>8082(2)</td>
<td>6778(2)</td>
<td>34(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>5641(3)</td>
<td>7228(3)</td>
<td>5630(2)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>6847(3)</td>
<td>7157(3)</td>
<td>4691(2)</td>
<td>49(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>8438(3)</td>
<td>7929(3)</td>
<td>4900(2)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>8852(2)</td>
<td>8781(3)</td>
<td>6050(2)</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>6991(2)</td>
<td>11545(2)</td>
<td>8554(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>7272(2)</td>
<td>13134(3)</td>
<td>7583(2)</td>
<td>40(1)</td>
</tr>
</tbody>
</table>
# Appendix

## Table iii

Selected bond lengths (Å) for δ-lactone 527

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(1)</td>
<td>1.4286(19)</td>
</tr>
<tr>
<td>O(1)-H(1A)</td>
<td>0.81(2)</td>
</tr>
<tr>
<td>O(2)-C(4)</td>
<td>1.2150(18)</td>
</tr>
<tr>
<td>O(3)-C(4)</td>
<td>1.3384(17)</td>
</tr>
<tr>
<td>O(3)-C(5)</td>
<td>1.4714(17)</td>
</tr>
<tr>
<td>C(1)-C(12)</td>
<td>1.525(2)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.526(2)</td>
</tr>
<tr>
<td>C(1)-H(1)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(2)-C(4)</td>
<td>1.514(2)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.527(2)</td>
</tr>
<tr>
<td>C(2)-H(2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(3)-H(3A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(3)-H(3B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(3)-H(3C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.506(2)</td>
</tr>
<tr>
<td>C(5)-C(12)</td>
<td>1.525(2)</td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(6)-C(11)</td>
<td>1.390(2)</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.393(2)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.389(2)</td>
</tr>
<tr>
<td>C(7)-H(7)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.388(3)</td>
</tr>
<tr>
<td>C(8)-H(8)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.373(3)</td>
</tr>
<tr>
<td>C(9)-H(9)</td>
<td>0.9500</td>
</tr>
<tr>
<td>Bond</td>
<td>Length</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.392(3)</td>
</tr>
<tr>
<td>C(10)-H(10)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(11)-H(11)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.527(2)</td>
</tr>
<tr>
<td>C(12)-H(12)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(13)-H(13A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(13)-H(13B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(13)-H(13C)</td>
<td>0.9800</td>
</tr>
</tbody>
</table>
Table iv
Selected bond angles (*) for δ-lactone 527

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-O(1)-H(1A)</td>
<td>108.9(15)</td>
</tr>
<tr>
<td>C(4)-O(3)-C(5)</td>
<td>122.58(11)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(12)</td>
<td>109.85(12)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>106.95(11)</td>
</tr>
<tr>
<td>C(12)-C(1)-C(2)</td>
<td>111.07(13)</td>
</tr>
<tr>
<td>O(1)-C(1)-H(1)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(12)-C(1)-H(1)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(2)-C(1)-H(1)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(4)-C(2)-C(1)</td>
<td>115.08(12)</td>
</tr>
<tr>
<td>C(4)-C(2)-C(3)</td>
<td>110.53(12)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>111.84(13)</td>
</tr>
<tr>
<td>C(4)-C(2)-H(2)</td>
<td>106.2</td>
</tr>
<tr>
<td>C(1)-C(2)-H(2)</td>
<td>106.2</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2)</td>
<td>106.2</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3A)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3A)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3B)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(2)-C(4)-O(3)</td>
<td>117.07(13)</td>
</tr>
<tr>
<td>O(2)-C(4)-C(2)</td>
<td>122.19(13)</td>
</tr>
<tr>
<td>O(3)-C(4)-C(2)</td>
<td>120.68(12)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(6)</td>
<td>105.78(12)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(12)</td>
<td>112.21(11)</td>
</tr>
</tbody>
</table>
Appendix

C(6)-C(5)-C(12)  114.26(13)
O(3)-C(5)-H(5)  108.1
C(6)-C(5)-H(5)  108.1
C(12)-C(5)-H(5)  108.1
C(11)-C(6)-C(7)  119.09(14)
C(11)-C(6)-C(5)  120.48(15)
C(7)-C(6)-C(5)  120.44(13)
C(8)-C(7)-C(6)  120.37(15)
C(8)-C(7)-H(7)  119.8
C(6)-C(7)-H(7)  119.8
C(9)-C(8)-C(7)  120.00(18)
C(9)-C(8)-H(8)  120.0
C(7)-C(8)-H(8)  120.0
C(10)-C(9)-C(8)  119.93(17)
C(10)-C(9)-H(9)  120.0
C(8)-C(9)-H(9)  120.0
C(9)-C(10)-C(11)  120.42(16)
C(9)-C(10)-H(10)  119.8
C(11)-C(10)-H(10)  119.8
C(6)-C(11)-C(10)  120.2(17)
C(6)-C(11)-H(11)  119.9
C(10)-C(11)-H(11)  119.9
C(1)-C(12)-C(5)  108.27(12)
C(1)-C(12)-C(13)  111.18(13)
C(5)-C(12)-C(13)  109.57(12)
C(1)-C(12)-H(12)  109.3
C(5)-C(12)-H(12)  109.3
C(13)-C(12)-H(12)  109.5
Appendix

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(12)-C(13)-H(13A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(12)-C(13)-H(13B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(13A)-C(13)-H(13B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(12)-C(13)-H(13C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(13A)-C(13)-H(13C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(13B)-C(13)-H(13C)</td>
<td>109.5</td>
</tr>
</tbody>
</table>

Table v

Anisotropic displacement parameters (Å² × 10³) for δ-lactone 527. The anisotropic displacement factor exponent takes the form: -2π²(\hat{h}^2a^*U11 + ... + 2\hat{h}\hat{k}a^*b^*U12).

<table>
<thead>
<tr>
<th></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>33(1)</td>
<td>20(1)</td>
<td>53(1)</td>
<td>-5(1)</td>
<td>0(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>49(1)</td>
<td>23(1)</td>
<td>37(1)</td>
<td>3(1)</td>
<td>-4(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>41(1)</td>
<td>22(1)</td>
<td>31(1)</td>
<td>1(1)</td>
<td>0(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>26(1)</td>
<td>19(1)</td>
<td>42(1)</td>
<td>-2(1)</td>
<td>0(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>26(1)</td>
<td>23(1)</td>
<td>34(1)</td>
<td>-2(1)</td>
<td>-1(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>41(1)</td>
<td>31(1)</td>
<td>39(1)</td>
<td>-6(1)</td>
<td>-6(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>26(1)</td>
<td>25(1)</td>
<td>34(1)</td>
<td>0(1)</td>
<td>-2(1)</td>
<td>-1(1)</td>
</tr>
</tbody>
</table>
### Table vi

Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for δ-lactone 527.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>Y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1A)</td>
<td>7010(30)</td>
<td>14710(30)</td>
<td>10433(18)</td>
<td>42(6)</td>
</tr>
<tr>
<td>H(1)</td>
<td>8698</td>
<td>12651</td>
<td>9892</td>
<td>35</td>
</tr>
<tr>
<td>H(2)</td>
<td>5973</td>
<td>10590</td>
<td>11005</td>
<td>33</td>
</tr>
<tr>
<td>H(3A)</td>
<td>9335</td>
<td>11027</td>
<td>12002</td>
<td>56</td>
</tr>
<tr>
<td>H(3B)</td>
<td>7738</td>
<td>10163</td>
<td>12731</td>
<td>56</td>
</tr>
<tr>
<td>H(3C)</td>
<td>7777</td>
<td>12400</td>
<td>12360</td>
<td>56</td>
</tr>
<tr>
<td>H(5)</td>
<td>9303</td>
<td>10232</td>
<td>8217</td>
<td>34</td>
</tr>
<tr>
<td>H(7)</td>
<td>5215</td>
<td>8129</td>
<td>7420</td>
<td>41</td>
</tr>
<tr>
<td>H(8)</td>
<td>4542</td>
<td>6692</td>
<td>5488</td>
<td>50</td>
</tr>
<tr>
<td>H(9)</td>
<td>6573</td>
<td>6575</td>
<td>3905</td>
<td>58</td>
</tr>
<tr>
<td>H(10)</td>
<td>9260</td>
<td>7882</td>
<td>4255</td>
<td>56</td>
</tr>
<tr>
<td>H(11)</td>
<td>9958</td>
<td>9302</td>
<td>6189</td>
<td>45</td>
</tr>
<tr>
<td>(12)</td>
<td>5764</td>
<td>11158</td>
<td>8536</td>
<td>34</td>
</tr>
<tr>
<td>H(13A)</td>
<td>8489</td>
<td>13437</td>
<td>7546</td>
<td>59</td>
</tr>
<tr>
<td>H(13B)</td>
<td>6640</td>
<td>14291</td>
<td>7826</td>
<td>59</td>
</tr>
<tr>
<td>H(13C)</td>
<td>6866</td>
<td>12692</td>
<td>6756</td>
<td>59</td>
</tr>
</tbody>
</table>
X-Ray Crystal Structure Data for γ-Lactone 633

Figure ii X-Ray crystal structure for (3S,4S,5R)-5-(2-(benzyloxy)ethyl)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one
### Table I  Crystal data and structure refinement for γ-lactone 633

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
<td>C₁₅H₂₀O₅</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>280.31</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>150(2) K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>0.71073 Å</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Orthorhombic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P 2₁ 2₁ 2₁</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>a</strong></td>
<td>5.8808(2) Å</td>
</tr>
<tr>
<td><strong>b</strong></td>
<td>11.1665(2) Å</td>
</tr>
<tr>
<td><strong>c</strong></td>
<td>21.9865(6) Å</td>
</tr>
<tr>
<td><strong>α</strong></td>
<td>90°</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>90°</td>
</tr>
<tr>
<td><strong>γ</strong></td>
<td>90°</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>1443.81(7) Å³</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Calculated density</strong></td>
<td>1.290 Mg/m³</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.096 mm⁻¹</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>600</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.60 x 0.25 x 0.05 mm</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
<td>3.71 to 27.49 °</td>
</tr>
<tr>
<td><strong>Limiting indices</strong></td>
<td>-7 ≤ h ≤ 7, -14 ≤ k ≤ 14, -28 ≤ l ≤ 28</td>
</tr>
<tr>
<td><strong>Reflections collected/unique</strong></td>
<td>19206 / 3314 [R(int) = 0.0834]</td>
</tr>
<tr>
<td><strong>Completeness to theta= 27.48</strong></td>
<td>99.5 %</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td><strong>Max. and min. Transmission</strong></td>
<td>0.9952 and 0.9445</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>3314/0/190</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
<td>1.079</td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2sigma(I)]</strong></td>
<td>R1 = 0.0408, wR2 = 0.0915</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>R1 = 0.0555, wR2 = 0.0981</td>
</tr>
<tr>
<td><strong>Extinction coefficient</strong></td>
<td>0.2(8)</td>
</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.246 and -0.334 e. Å³</td>
</tr>
</tbody>
</table>
### Table ii

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for $\gamma$-lactone 633. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U(\text{eq})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>3893</td>
<td>9427</td>
<td>8690</td>
<td>24(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>1912</td>
<td>11108</td>
<td>8549</td>
<td>33(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>6849</td>
<td>9827</td>
<td>10107</td>
<td>30(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>2749</td>
<td>7371</td>
<td>9350</td>
<td>27(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>9699</td>
<td>7557</td>
<td>8388</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>3148</td>
<td>10521</td>
<td>8869</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>4077</td>
<td>10828</td>
<td>9490</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2359</td>
<td>11457</td>
<td>9897</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>4969</td>
<td>9636</td>
<td>9721</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>5529</td>
<td>8935</td>
<td>9132</td>
<td>22(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>5045</td>
<td>7603</td>
<td>9177</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>7918</td>
<td>9211</td>
<td>8901</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>8551</td>
<td>8676</td>
<td>8290</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>10498</td>
<td>7064</td>
<td>7823</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>11976</td>
<td>6002</td>
<td>7958</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>14101</td>
<td>5890</td>
<td>7683</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>15495</td>
<td>4924</td>
<td>7810</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>14782</td>
<td>4059</td>
<td>8218</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>12669</td>
<td>4151</td>
<td>8492</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>11273</td>
<td>5118</td>
<td>8365</td>
<td>34(1)</td>
</tr>
</tbody>
</table>
Table iii

Selected bond lengths (Å) for γ-lactone 633

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(1)</td>
<td>1.3557(18)</td>
</tr>
<tr>
<td>O(1)-C(5)</td>
<td>1.4734(17)</td>
</tr>
<tr>
<td>O(2)-C(1)</td>
<td>1.2055(19)</td>
</tr>
<tr>
<td>O(3)-C(4)</td>
<td>1.4091(18)</td>
</tr>
<tr>
<td>O(3)-H(3)</td>
<td>0.83(2)</td>
</tr>
<tr>
<td>O(4)-C(6)</td>
<td>1.4271(19)</td>
</tr>
<tr>
<td>O(4)-H(4A)</td>
<td>0.82(2)</td>
</tr>
<tr>
<td>O(5)-C(8)</td>
<td>1.4368(19)</td>
</tr>
<tr>
<td>O(5)-C(9)</td>
<td>1.4368(18)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.510(2)</td>
</tr>
<tr>
<td>C(2)-C(4)</td>
<td>1.518(2)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.522(2)</td>
</tr>
<tr>
<td>C(2)-H(2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(3)-H(3A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(3)-H(3B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(3)-H(3C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.5501(19)</td>
</tr>
<tr>
<td>C(4)-H(4)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.518(2)</td>
</tr>
<tr>
<td>C(5)-C(7)</td>
<td>1.524(2)</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(6)-H(6B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.517(2)</td>
</tr>
<tr>
<td>C(7)-H(7A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(7)-H(7B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>Bond</td>
<td>Distance (Å)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>C(8)-H(8A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(8)-H(8B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.500(2)</td>
</tr>
<tr>
<td>C(9)-H(9A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(9)-H(9B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(10)-C(15)</td>
<td>1.394(2)</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.395(2)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.383(2)</td>
</tr>
<tr>
<td>C(11)-H(11)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.385(3)</td>
</tr>
<tr>
<td>C(12)-H(12)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.385(3)</td>
</tr>
<tr>
<td>C(13)-H(13)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.385(2)</td>
</tr>
<tr>
<td>C(14)-H(14)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(15)-H(15)</td>
<td>0.9500</td>
</tr>
</tbody>
</table>
Selected bond angles (°) for γ-lactone 633

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-O(1)-C(5)</td>
<td>110.83(11)</td>
</tr>
<tr>
<td>C(4)-O(3)-H(3)</td>
<td>108.1(15)</td>
</tr>
<tr>
<td>C(6)-O(4)-H(4A)</td>
<td>107.3(15)</td>
</tr>
<tr>
<td>C(8)-O(5)-C(9)</td>
<td>110.97(11)</td>
</tr>
<tr>
<td>O(2)-C(1)-O(1)</td>
<td>121.00(14)</td>
</tr>
<tr>
<td>O(2)-C(1)-C(2)</td>
<td>128.52(15)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>110.48(12)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(4)</td>
<td>103.26(11)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>113.37(14)</td>
</tr>
<tr>
<td>C(4)-C(2)-C(3)</td>
<td>115.88(13)</td>
</tr>
<tr>
<td>C(1)-C(2)-H(2)</td>
<td>108.0</td>
</tr>
<tr>
<td>C(4)-C(2)-H(2)</td>
<td>108.0</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2)</td>
<td>108.0</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3A)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3A)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3B)-C(3)-H(3C)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(3)-C(4)-C(2)</td>
<td>109.91(12)</td>
</tr>
<tr>
<td>O(3)-C(4)-C(5)</td>
<td>114.36(12)</td>
</tr>
<tr>
<td>C(2)-C(4)-C(5)</td>
<td>103.63(11)</td>
</tr>
<tr>
<td>O(3)-C(4)-H(4)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(2)-C(4)-H(4)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(5)-C(4)-H(4)</td>
<td>109.6</td>
</tr>
<tr>
<td>O(1)-C(5)-C(6)</td>
<td>106.64(12)</td>
</tr>
</tbody>
</table>
Appendix

O(1)-C(5)-C(7) 107.93(11)
C(6)-C(5)-C(7) 113.10(13)
O(1)-C(5)-C(4) 102.95(11)
C(6)-C(5)-C(4) 113.59(12)
C(7)-C(5)-C(4) 111.81(13)
O(4)-C(6)-C(5) 111.87(13)
O(4)-C(6)-H(6A) 109.2
C(5)-C(6)-H(6A) 109.2
O(4)-C(6)-H(6B) 109.2
C(5)-C(6)-H(6B) 109.2
H(6A)-C(6)-H(6B) 107.9
C(8)-C(7)-C(5) 116.16(13)
C(8)-C(7)-H(7A) 108.2
C(5)-C(7)-H(7A) 108.2
C(8)-C(7)-H(7B) 108.2
C(5)-C(7)-H(7B) 108.2
H(7A)-C(7)-H(7B) 107.4
O(5)-C(8)-C(7) 109.03(12)
O(5)-C(8)-H(8A) 109.9
C(7)-C(8)-H(8A) 109.9
O(5)-C(8)-H(8B) 109.9
C(7)-C(8)-H(8B) 109.9
H(8A)-C(8)-H(8B) 108.3
O(5)-C(9)-C(10) 108.67(12)
O(5)-C(9)-H(9A) 110.0
C(10)-C(9)-H(9A) 110.0
O(5)-C(9)-H(9B) 110.0
C(10)-C(9)-H(9B) 110.0
<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(9A)-C(9)-H(9B)</td>
<td>108.3</td>
</tr>
<tr>
<td>C(15)-C(10)-C(11)</td>
<td>118.73(15)</td>
</tr>
<tr>
<td>C(15)-C(10)-C(9)</td>
<td>121.01(15)</td>
</tr>
<tr>
<td>C(11)-C(10)-C(9)</td>
<td>120.25(15)</td>
</tr>
<tr>
<td>C(12)-C(11)-C(10)</td>
<td>120.91(16)</td>
</tr>
<tr>
<td>C(12)-C(11)-H(11)</td>
<td>119.5</td>
</tr>
<tr>
<td>C(10)-C(11)-H(11)</td>
<td>119.5</td>
</tr>
<tr>
<td>C(11)-C(12)-C(13)</td>
<td>119.69(18)</td>
</tr>
<tr>
<td>C(11)-C(12)-H(12)</td>
<td>120.2</td>
</tr>
<tr>
<td>C(13)-C(12)-H(12)</td>
<td>120.2</td>
</tr>
<tr>
<td>C(14)-C(13)-C(12)</td>
<td>120.17(18)</td>
</tr>
<tr>
<td>C(14)-C(13)-H(13)</td>
<td>119.9</td>
</tr>
<tr>
<td>C(12)-C(13)-H(13)</td>
<td>119.9</td>
</tr>
<tr>
<td>C(13)-C(14)-C(15)</td>
<td>120.10(17)</td>
</tr>
<tr>
<td>C(13)-C(14)-H(14)</td>
<td>119.9</td>
</tr>
<tr>
<td>C(15)-C(14)-H(14)</td>
<td>119.9</td>
</tr>
<tr>
<td>C(14)-C(15)-C(10)</td>
<td>120.39</td>
</tr>
<tr>
<td>C(14)-C(15)-H(15)</td>
<td>119.8</td>
</tr>
<tr>
<td>C(10)-C(15)-H(15)</td>
<td>119.8</td>
</tr>
</tbody>
</table>
Table iv

Anisotropic displacement parameters (Å² ×10³) for γ-lactone 633. The anisotropic displacement factor exponent takes the form: -2π²h²a*²U11 + ... + Zha*b*U12.

<table>
<thead>
<tr>
<th></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>25(1)</td>
<td>26(1)</td>
<td>21(1)</td>
<td>0(1)</td>
<td>-2(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>34(1)</td>
<td>30(1)</td>
<td>35(1)</td>
<td>7(1)</td>
<td>-5(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>39(1)</td>
<td>28(1)</td>
<td>24(1)</td>
<td>0(1)</td>
<td>-9(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>29(1)</td>
<td>29(1)</td>
<td>22(1)</td>
<td>2(1)</td>
<td>-1(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>27(1)</td>
<td>28(1)</td>
<td>20(1)</td>
<td>-1(1)</td>
<td>1(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>23(1)</td>
<td>24(1)</td>
<td>28(1)</td>
<td>3(1)</td>
<td>2(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>28(1)</td>
<td>24(1)</td>
<td>25(1)</td>
<td>-1(1)</td>
<td>0(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>41(1)</td>
<td>35(1)</td>
<td>36(1)</td>
<td>-8(1)</td>
<td>3(1)</td>
<td>8(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>27(1)</td>
<td>24(1)</td>
<td>19(1)</td>
<td>-1(1)</td>
<td>-1(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>22(1)</td>
<td>26(1)</td>
<td>19(1)</td>
<td>-1(1)</td>
<td>-3(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>26(1)</td>
<td>27(1)</td>
<td>24(1)</td>
<td>0(1)</td>
<td>-2(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>25(1)</td>
<td>28(1)</td>
<td>28(1)</td>
<td>-4(1)</td>
<td>1(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>26(1)</td>
<td>31(1)</td>
<td>25(1)</td>
<td>2(1)</td>
<td>0(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>36(1)</td>
<td>34(1)</td>
<td>20(1)</td>
<td>-3(1)</td>
<td>3(1)</td>
<td>4(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>34(1)</td>
<td>27(1)</td>
<td>22(1)</td>
<td>-5(1)</td>
<td>-2(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>35(1)</td>
<td>32(1)</td>
<td>27(1)</td>
<td>-4(1)</td>
<td>1(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>38(1)</td>
<td>43(1)</td>
<td>34(1)</td>
<td>-11(1)</td>
<td>0(1)</td>
<td>7(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>57(1)</td>
<td>39(1)</td>
<td>33(1)</td>
<td>-7(1)</td>
<td>-6(1)</td>
<td>17(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>65(1)</td>
<td>31(1)</td>
<td>31(1)</td>
<td>1(1)</td>
<td>3(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>41(1)</td>
<td>34(1)</td>
<td>26(1)</td>
<td>-3(1)</td>
<td>4(1)</td>
<td>-2(1)</td>
</tr>
</tbody>
</table>
### Table v

Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^2 x 10^3) for γ-lactone 633.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>5405</td>
<td>11376</td>
<td>9433</td>
<td>31</td>
</tr>
<tr>
<td>H(3A)</td>
<td>3012</td>
<td>11565</td>
<td>10304</td>
<td>56</td>
</tr>
<tr>
<td>H(3B)</td>
<td>977</td>
<td>10970</td>
<td>9927</td>
<td>56</td>
</tr>
<tr>
<td>H(3C)</td>
<td>1982</td>
<td>12241</td>
<td>9724</td>
<td>56</td>
</tr>
<tr>
<td>H(4)</td>
<td>3741</td>
<td>9212</td>
<td>9950</td>
<td>28</td>
</tr>
<tr>
<td>H(6A)</td>
<td>5350</td>
<td>7222</td>
<td>8779</td>
<td>31</td>
</tr>
<tr>
<td>H(6B)</td>
<td>6083</td>
<td>7240</td>
<td>9480</td>
<td>31</td>
</tr>
<tr>
<td>H(7A)</td>
<td>8087</td>
<td>10091</td>
<td>8874</td>
<td>32</td>
</tr>
<tr>
<td>H(7B)</td>
<td>9022</td>
<td>8922</td>
<td>9208</td>
<td>32</td>
</tr>
<tr>
<td>H(8A)</td>
<td>7164</td>
<td>8545</td>
<td>8044</td>
<td>33</td>
</tr>
<tr>
<td>H(8B)</td>
<td>9558</td>
<td>9233</td>
<td>8066</td>
<td>33</td>
</tr>
<tr>
<td>H(9A)</td>
<td>11378</td>
<td>7675</td>
<td>7597</td>
<td>36</td>
</tr>
<tr>
<td>H(9B)</td>
<td>9190</td>
<td>6816</td>
<td>7568</td>
<td>36</td>
</tr>
<tr>
<td>H(11)</td>
<td>14598</td>
<td>6485</td>
<td>7404</td>
<td>38</td>
</tr>
<tr>
<td>H(12)</td>
<td>16935</td>
<td>4855</td>
<td>7617</td>
<td>46</td>
</tr>
<tr>
<td>H(13)</td>
<td>15745</td>
<td>3401</td>
<td>8311</td>
<td>51</td>
</tr>
<tr>
<td>H(14)</td>
<td>12175</td>
<td>3549</td>
<td>8768</td>
<td>51</td>
</tr>
<tr>
<td>H(15)</td>
<td>9828</td>
<td>5180</td>
<td>8556</td>
<td>41</td>
</tr>
<tr>
<td>H(4A)</td>
<td>1960(40)</td>
<td>7470(17)</td>
<td>9047(10)</td>
<td>46(6)</td>
</tr>
<tr>
<td>H(3)</td>
<td>7160(40)</td>
<td>9178(18)</td>
<td>10274(10)</td>
<td>45(6)</td>
</tr>
</tbody>
</table>