Unsaturated Aldols as Useful Substrates in Natural Product Synthesis

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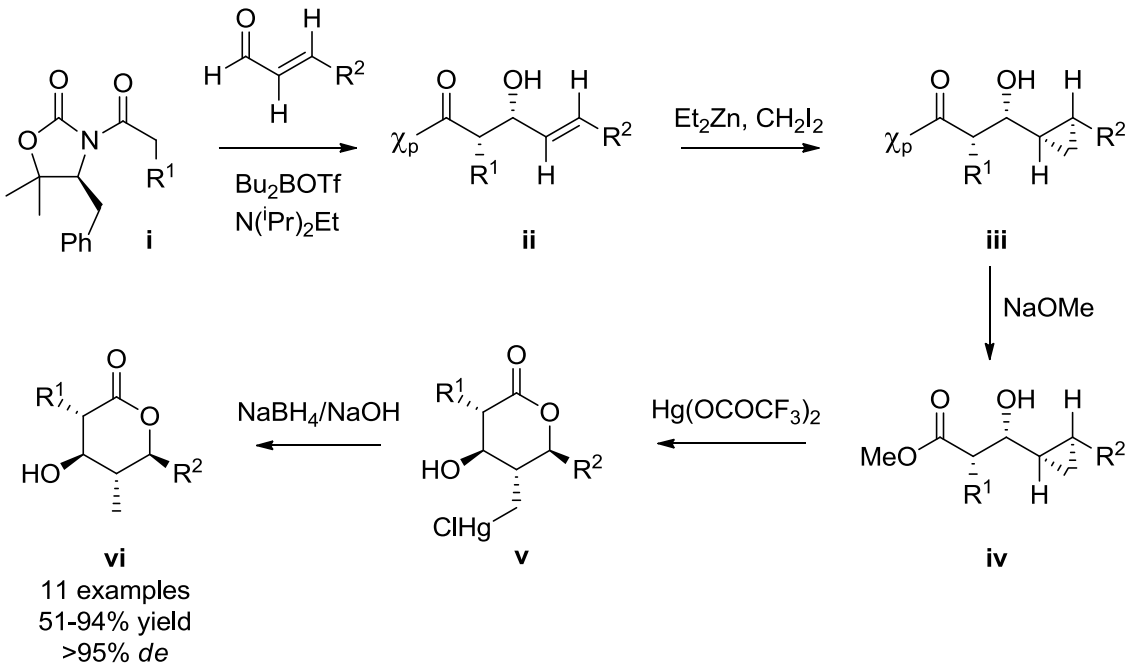
Abstract

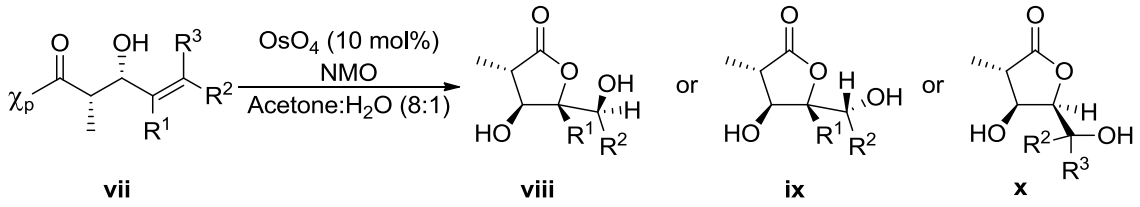
This thesis focuses on the use of unsaturated aldols as useful substrates in natural product synthesis. Two methodologies have been investigated for the asymmetric synthesis of highly substituted lactones containing multiple contiguous stereocentres from unsaturated aldol precursors. These lactones have 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 **iii**. Mercury mediated cyclopropane ring-opening of the methyl ester cyclopropanes **iv** followed by concomitant cyclisation produced organomercurial δ-lactones **v**, which subsequently undergo reductive demercuration in basic sodium borohydride to afford the highly substituted δ-lactones **vi** in good yield and excellent diastereoselectivity. The scope of this method was investigated with variation of the R^1 and R^2 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

The third chapter decribes 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.



vii **viii** **ix** **x**

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-D-ribonolactone.

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X-Ray Crystal Structure Data for δ-Lactone **527** i

X-Ray Crystal Structure Data for γ-Lactone **633** x

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Abbreviations

2,2-DMP	2,2-Dimethoxypropane
9-BBN	9-Borabicyclononane
Ac	Acetyl
acac	Acetylacetone
AD	Asymmetric dihydroxylation
AIBN	2,2'-Azobisisobutyronitrile
Ar	Aryl
atm	Atmosphere
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carbobenzyloxy
cat.	Catalytic
conc.	Concentrated
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DME	Dimethyl ether
de	Diastereomeric excess
dr	Diastereomeric ratio

DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Equiv	Equivalents
Et	Ethyl
g	Gram
h	Hours
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High-resolution mass spectrometry
HPLC	High-performance liquid chromatography
Hz	Hertz
^{i}Pr	*iso*-Propyl
IR	Infra-red
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
K	Kelvin
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazane
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl

min	Minutes
mL	Millilitre
mol	Mole
MOM	Methoxymethyl ether
MS	Molecular sieves
Ms	Mesylate
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
PBS	Sodium perborate
PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivaloyl
ppm	Parts per million
p-TSA	*para*-Toluene sulphonic acid
rac	Racemic
rt	Room temperature
S_N2	Bimolecular nucleophilic substitution

TBAF	Tetra-n-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl
UV	Ultraviolet
χ_p	SuperQuat auxiliary

1 Literature Review

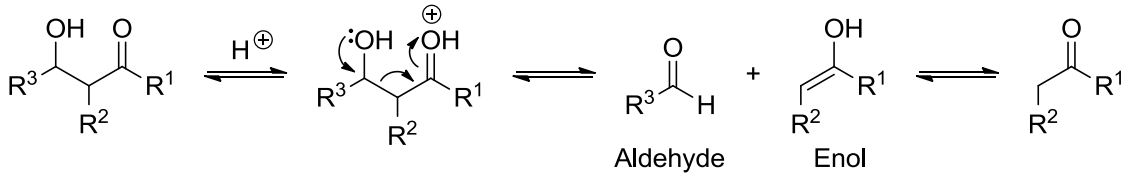
Synthetic Applications of the Retro Aldol Reaction

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.[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 *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.

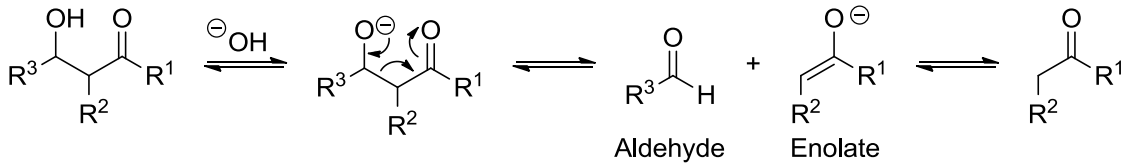
1.1 Introduction

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.[4]

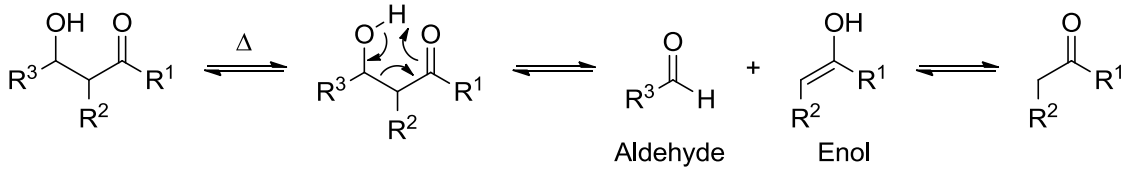
a) Acid Catalysed Retro Aldol:



b) Base Catalysed Retro Aldol:



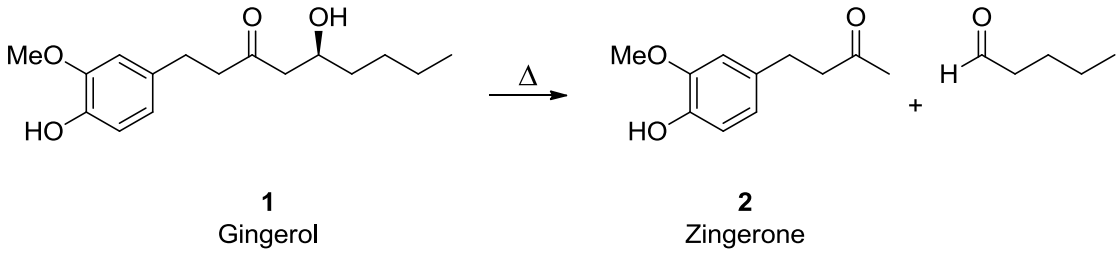
c) Thermal Retro Aldol:



Scheme 1 a) Acid catalysed, b) Base catalysed and c) Thermal retro aldol mechanism

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.[5] It is also an important reaction in producing flavours in food,[6] where many desirable flavours are created as thermal retro aldol products of sugars in Maillard reactions and associated degradation reactions.[7-8] 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.[9]

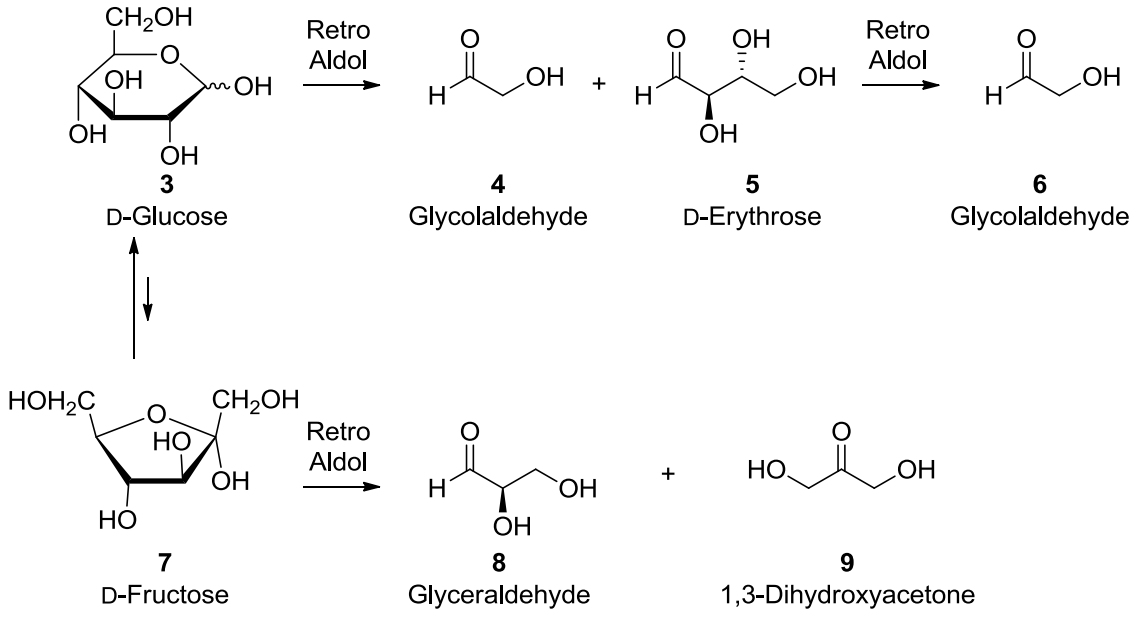


1
Gingerol

2
Zingerone

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

Retro aldol reactions of sugars in biomass conversion have also been demonstrated as a potential renewable energy source.[10] 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.[11] 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.[12]



3
D-Glucose

4
Glycolaldehyde

5
D-Erythrose

6
Glycolaldehyde

7
D-Fructose

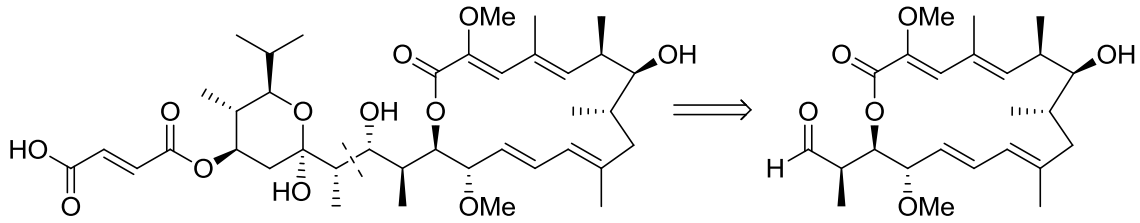
8
Glyceraldehyde

9
1,3-Dihydroxyacetone

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.[13] 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.[14]

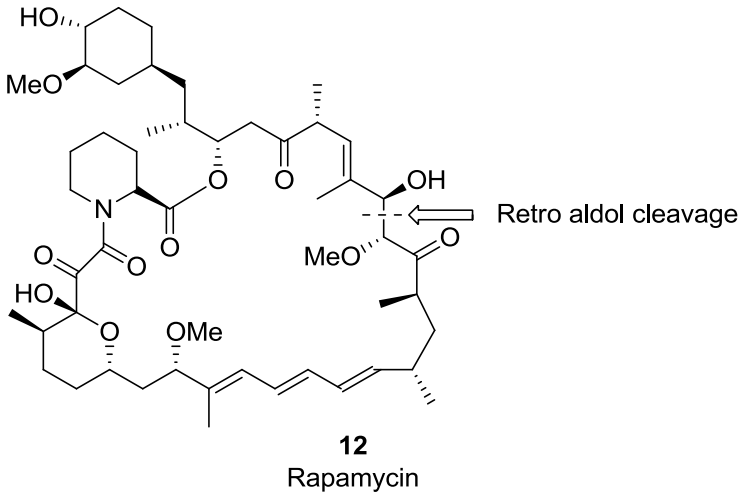


10
Bafilomycin C_1

11

Scheme 4 Thermal retro aldol cleavage of Bafilomycin C_1 **10** for the synthesis of intermediate **11** that is useful for the synthesis of new bafilomycin analogues

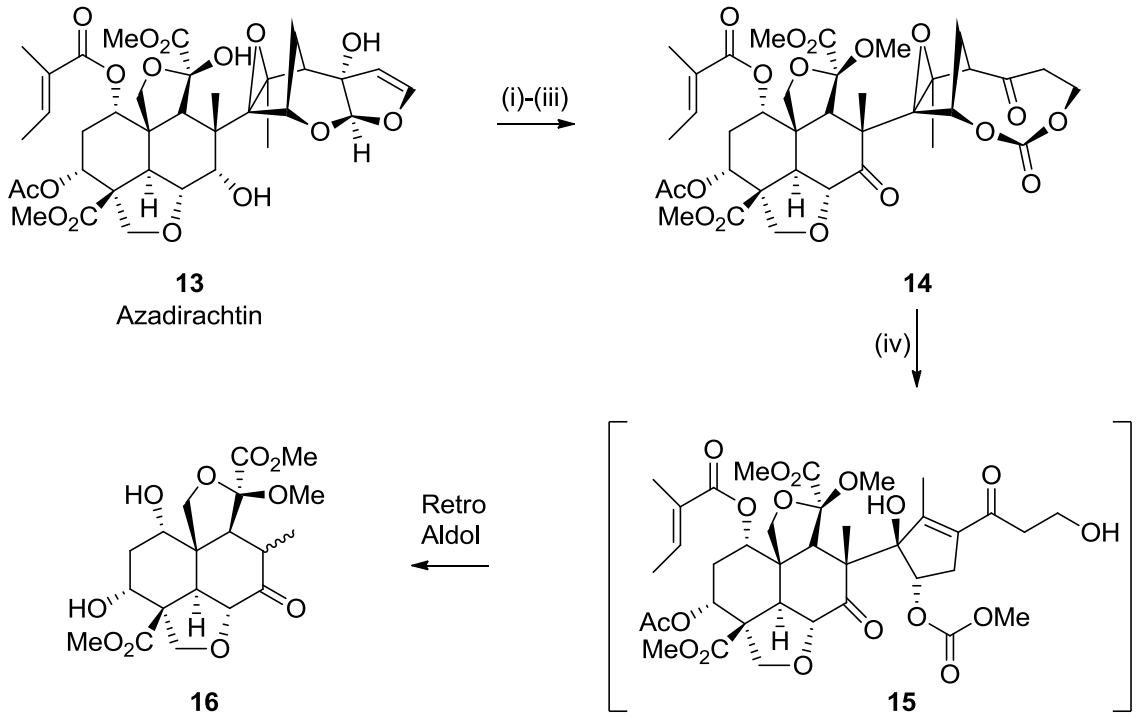
There has also been considerable interest in employing the retro aldol reaction for the degradation of the immunosuppressive antibiotic Rapamycin **12** to prepare fragmentation products for synthetic and biological studies. It has been found that Rapamycin **12** is particularly susceptible to base 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.[15] Danishefsky also treated derivatives of Rapamycin **12** with lithium diisopropylamide to obtain advanced synthetic intermediates via a retro aldol pathway.[16-17] It was found by Luengo and co-workers that retro aldolisation could be promoted exclusively using the Lewis acid $ZnCl_2$.[18] 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.[19]



12
Rapamycin

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]



13
Azadirachtin

14

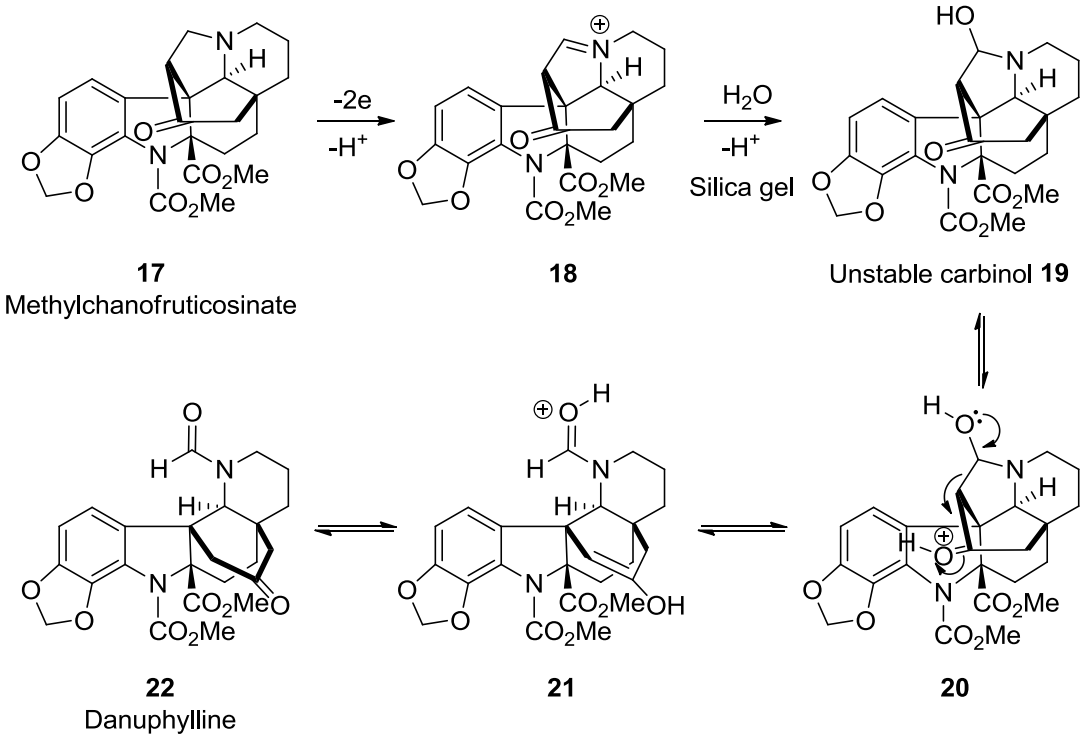
16

15

Reagents and conditions: (i) MeI, Ag_2O; (ii) H_2 (1 atm), Pd/C, MeOH, 20 min; (iii) PCC, 4Å MS, CH_2Cl_2, rt, 48 h; (iv) NaOMe, MeOH, rt, 24 h.

Scheme 5 Retro aldol cleavage of a derivative of Azadirachtin

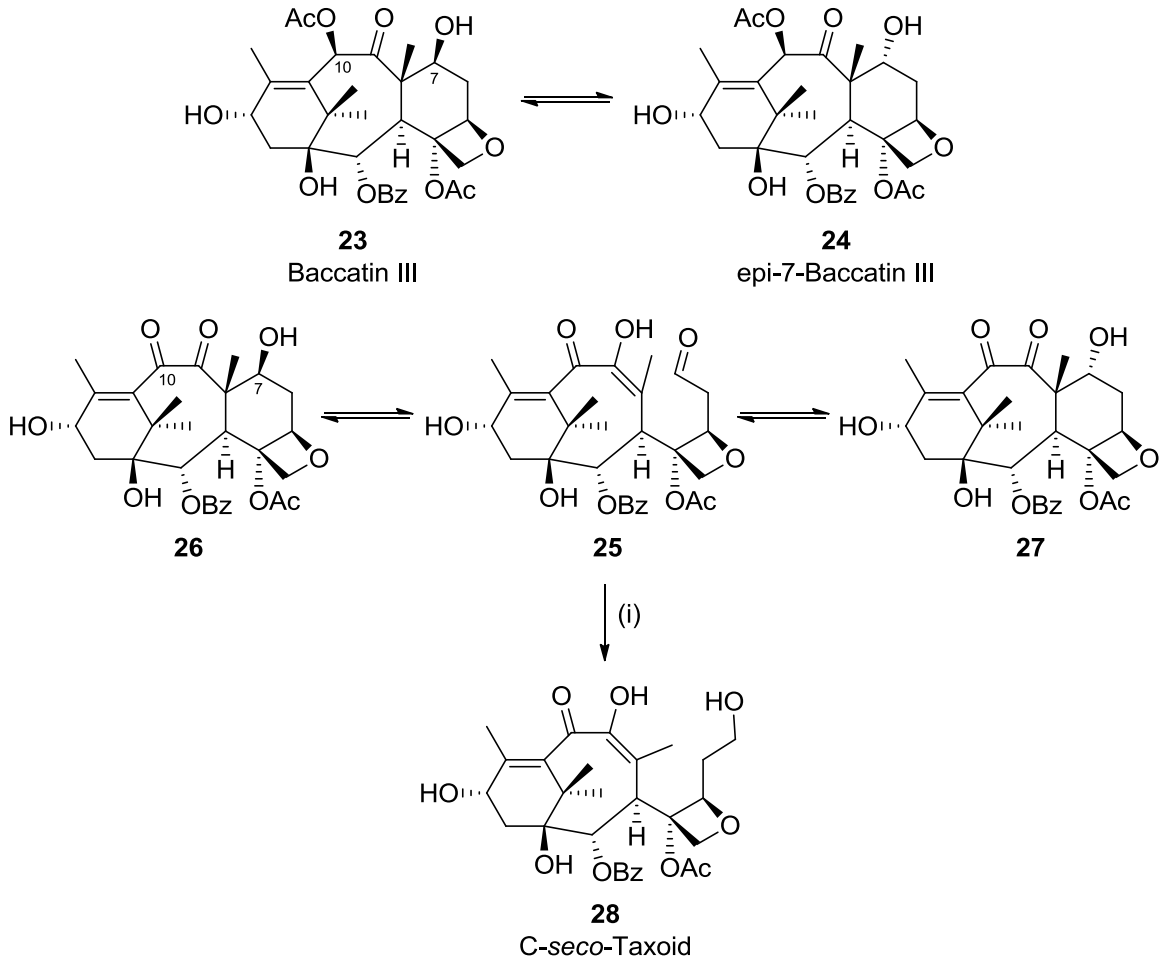
Kam and co-workers showed in 1999 that the likely origin of the novel pentacyclic indole alkaloid Danuphylline **22** is via a pathway involving a retro aldol reaction of precursor **17** found in the same leaf extract. It was proposed that the ring-opened alkaloid arises from the methylchanofruticosinate precursor **17** that provides the iminium ion **18**, which is hydrolysed to give an unstable carbinolamine **19** that then undergoes a retro adol 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**

1.2 Epimerisation

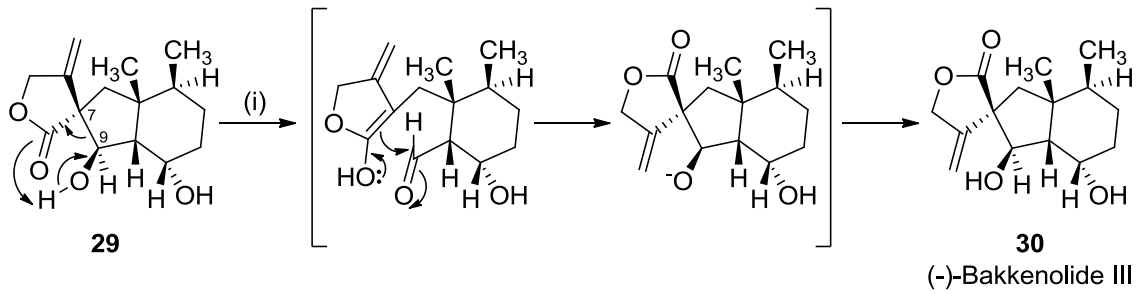
Retro aldol reactions are often associated with the epimerisation of one or more stereocentres of β-hydroxy-carbonyl fragments in natural products. For example, Appendino and co-workers utilised a retro aldol epimerisation reaction that is typical of the 7-hydroxy group of Baccatin III **23** to reductively 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]



Reagents and conditions: (i) $CeCl_3$, $NaBH_4$, MeOH, rt.

Scheme 7 Retro aldol epimerisation of Baccatin III derivatives

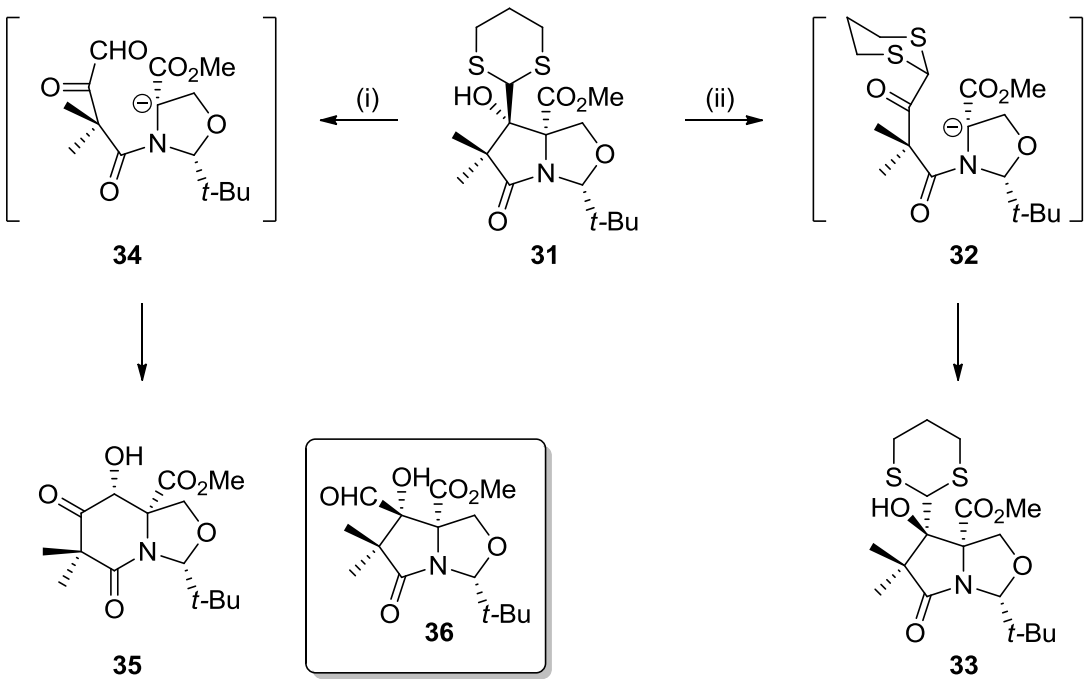
Studies by Deprés, Greene and co-workers into the first comprehensive total synthesis of the Bakkane family of natural products serendipitously revealed a crucial retro aldol/aldol epimerisation reaction of the spiro-fused γ-butyrolactone motif in favour of the natural configuration (Scheme 8). Upon 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]



Reagents and conditions: (i) TBAF, THF, 0 ˚C.

Scheme 8 Epimerisation of C-7 spiro-centre via retro aldol reaction of Bakkane ring system

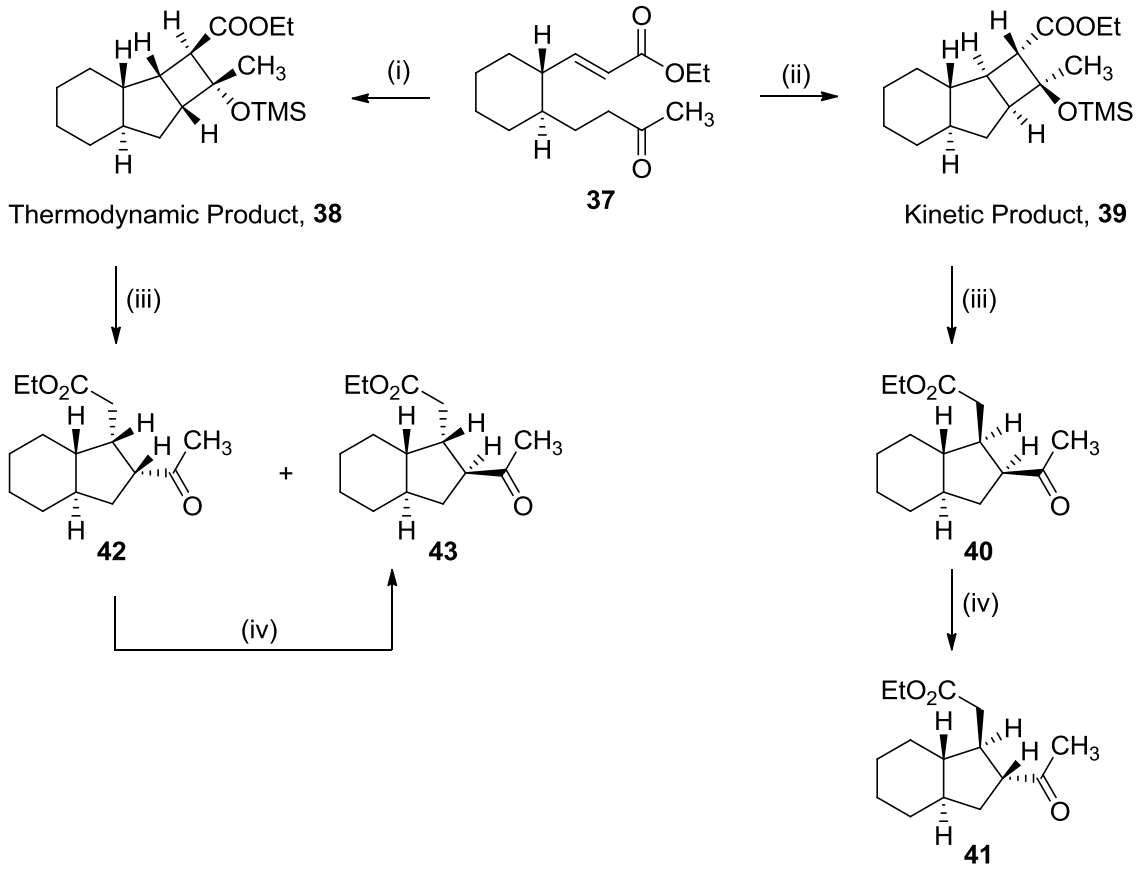
In 2008, Moloney and co-workers showed that bicyclic hydroxypyroglutamate **31** underwent epimerisation via a reversible retro aldol reaction. Under mild basic conditions, **31** epimerised to give the thermodynamically preferred stereochemistry via a sequence of retro aldol/aldol reactions to afford **33** in 80% yield. Alternatively, treatment with MeI/$CaCO_3$ 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.[26]



Reagents and conditions: (i) MeI/$CaCO_3$, CH_3CN-H_2O (5:1), 70 ˚C, overnight; (ii) NEt_3/THF, 0 ˚C, 1 h.

Scheme 9 Retro aldol equilibration of hydroxypyroglutamates

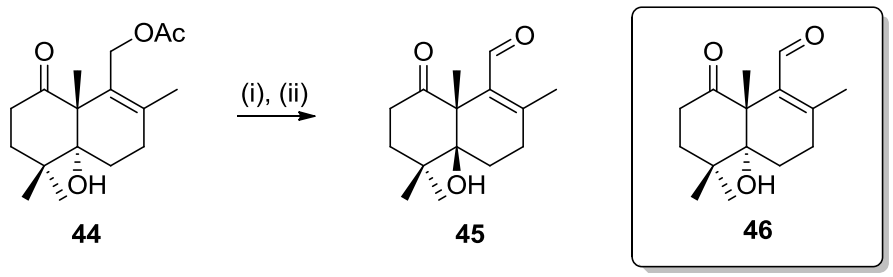
In 2006, Kalesse and co-workers developed novel methodology to access four diastereomeric bicyclic [4.3.0] derivatives by a retro aldol reaction and subsequent epimerisation as potential building blocks for natural product synthesis. Unsaturated ester **37** underwent a tandem intramolecular Michael-aldol 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, $ClCH_2CH_2Cl$; (ii) TMSCl, HMDS, -30 ˚C, 3 h, $ClCH_2CH_2Cl$; (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 K_2CO_3/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^{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.[28-29]



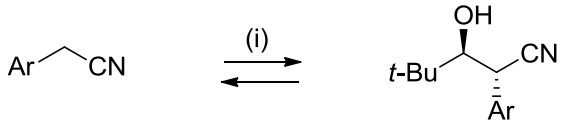
44 **45** **46**

Reagents and conditions: (i) K_2CO_3, 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.[30]



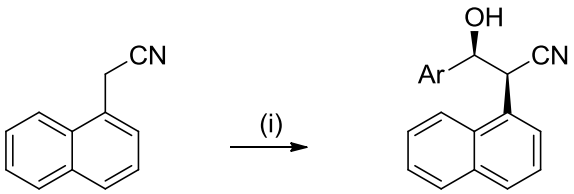
47
Ar = Ph, 2-Napthyl

48
2 examples
Ar = Ph 40% ee, 86% yield
Ar = 2-naphthyl, 77% ee, 61% yield

Reagents and conditions: (i) (-)-Ephedrine (1.1 equiv), ^{n}BuLi (2.2 equiv), -78 ˚C, 30 min, ^{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]



49

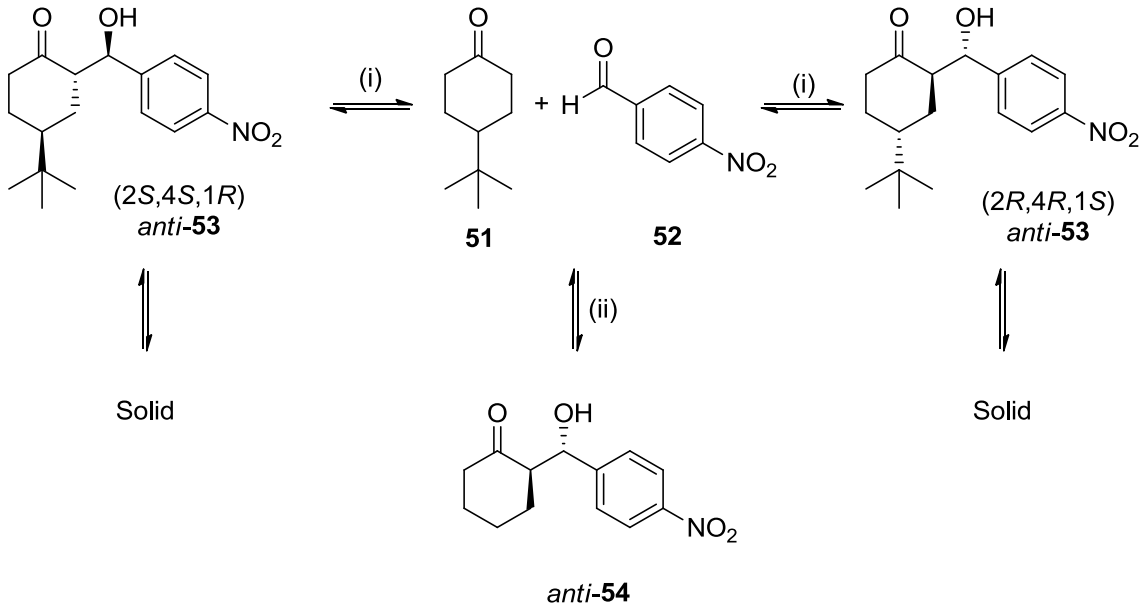
50
7 examples
96:4 to 98:2 *syn*:*anti*

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 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

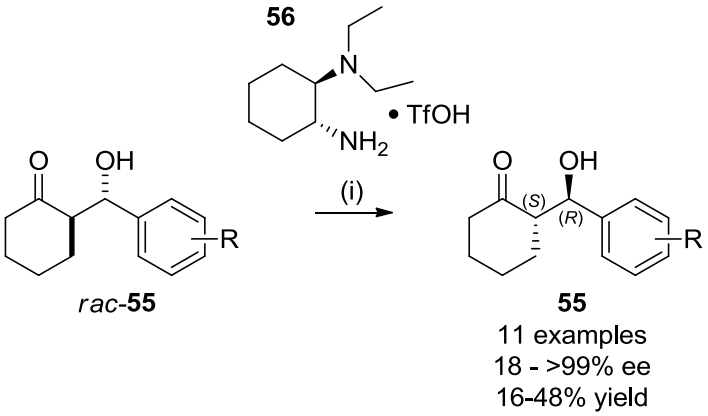
analysed over time, showing that the enantiomeric ratio of the solid **53** changed significantly over time, to a ratio of 96:4 over one day and 98:2 after eleven days. The authors demonstrated that a reversible retro aldol reaction was operating to racemise **53** by introducing cyclohexanone as a co-reactant, which gave 43% of *anti*-**54** after six days.[32]



Reagents and conditions: (i) Catalyst (10 mol%) (pyrrolidine, piperidine or rac-proline), DMSO; (ii) cyclohexanone.

Scheme 14 Enantioenrichment of conglomerate crystalline aldol product **53**

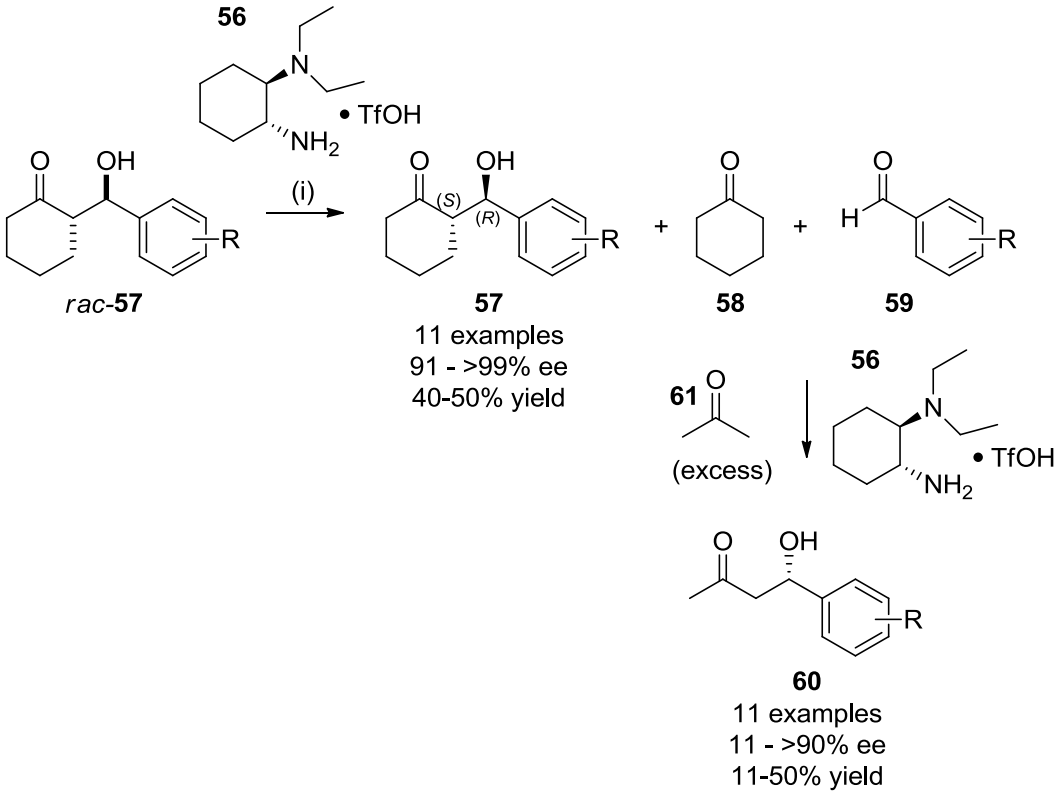
In 2010, Luo, Cheng and co-workers reported the first asymmetric retro aldol reaction catalysed by a simple primary amine as an aldolase antibody mimic of imine/enamine catalysis. This method enables the kinetic resolution of racemic aldol products to access enantiomerically enriched aldols that are difficult to prepare by other methods. The best catalyst was found to be the cyclohexyl diamine **56** in $CDCl_3$, with the conversion and enantiomeric excess of the kinetic resolution of *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.



Reagents and conditions: (i) ***56*** *(20 mol%),* $CDCl_3$.

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

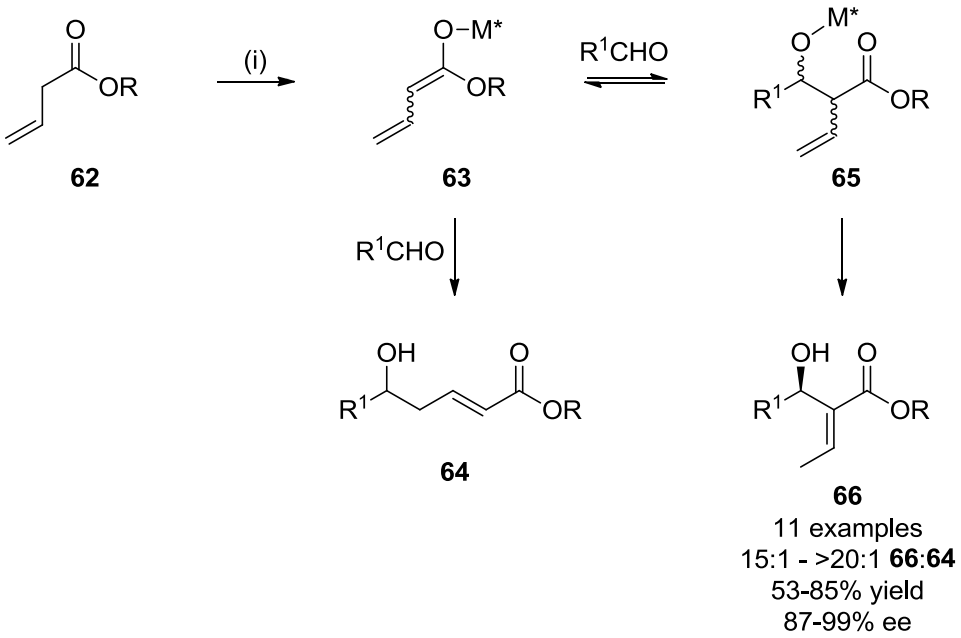
The authors also reported a novel transfer aldol reaction, in which excess acetone **61** was used to trap out the aryl aldehyde **59** generated by the initial retro aldol reaction via a forward aldol reaction, whereby the chiral catalyst **56** also mediates formation of a new enantiomerically pure 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]



Reagents and conditions: (i) ***56*** *(20 mol%),* $CDCl_3$.

Scheme 16 Transfer aldol reaction using excess acetone to facilitate kinetic resolution of *rac*-**57**

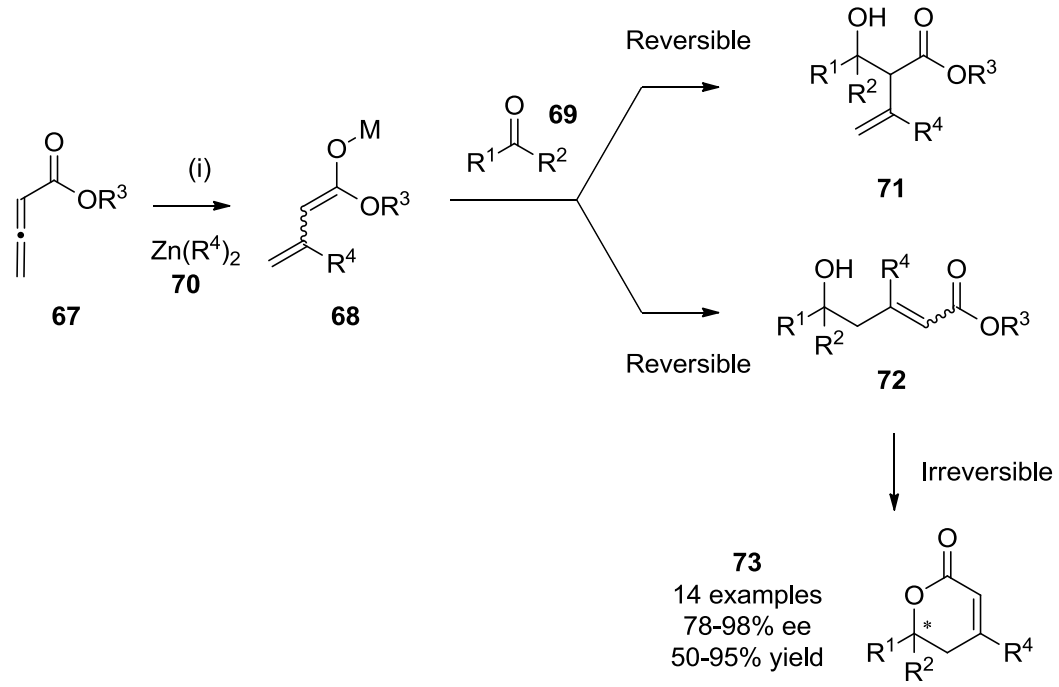
In 2009, Shibasaki and co-workers developed a dynamic kinetic asymmetric transformation (DYKAT) process for the asymmetric synthesis of α-alkylidene-β-hydroxy esters **66**. An (*S*)-barium-BINOL complex generates dienolate **63** *in situ*, which can undergo either α- or γ-addition to an aldehyde to 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.[34]



Reagents and conditions: (i) Ba(O^iPr)$_2$ (10 mol%), (S)-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 (Ph_2S=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**.[35]

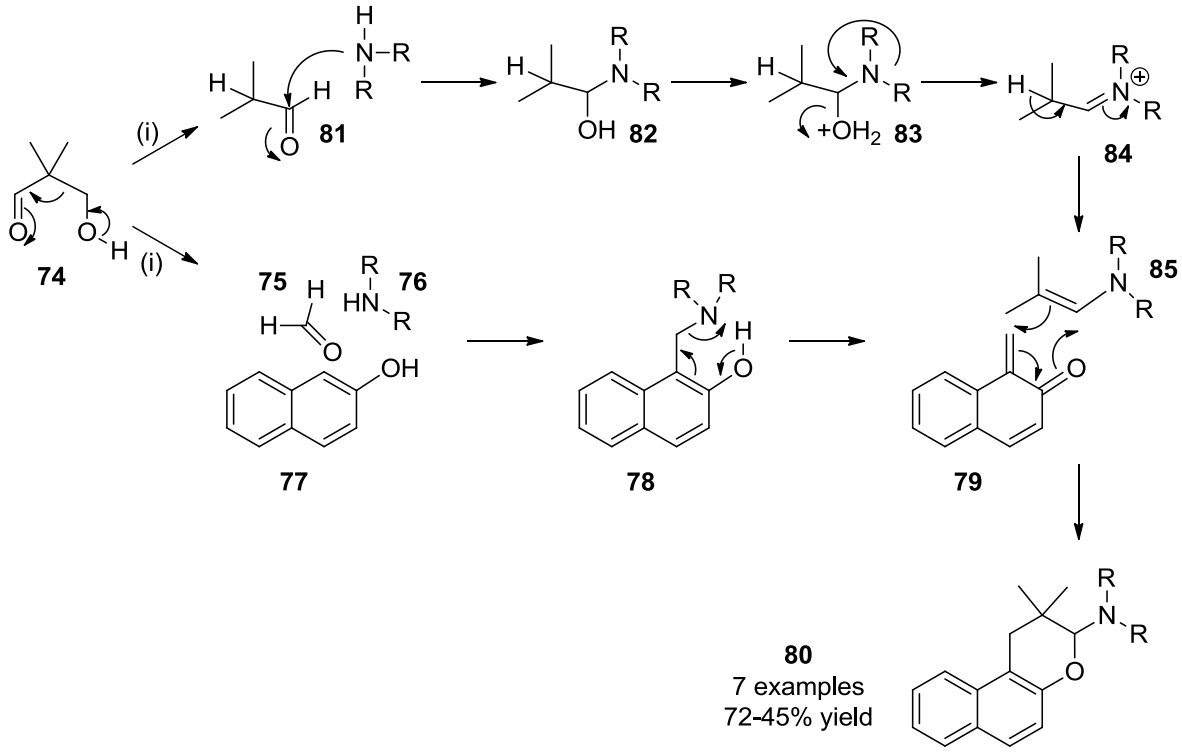


Reagents and conditions: (i) $Cu(OAc)_2$ (5 mol%), (R)-DIFLUORPHOS (6 mol%), additive (DMSO, HMPA or Ph_2S=O) (20 mol%), 4Å MS, THF, -20 ˚C.

Scheme 18 Catalytic asymmetric multi-component reaction incorporating a crucial retro aldol pathway to improve the yield of lactones **73**

1.4 Synthetically Useful Retro Aldol Reactions of Acyclic Aldol Substrates

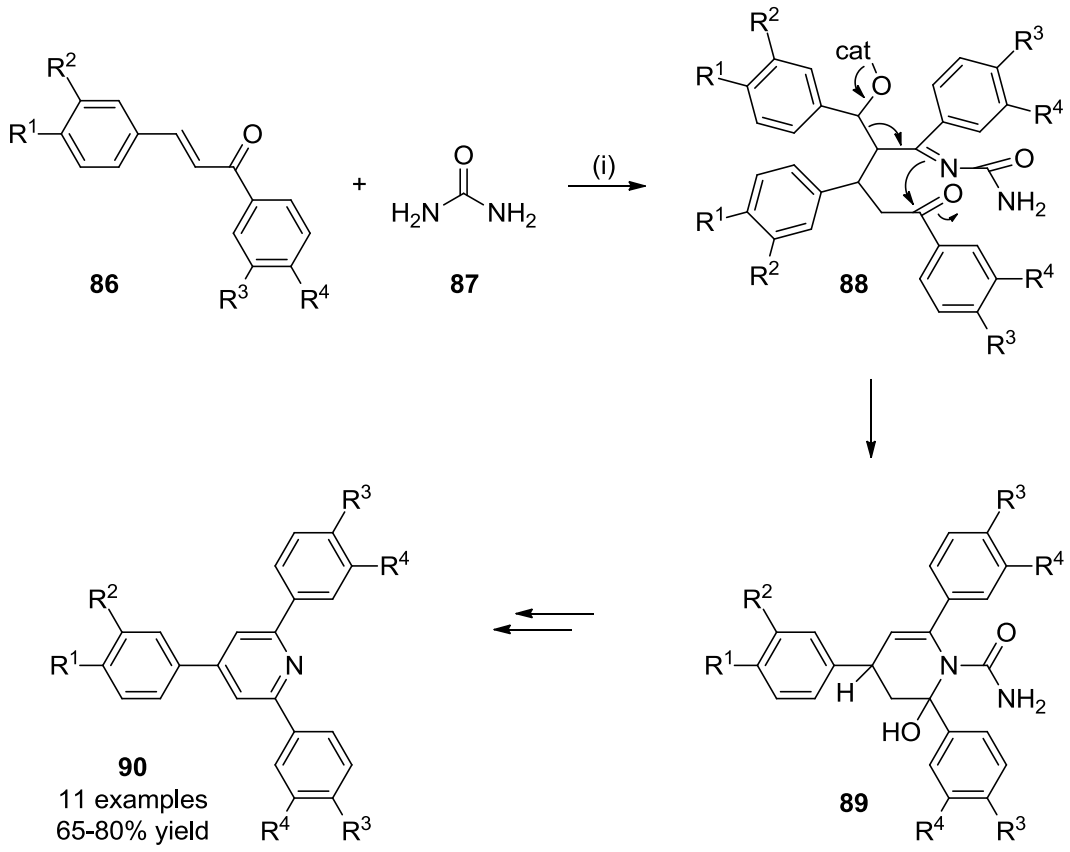
Retro aldol reactions of acyclic aldol systems are not normally that synthetically useful since they result in cleavage into a mixture of structurally less complex enolate and aldehyde products. Retro aldol reactions of stable aldol substrates can be used to generate reactive carbonyl components *in 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 isobutyroaldehyde) to afford naphthopyran **80**.[36]



Reagents and conditions: (i) p-TSA (cat), microwave.

Scheme 19 Mechanism for the formation of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1H-naphtho[2,1-b]pyran **80**

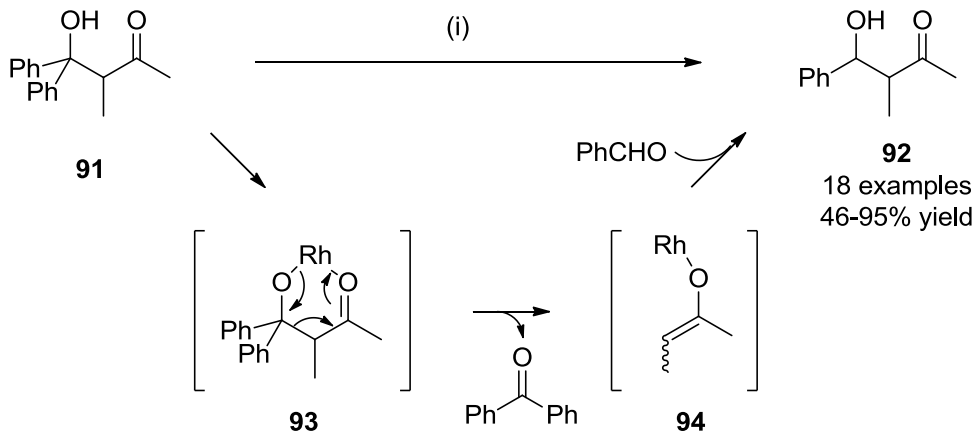
Another less well explored approach is to generate an aldol product via nucelophilic addition of an oxygen nucleophile to a Michael acceptor, whose retro aldol cleavage is then employed to trigger a cyclisation event. For example, Razdan and co-workers have described a one pot synthesis of 2,4,6-triarylpyridines **90** from benzylideneacetophenones **86** using Bi(III) nitrate-Al_2O_3. Formally, Micahel 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]



Reagents and conditions: (i) $Bi(NO_3)_3$-Al_2O_3, (5% w/w), 125-135 ˚C.

Scheme 20 A retro aldol reaction facilitates the solid supported catalytic synthesis of 2,4,6-triarylpyridines **90**

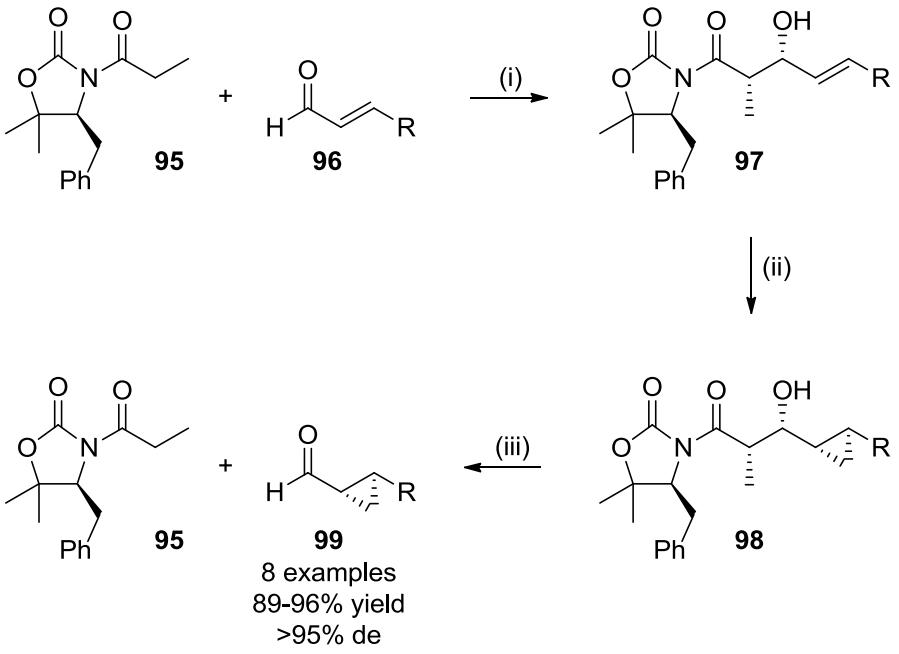
A potentially useful application of the retro aldol reaction is to employ a metal alkoxide of an aldol product that fragments to afford a metal enolate that is difficult to prepare via traditional metalation of the parent carbonyl compound. Yorimitsu and co-workers have reported the rhodium catalysed retro aldol reaction of tertiary β-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.[38]



Reagents and conditions: (i) $[RhCl(cod)]_2$ (2.5 mol%), PhCHO, TMEDA, Cs_2CO_3 (20 mol%), 1,4-dioxane, 20 ˚C, 3 h.

Scheme 21 Retro aldol of β-hydoxyketones to generate rhodium enolates and subsequent aldol reaction

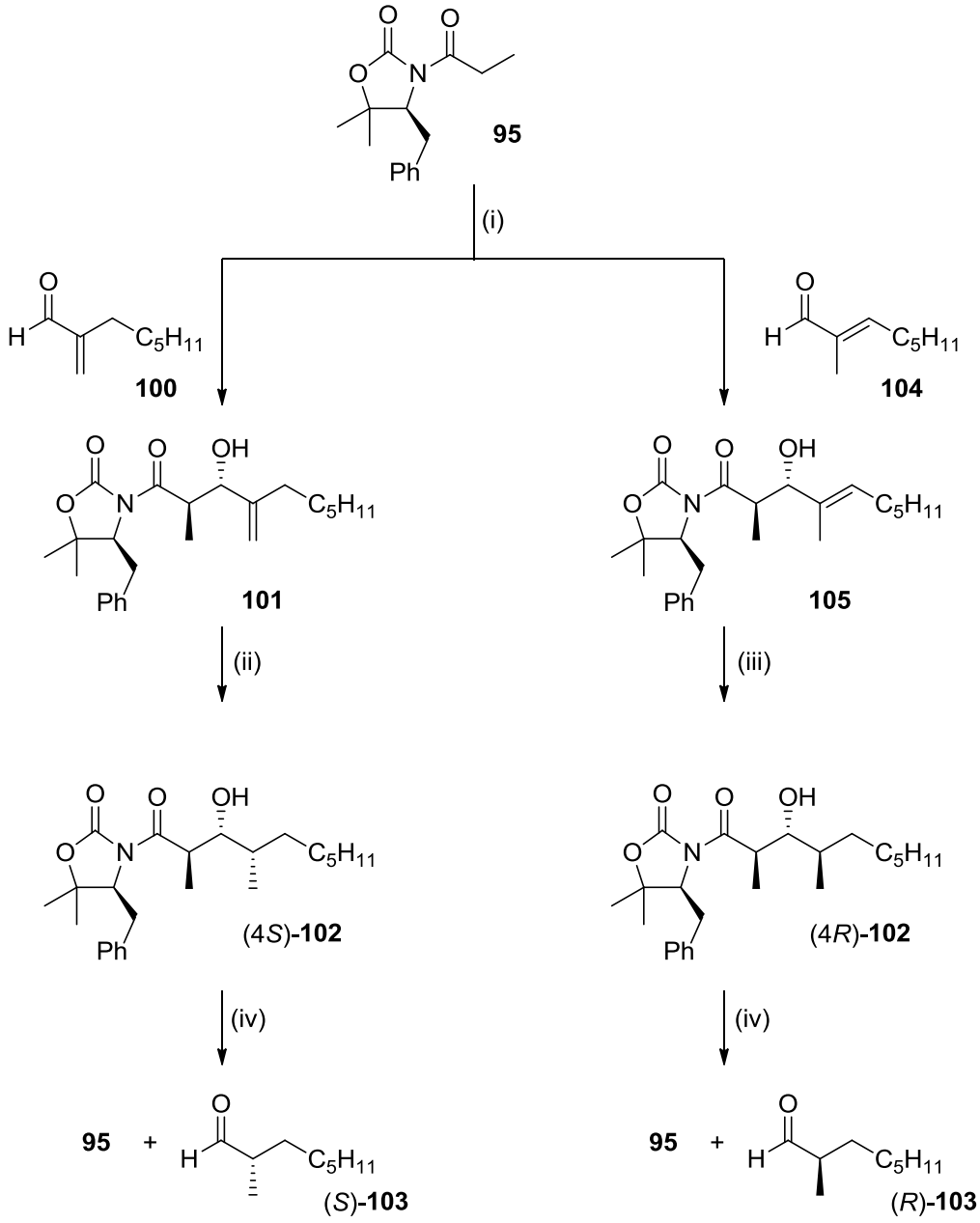
Bull and co-workers have developed 'temporary stereocentre' methodology for the asymmetric synthesis of chiral aldehydes using the SuperQuat oxazolidin-2-one to relay stereocontrol. For example, a novel three step aldol/cyclopropanation/retro aldol sequence was developed to produce enantiopure chiral 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]



*Reagents and conditions: (i) 9-BBN-OTf, N(^{i}Pr)$_2$Et, CH_2Cl_2, 0 ˚C then **96**, -78 ˚C; (ii) $ZnEt_2$, CH_2I_2, CH_2Cl_2, -10 ˚C to 0 ˚C; (iii) LiHMDS, toluene, 0 ˚C.*

Scheme 22 Temporary stereocentre approach for the synthesis of chiral cyclopropane-carboxaldehydes **99**

This 'temporary stereocentre' methodology has also been utilised for the stereodivergent synthesis of either enantiomer of α-methyloctanal using an asymmetric hydrogenation procedure. Aldol products **101** and **105** were synthesised using the Evans' *anti*-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 (4*S*)-**102** in 96% de. Aldol **102** underwent asymmetric hydrogenation using Brown's catalyst to afford saturated aldol (4*R*)-**102** in a slightly lower 85% de, which was purified to >95% de. Retro aldol reactions of aldols (4*S*)-**102** and (4*R*)-**102** with LiHMDS in toluene afforded (*S*)-α-methyloctanal (*S*)-**103** and (*R*)-α-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 α-methyloctanal **103** could be derivatised *in situ* to afford dithiane and Wittig products as well as reduction to α-methyloctanol with no racemisation, which function as useful chiral building blocks.[41]

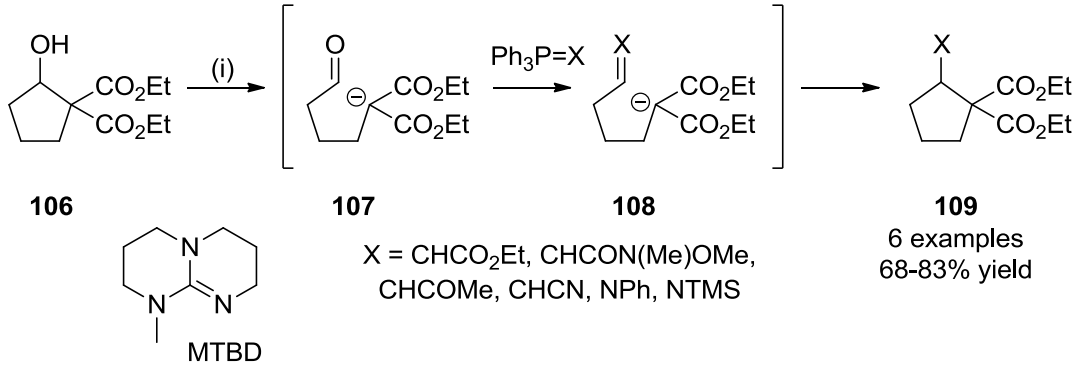


Reagents and conditions: (i) $MgCl_2$, NEt_3, TMSCl, EtOAc, rt, 24 h then TFA, MeOH; (ii) Wilkinson's catalyst (17.5 mol%), H_2 (5 bar), CH_2Cl_2; (iii) Brown's catalyst (17.5 mol%), H_2 (5 bar), CH_2Cl_2; (iv) LiHMDS, toluene, 0 ˚C.

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

1.5 Retro Aldol Reactions for the Ring-Opening Monocyclic Systems

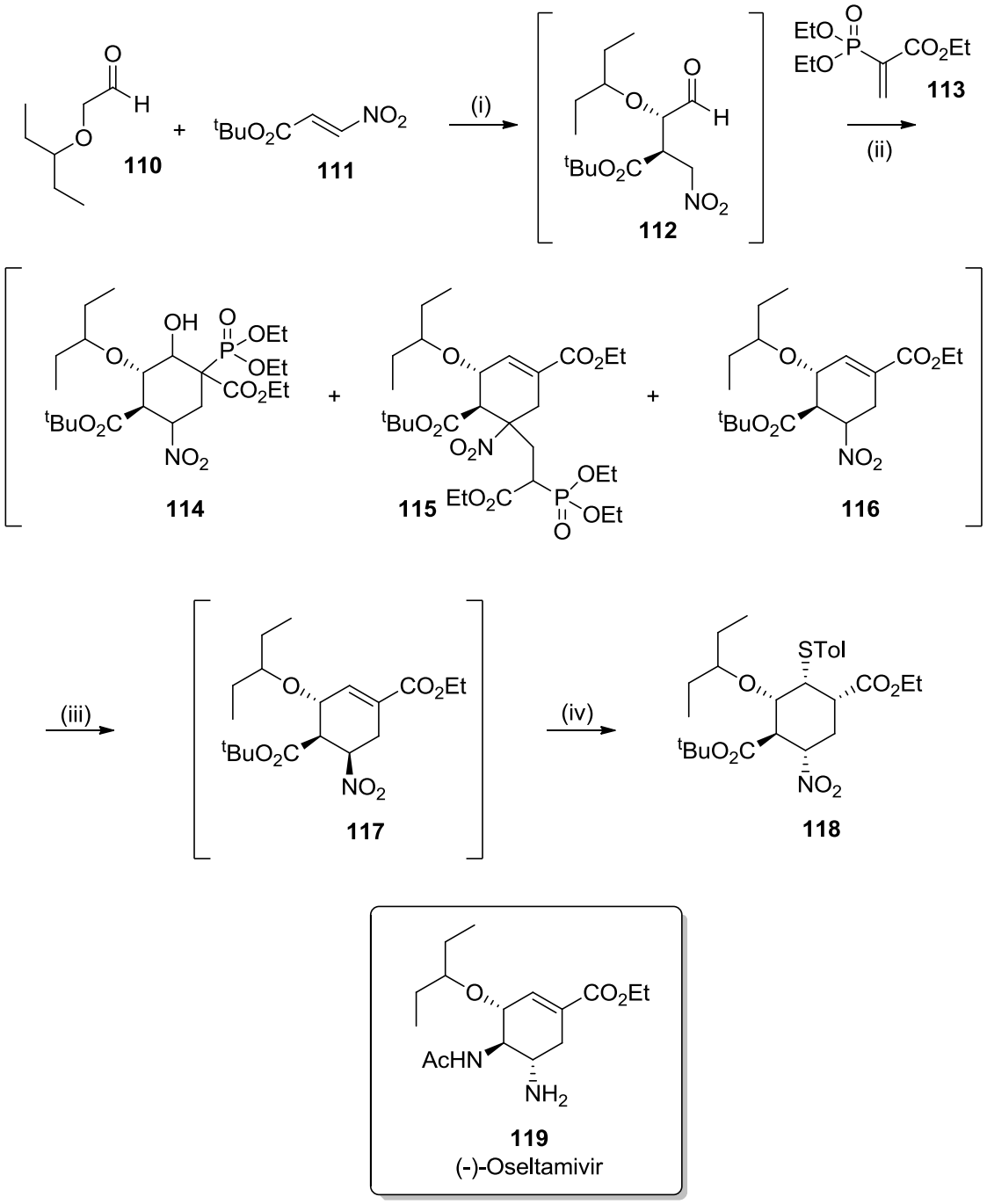
In 2009, Taylor and co-workers described a number of novel cascade sequences initiated by a retro aldol reaction to afford a range of novel functionalised cyclopentanes. Treatment of 2,2-di(carboethoxy)cyclopentanol **106** with MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) in the presence of Wittig 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]



Reagents and conditions: (i) Ph_3P=X, MTBD, MeCN, heat, 16-22 h.

Scheme 24 Retro aldol/Wittig/intramolecular Michael addition cascade reaction to afford **109**

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]

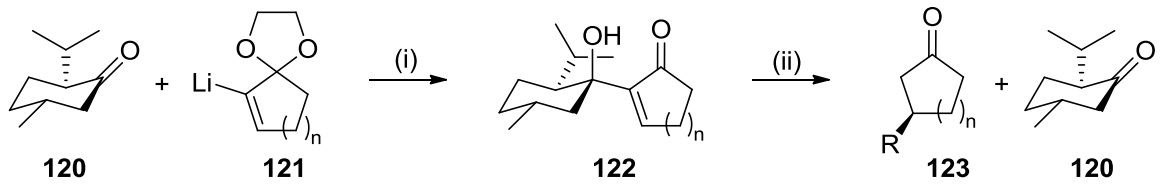


Reagents and conditions: (i) (R)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine, $ClCH_2CO_2H$ (20 mol%), toluene, rt, 6 h; (ii) ***113****, toluene, 0 ˚C to rt, 4 h; (iii) EtOH, rt, 10 min; (iv) TolSH, -15 ˚C, 36 h.*

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 β-alkylcycloalkanones **123** in high yield and good ee.[45]

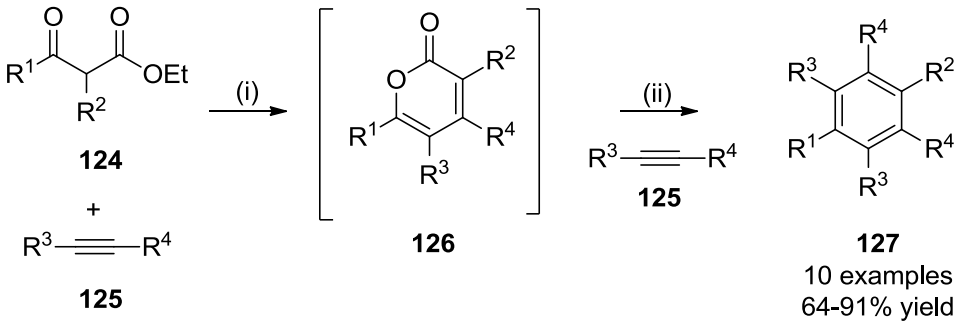


n = 1 R = Ph 73% yield, 80% ee
n = 1 R = Bu 66% yield 85% ee
n = 2 R = Ph 81% yield 91% ee
n = 2 R = Bu 85% yield 90% ee

Reagents and conditions: (i) ***121*** *then oxalic acid (2.5 equiv), CH_2Cl_2/H_2O (8:1), 27 ˚C, 8 h; (ii) $R_2CuCNLi_2$, -60 ˚C, 10-12 h, MeOH (10 equiv), 27 ˚C, 7-8 h.*

Scheme 26 Retro aldol reaction removes the (-)-menthone auxiliary fragment of cyclopentenone **122**

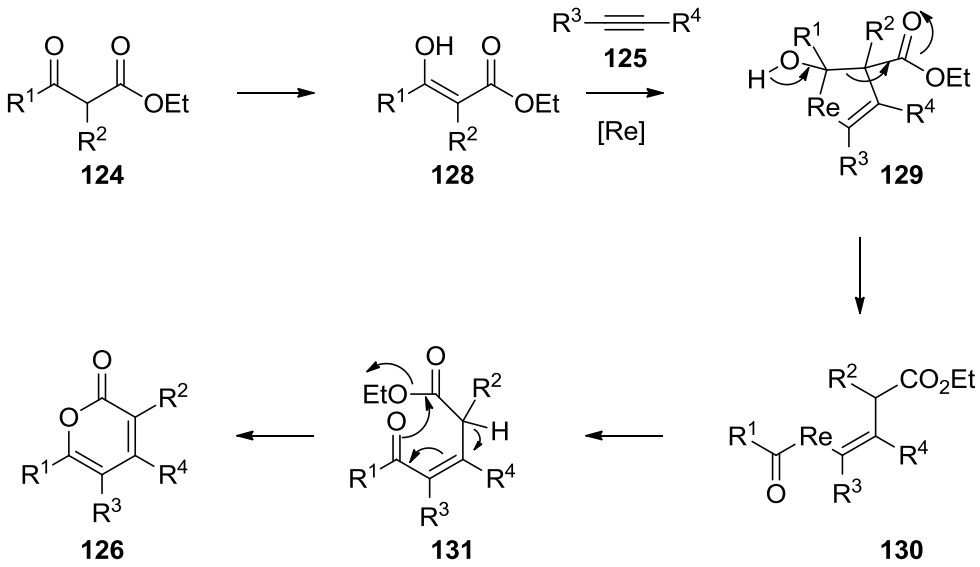
Takai and co-workers have developed a transition metal-catalysed synthesis of multisubstituted aromatic compounds that features a key retro aldol cleavage as part of its mechanism. Rhenium catalysed reaction between β-keto ester **124** and alkyne **125** results in formation of 2-pyranone **126**, which 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.



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

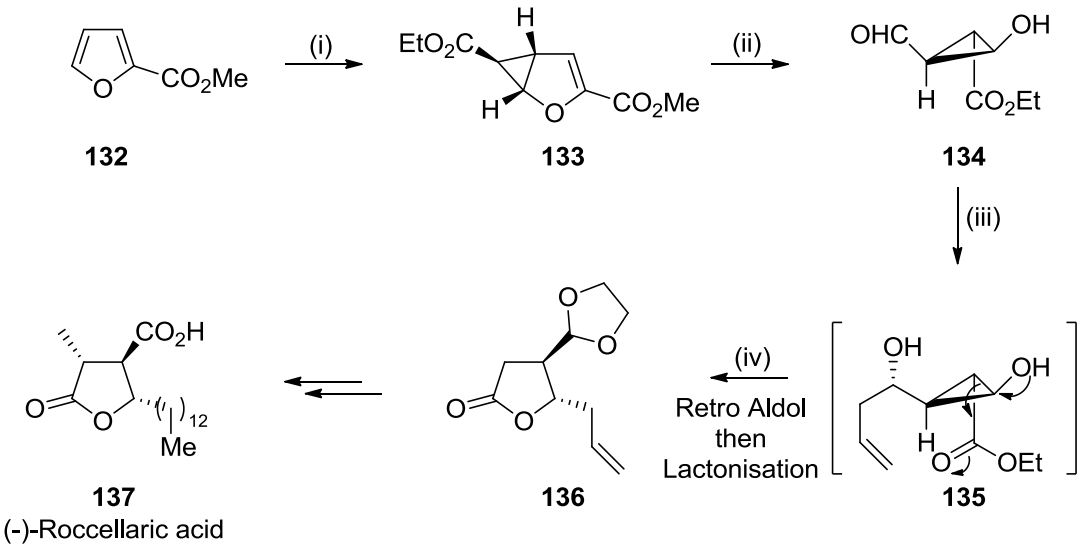
Scheme 27 Reaction conditions for the formation of multi-substituted aromatics

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**.[46]



Scheme 28 Proposed mechanism for the synthesis of pyranone intermediate **126**

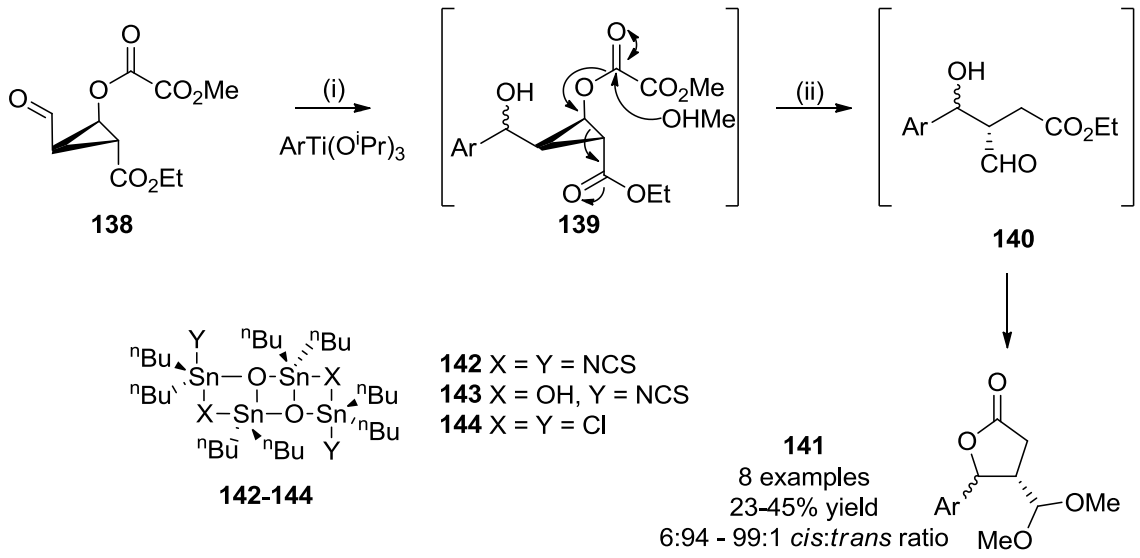
Reiser and co-workers have demonstrated a tin catalysed retro aldol reaction of cyclopropane **136** as part of their total synthesis of (-)-Roccellaric acid **137**. Furan **132** underwent asymmetric cyclopropanation to afford **133**, which was subsequently subjected to ozonolysis and nucleophilic allylation to afford **134**. The crude allyl product **134** was treated *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 *anti*/*syn* ratio. This intermediate was then used as a precursor to synthesise (-)-Roccellaric acid **137** in a further five steps.[47]



Reagents and conditions: (i) Ethyl diazoacetate, $Cu(OTf)_2$ (2 mol%), (–)-(S,S)- bis(4-tert-butyloxazoline), $PhNHNH_2$, CH_2Cl_2; (ii) O_3, CH_2Cl_2, -78 ˚C then Me_2S; (iii) $BF_3{\cdot}OEt_2$, -78 ˚C then allyltrimethylsilane; (iv) $[Sn_2(Bu)_4(NCS)_2O]_2$ (0.05 mol%), 1,2-ethyleneglycol, benzene, reflux.

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

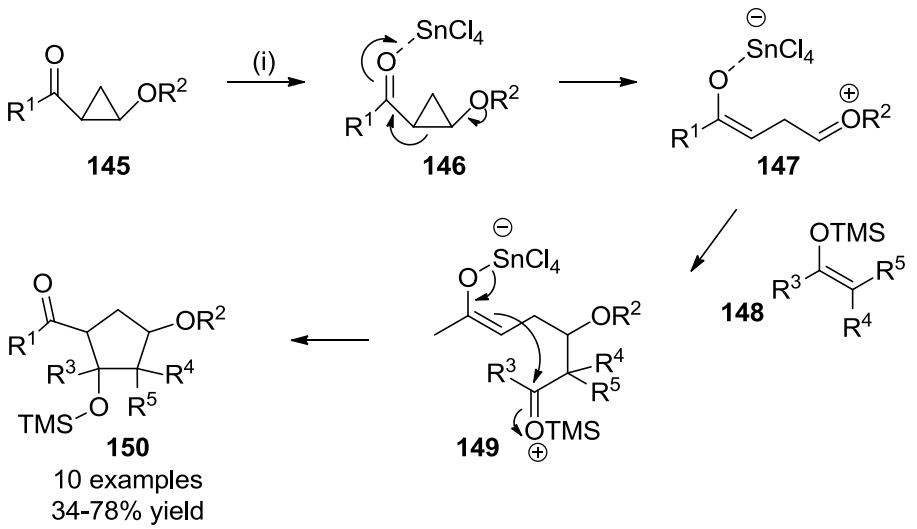
Reiser and co-workers also developed a diastereoselective method for the synthesis of highly substituted γ-butyrolactones **141** using aryl titanium reagents. Cyclopropanecarboxaldehyde **138** was treated with various aryl titanium reagents to generate intermediate **139**, which was treated *in situ* 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**.[48]



*Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, THF, -78 ˚C, 16 h; (ii) Catalyst **142**-**144** (10 mol%), MeOH, reflux, 12 h.*

Scheme 30 Synthesis of γ-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]

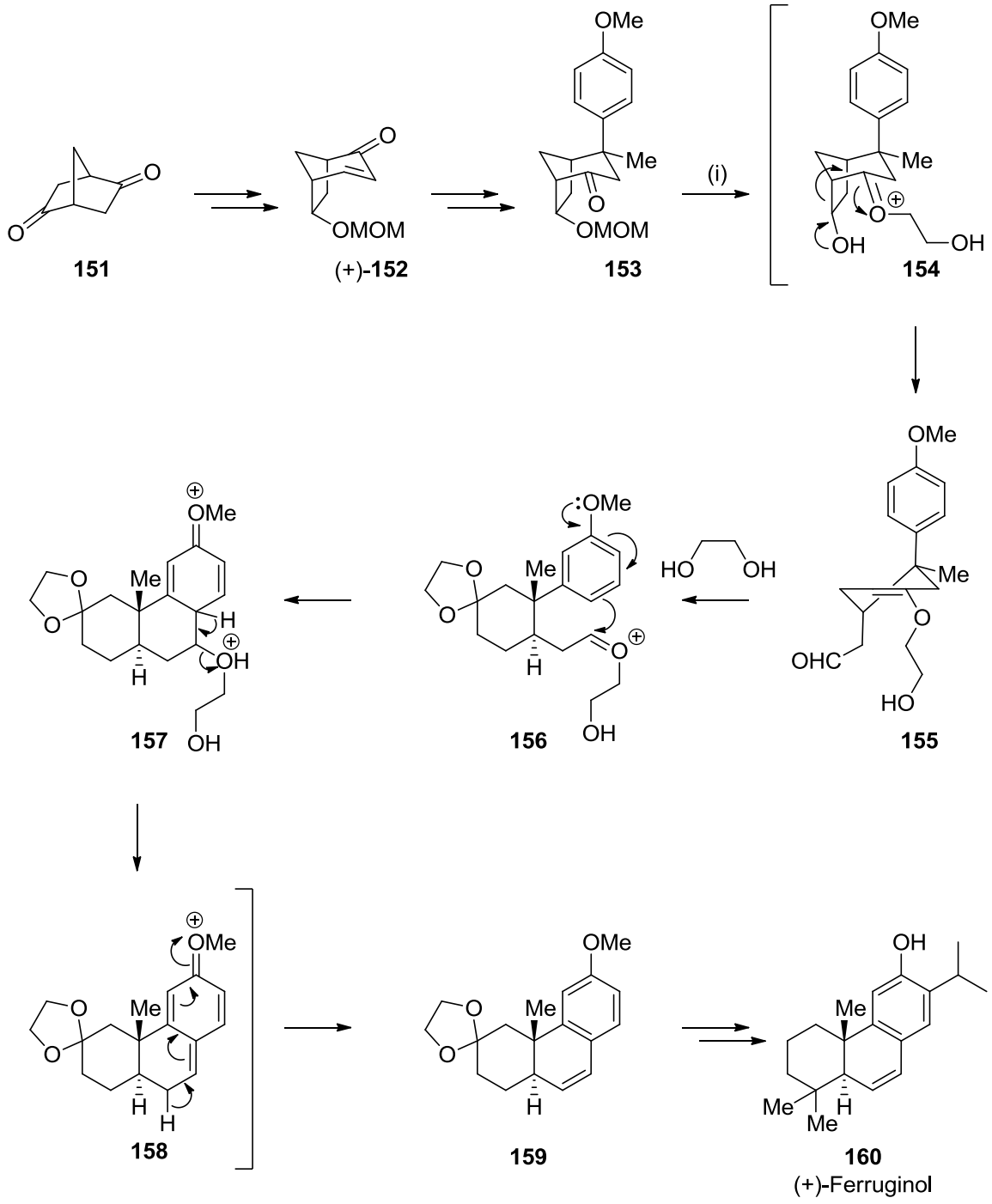


Reagents and conditions: (i) $SnCl_4$, CH_2Cl_2, -78 ˚C, 1h.

Scheme 31 Lewis acid mediated retro aldol reaction of **146** to form cyclopentanes **150**

1.6 Retro Aldol Reactions for the Ring Opening of Bicyclic Systems

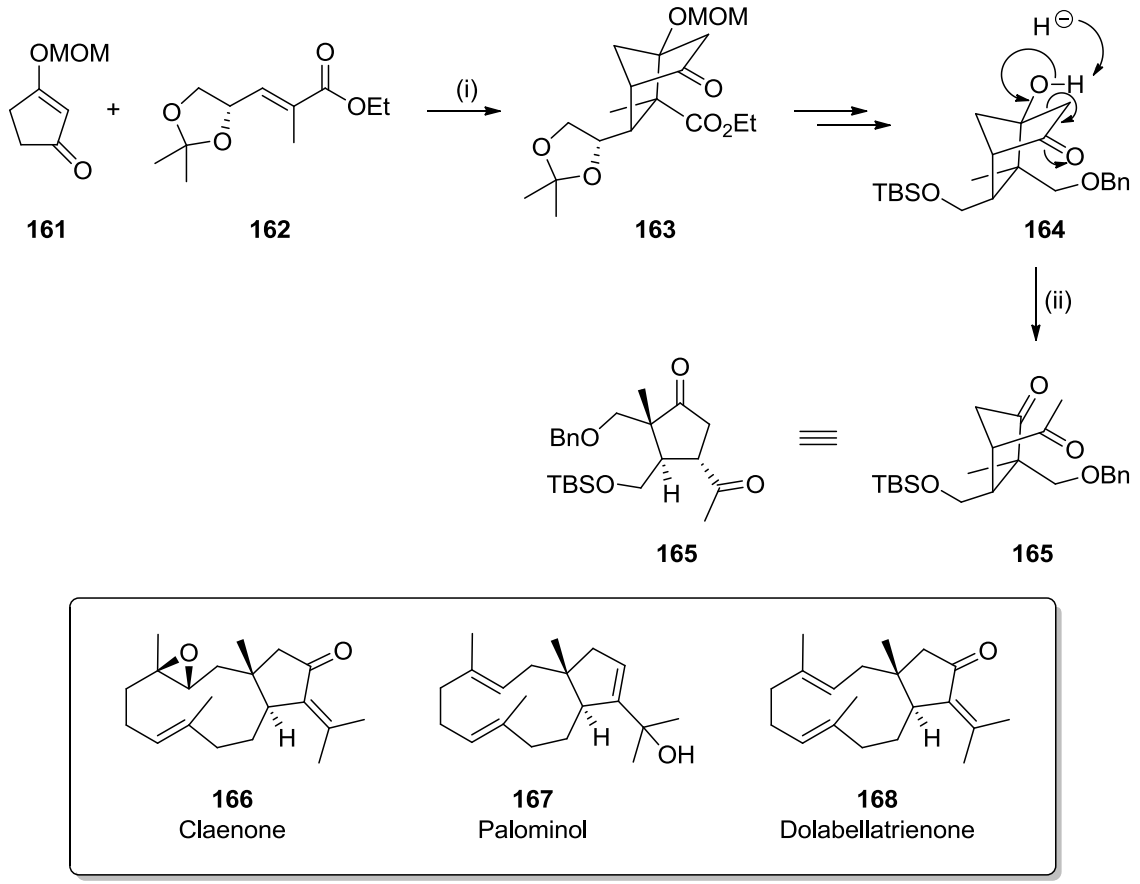
Bicyclic ring systems that undergo ring-strain promoted retro aldol rearrangements offer an attractive route into chiral building blocks for natural product synthesis that are difficult to access using more conventional methodology. Ogasawara and co-workers have employed a bicyclo[3.2.1]octane chiral 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]



Reagents and conditions: (i) $(CH_2OH)_2$, p-TSA (cat), toluene, reflux.

Scheme 32 Synthesis of hexahydrophenanthrene **159** via retro aldol reaction of bicyclo[3.2.1]octenone **152**

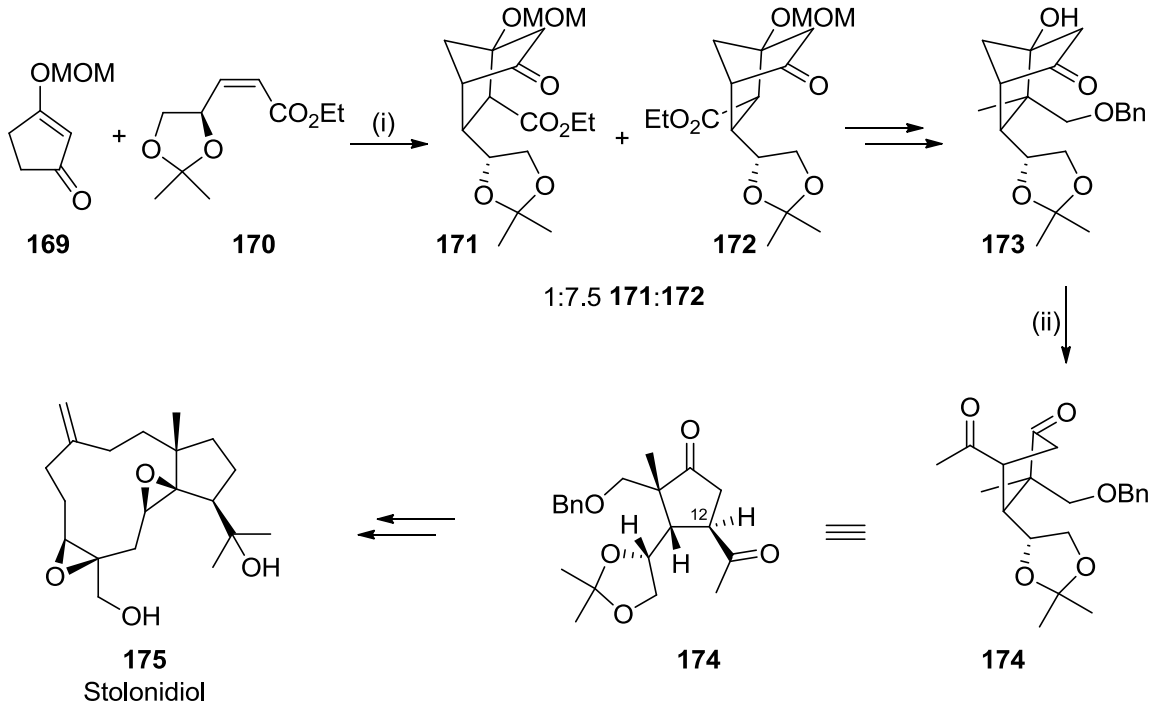
Yamada and co-workers have developed a fragmentation method employing a bicyclo[2.2.1]heptane derivative **163**, which undergoes a retro aldol reaction to afford a tetrasubstituted cyclopentane derivative **165**. Initially, bicyclo[2.2.1]heptane **163** was prepared from cyclopentanone **161** and 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**.[51-52]



*Reagents and conditions: (i) LDA, THF, -78 ˚C then **162**; (ii) NaH, 15-crown-5, toluene, rt.*

Scheme 33 Retro aldol cleavage of bicyclic β-hydroxyketone **164**

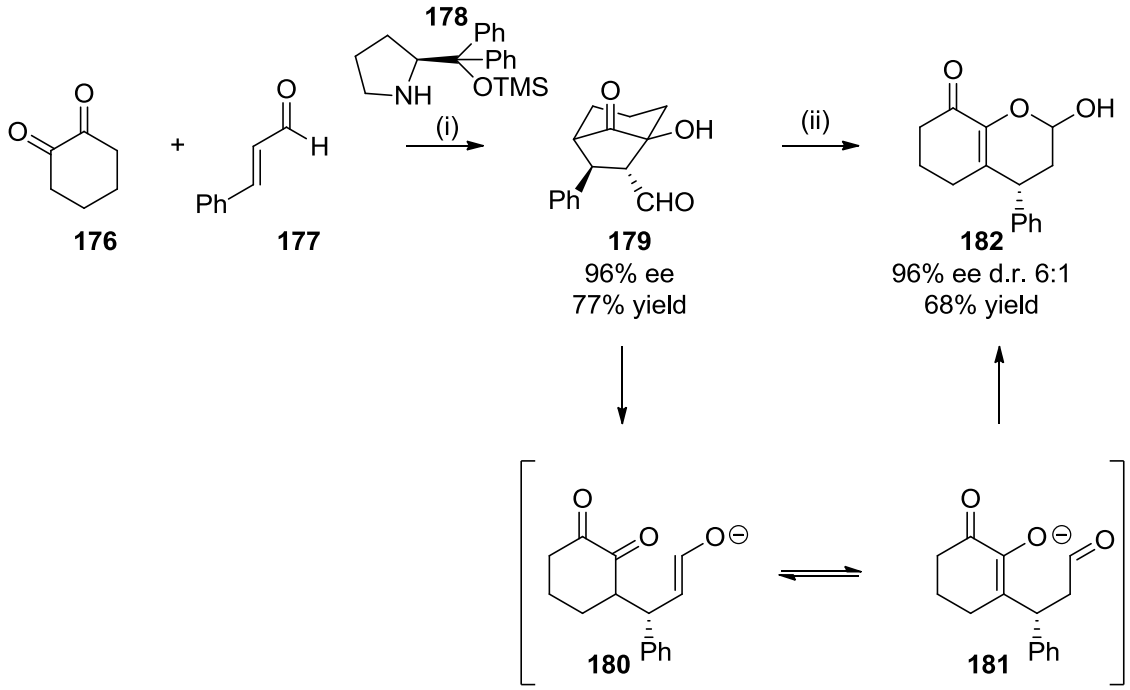
Yamada and co-workers have also used this type of fragmentation chemistry for the total synthesis of the marine diterpenoid Stolonidiol **175**. Bicyclic β-hydroxyketone **173** was treated with K_2CO_3 in methanol at 40 ˚C, which initiated the retro aldol rearrangement as well as epimerising the C-12 stereocentre to afford tetrasubstituted cyclopentane **174** in 92% yield.[53]



*Reagents and conditions: (i) LDA, THF, -78 ˚C then **170** to rt; (ii) K_2CO_3, MeOH, 40 ˚C.*

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

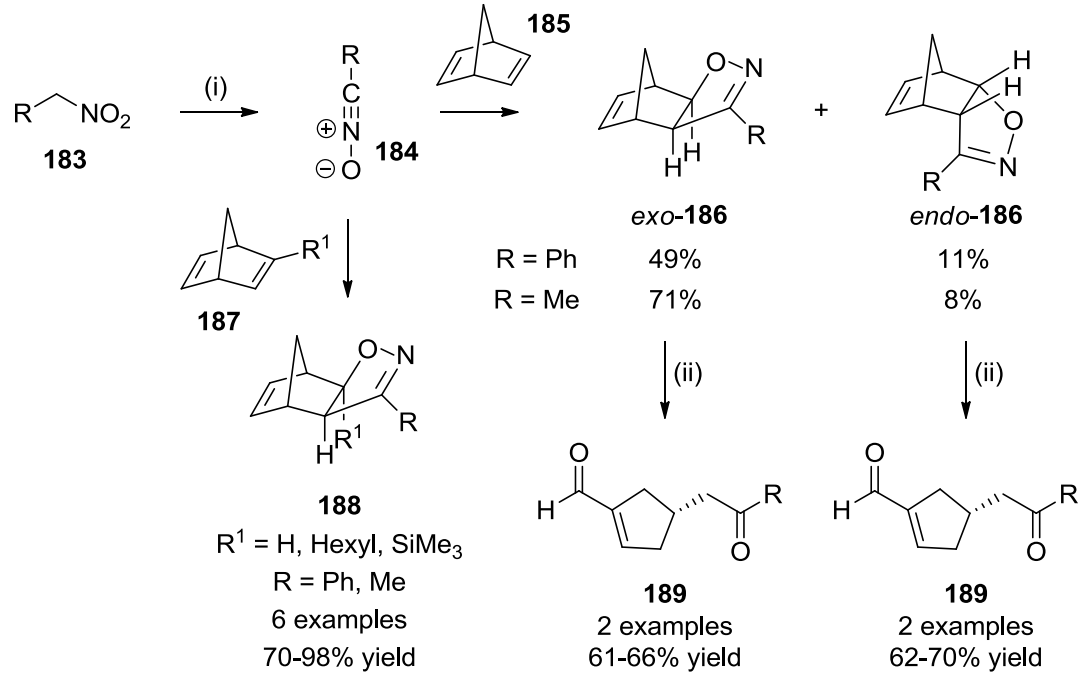
In 2009, Rueping and co-workers demonstrated a novel tandem retro aldol/cyclisation reaction to afford a tetrahydrochromenone product **182** in 96% ee and 68% yield. An asymmetric organocatalytic domino Michael/aldol reaction of diketone **176** and enone **177** was employed to afford bicyclo[3.2.1]octane-6-carbaldehyde **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]

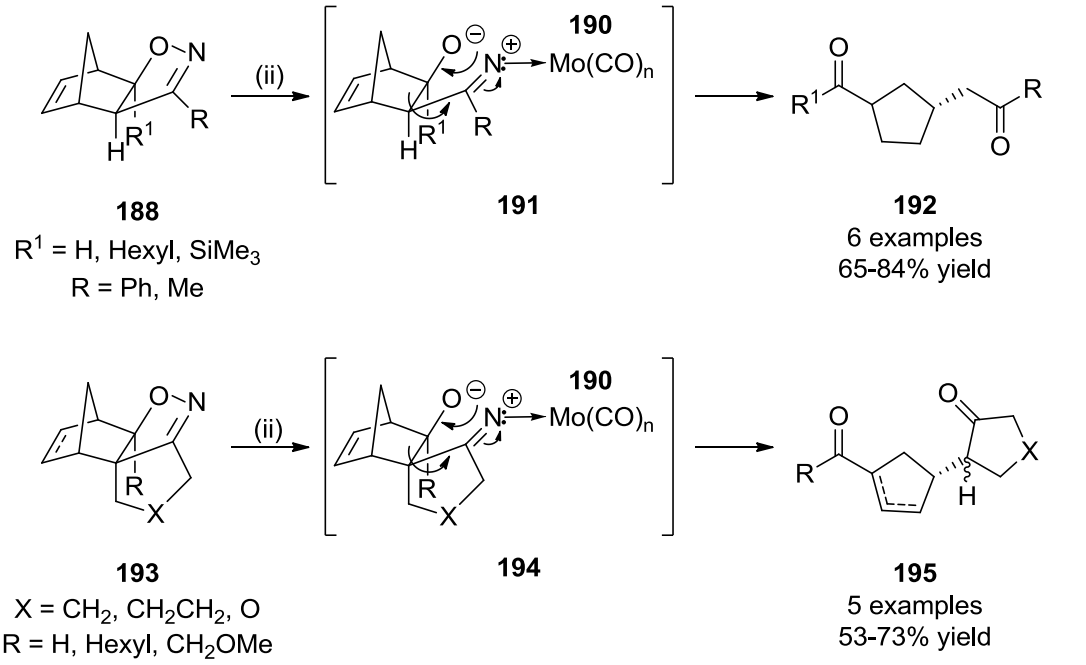


Reagents and conditions: (i) ***178*** *(10 mol%), EtOH, rt, 7-24 h; (ii)* K_2CO_3*, MeOH.*

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.[55]

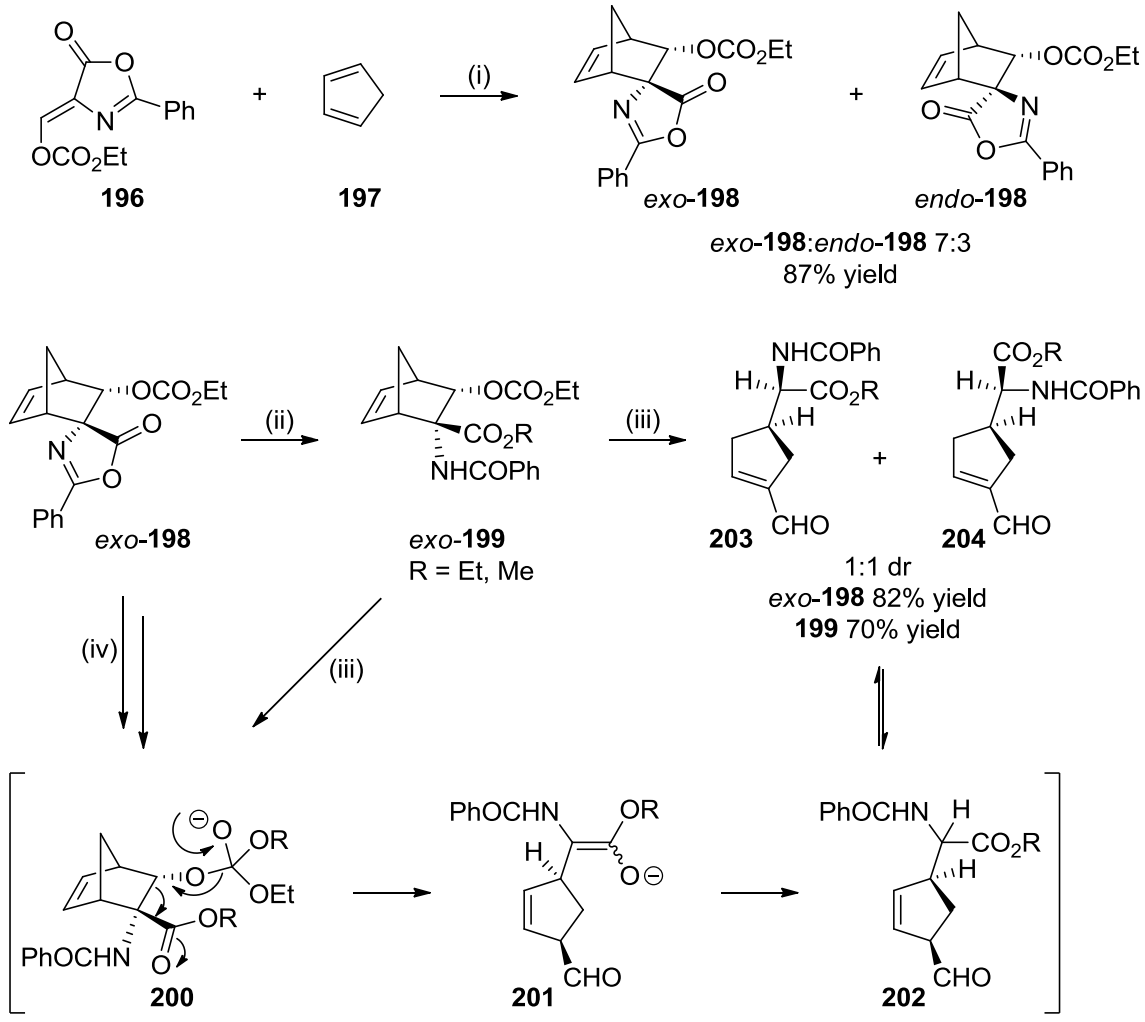




Reagents and conditions: (i) $(Boc)_2O$, DMAP, toluene, 25 ˚C; (ii) $Mo(CO)_6$, MeCN/H_2O, 80 ˚C.

Scheme 36 Formation of ring attached systems via two cleavage reactions

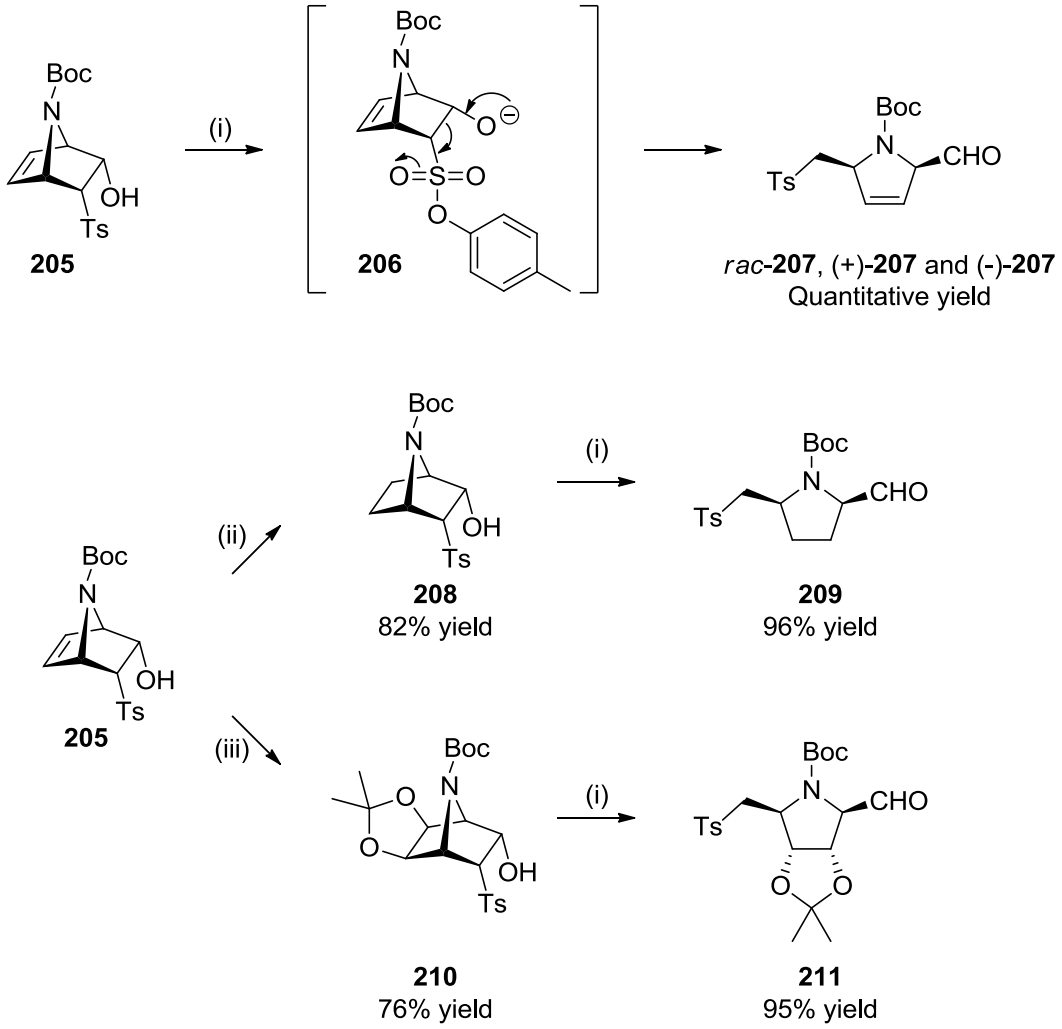
Gelmi and co-workers have developed a new synthetic approach to diastereomeric cyclopentene derivatives **203** and **204** arising from retro aldol reaction of functionalised spirocyclic norbornene derivatives *exo*-**198**. Spiro oxazolone *exo*-**198** was treated with the Lewis acid bis-(dibutylchlorotin)oxide 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 cyclopentane derivatives **203** and **204** could be accessed directly from spiro oxazolone *exo*-**199** via reflux in methanol with sodium carbonate.[56]



Reagents and conditions: (i) $Mg(ClO_4)_2$, CH_2Cl_2, 25 ˚C; (ii) EtOH, $(Bu_2ClSn)_2O$, reflux; (iii) EtOH, Na_2CO_3, reflux; (iv) MeOH, Na_2CO_3, 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]-aza-heptanes. 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 pyrollidine **207**, **209** and **211** in excellent yields. However, attempts to repeat this retro aldol reaction using O- and CH_2- 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]

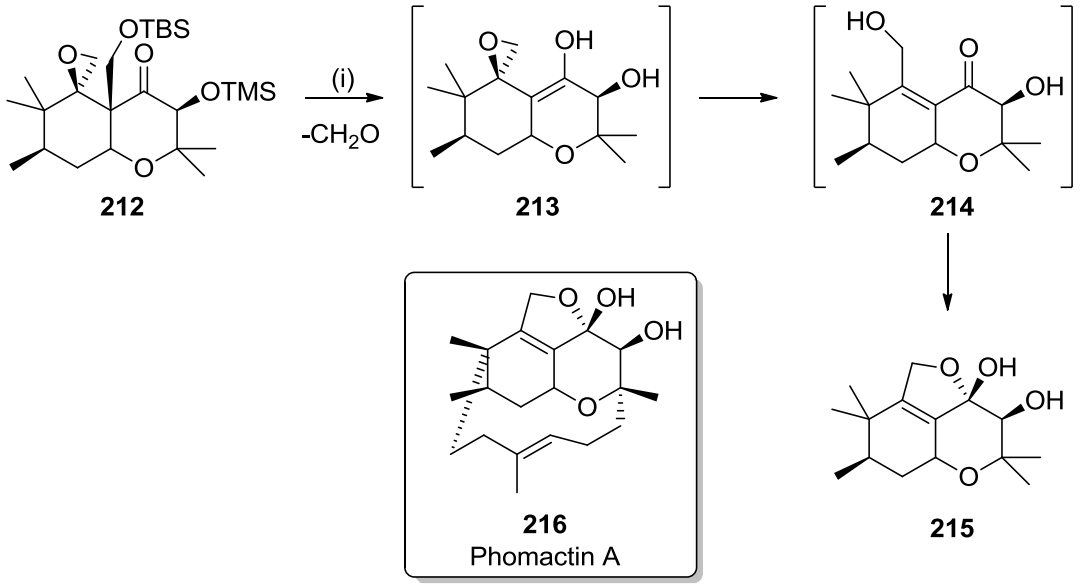


Reagents and conditions: (i) NaOMe (cat), MeOH, rt; (ii) H_2, Pd/C, MeOH; (iii) 1. OsO_4 (cat), NMO, acetone-H_2O (9:1); 2. 2,2-DMP, p-TSA, acetone.

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

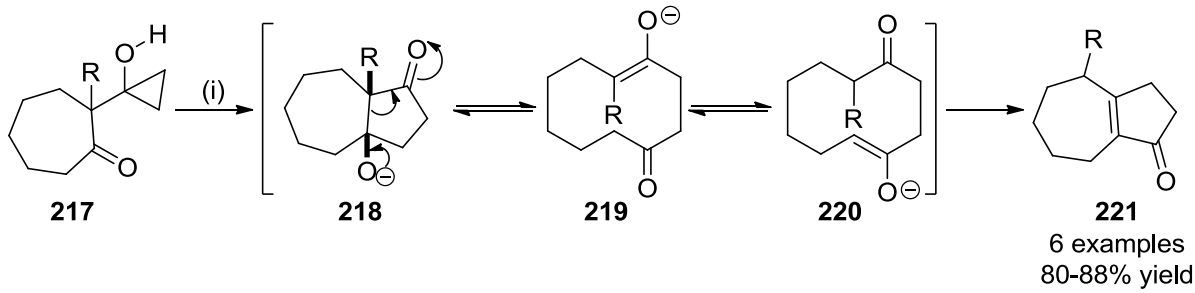
case, *O*-TBS deprotection of **212** triggers a retro aldol reaction that eliminates acetaldehyde to afford unstable epoxide **213** that is ring opened to generate the hemi-acetal functionality of **215**. This methodology was highly stereoselective, resulting in an impressive installation of three out of the five possible strereocentres required.[58]



Reagents and conditions: (i) TBAF.

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

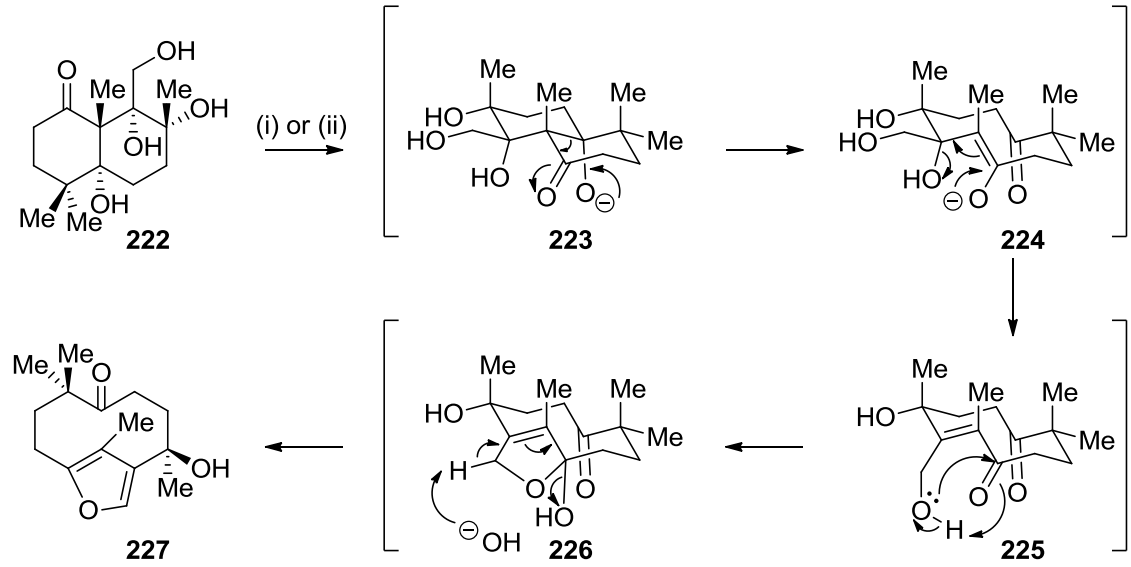
Helquist and co-workers reported the formation of γ-substituted conjugated hydrazulenones **221** via rearrangement reaction of cyclopropylcarbinol **217** to afford the unstable β-hydroxyketone **218**, which then undergoes a spontaneous retro aldol cleavage reaction to afford **220** followed by an 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]



Reagents and conditions: (i) NaH, Et_2O-hexane, 0 ˚C to rt.

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

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.[60]

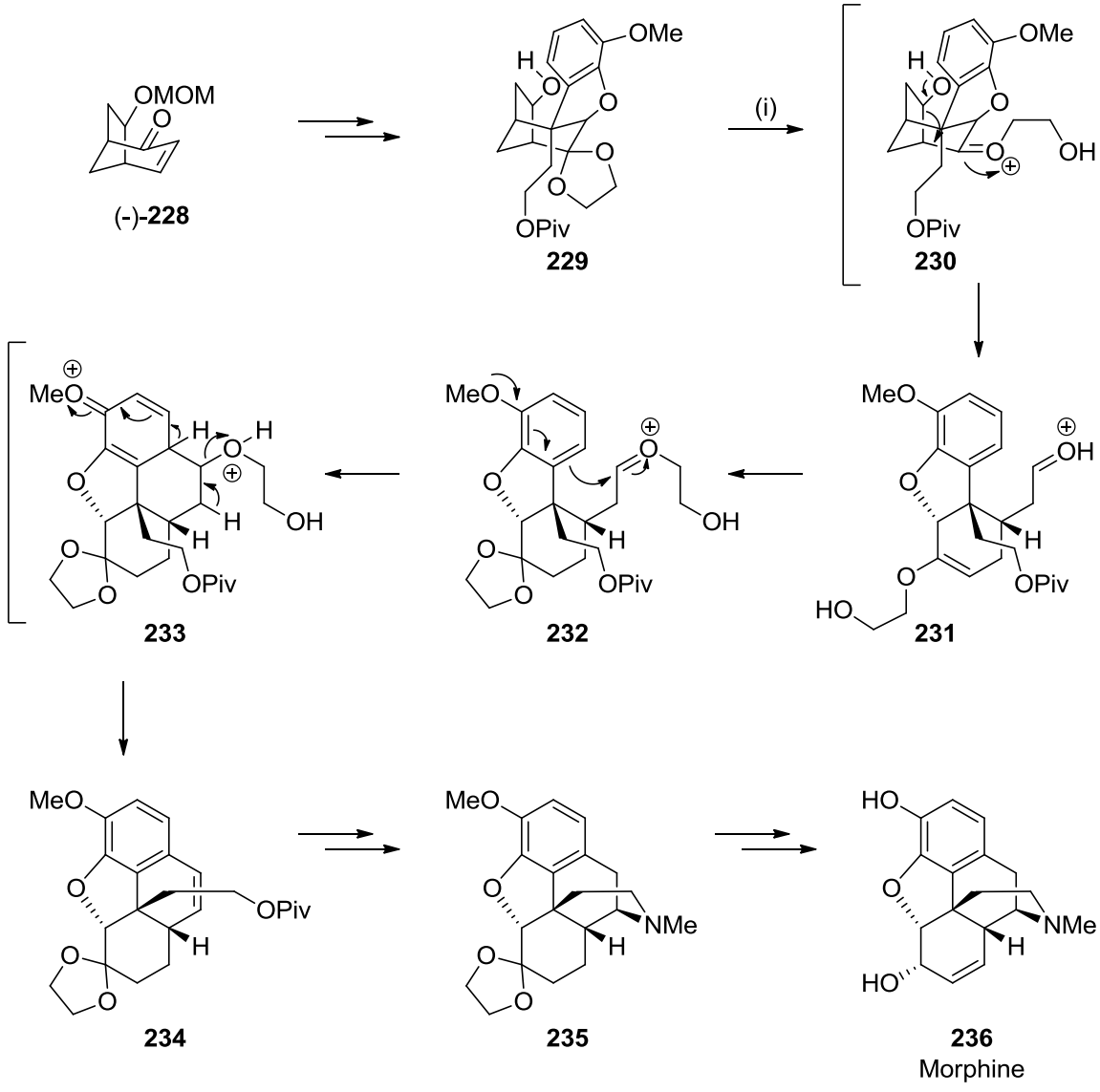


Reagents and conditions: (i) MsCl, DMAP, pyridine; (ii) TPAP, NMO, CH_2Cl_2.

Scheme 41 Unexpected formation of bridged bicyclic furan **227** from rearrangement of tetrahydroxydecalinone

1.7 Retro Aldol Reactions in Tricyclic Systems

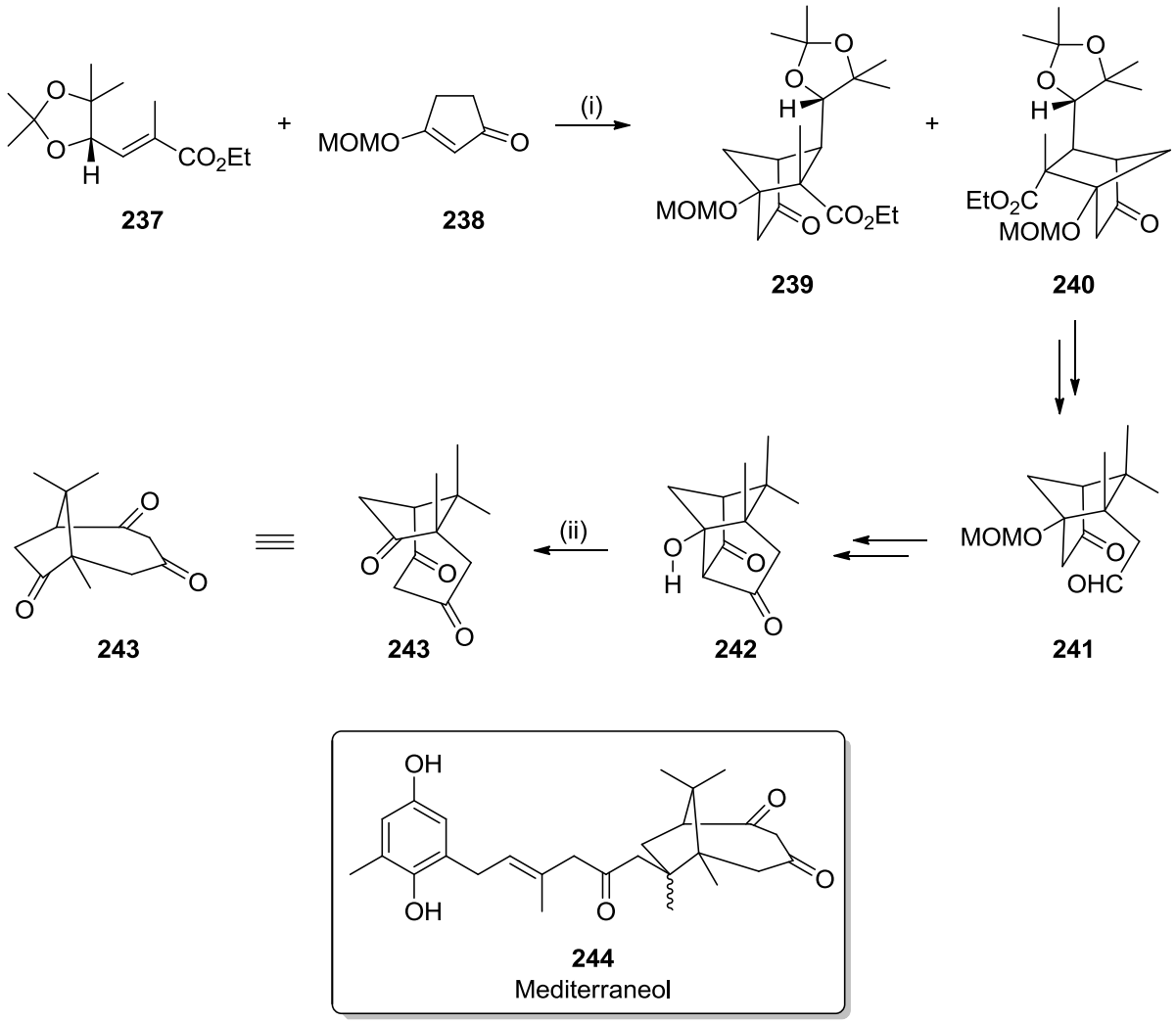
Ogasawara and co-workers have applied Yamada's retro aldol Friedal Crafts alkylation/dehydration/aromatisation methodology for the total synthesis of (-)-Morphine[61] as well as other natural products[62-65] containing hexahydrophenanthrene frameworks containing quaternary or tertiary benzylic stereocentres.



Reagents and conditions: (i) $(CH_2OH)_2$, p-TSA (cat), benzene, reflux.

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]

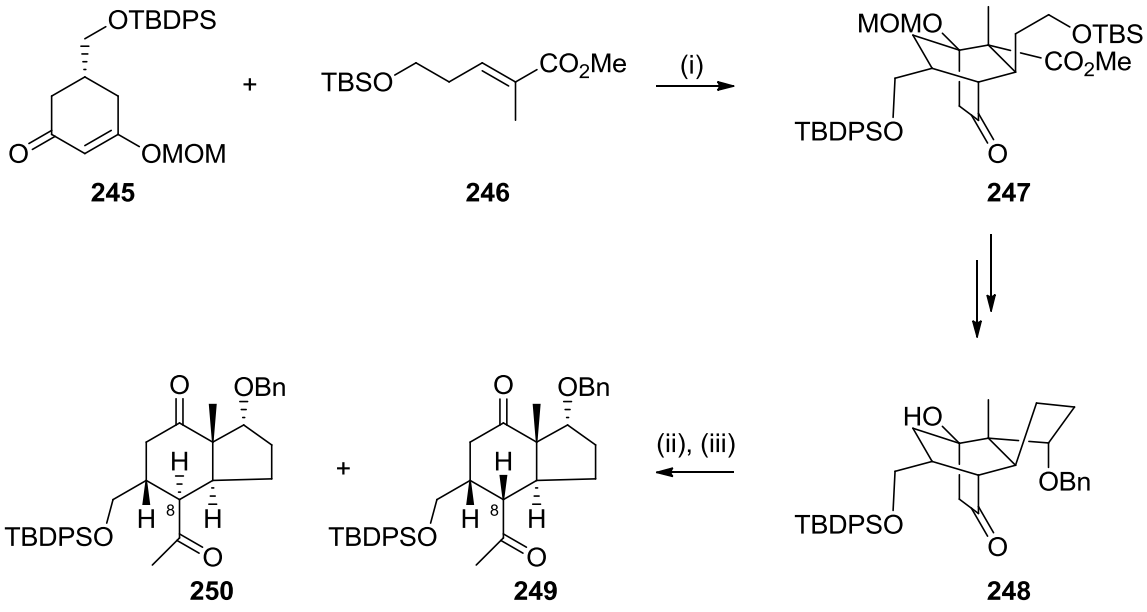


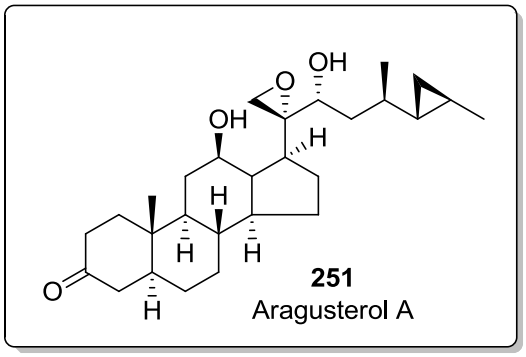
*Reagents and conditions: (i) LDA, THF, -78 ˚C then **238**; (ii) DBU, benzene, rt*.

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 $ZnCl_2$, NEt_3 and TMSCl, or NaH and 15-

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]

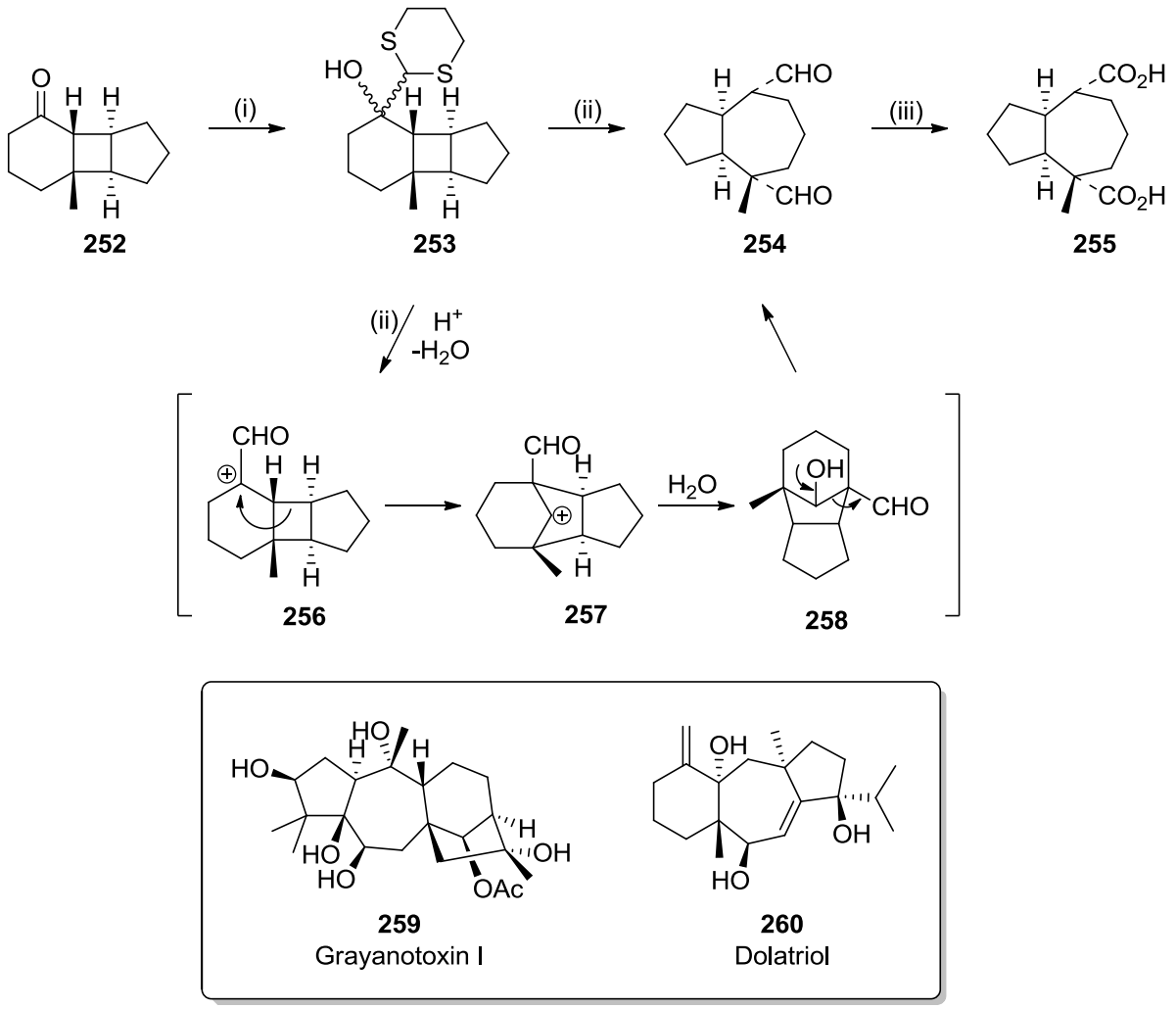




*Reagents and conditions: (i) LDA then **246**; (ii) TMSCl, $ZnCl_2$, NEt_3, 110 ˚C; (iii) AcOH-THF-H_2O (2:1:1)*.

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

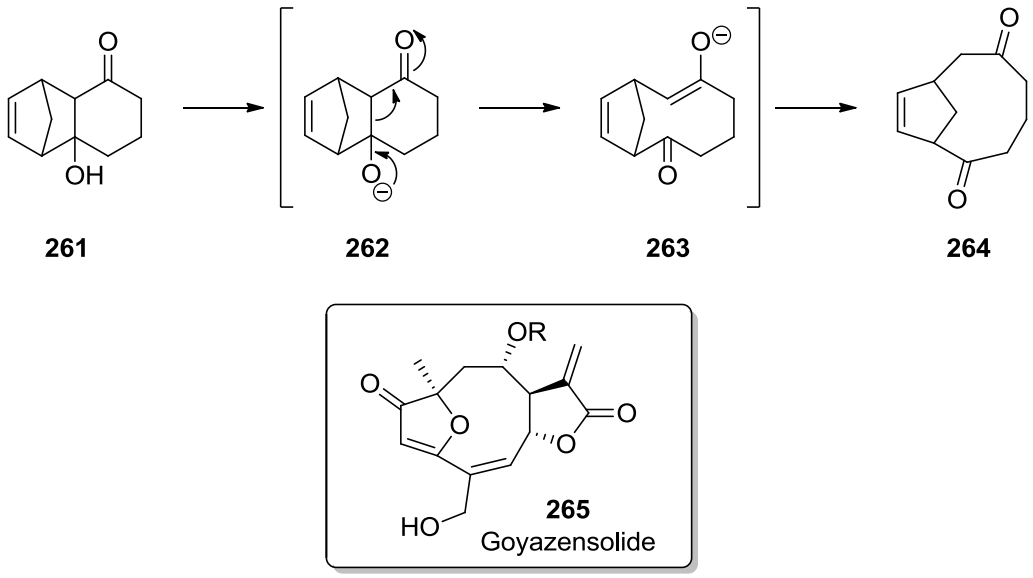
Ranu and co-workers demonstrated that acid catalysed rearrangements of α-hydroxycyclobutane derivatives **253** give transient cyclic β-hydroxyaldehydes **258** that undergo retro aldol cleavage to afford [5.3.0] ring systems **254** followed by subsequent Jones' oxidation to afford **255** in 77% yield. 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), HBF_4, THF; (iii) Jones' reagent.

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

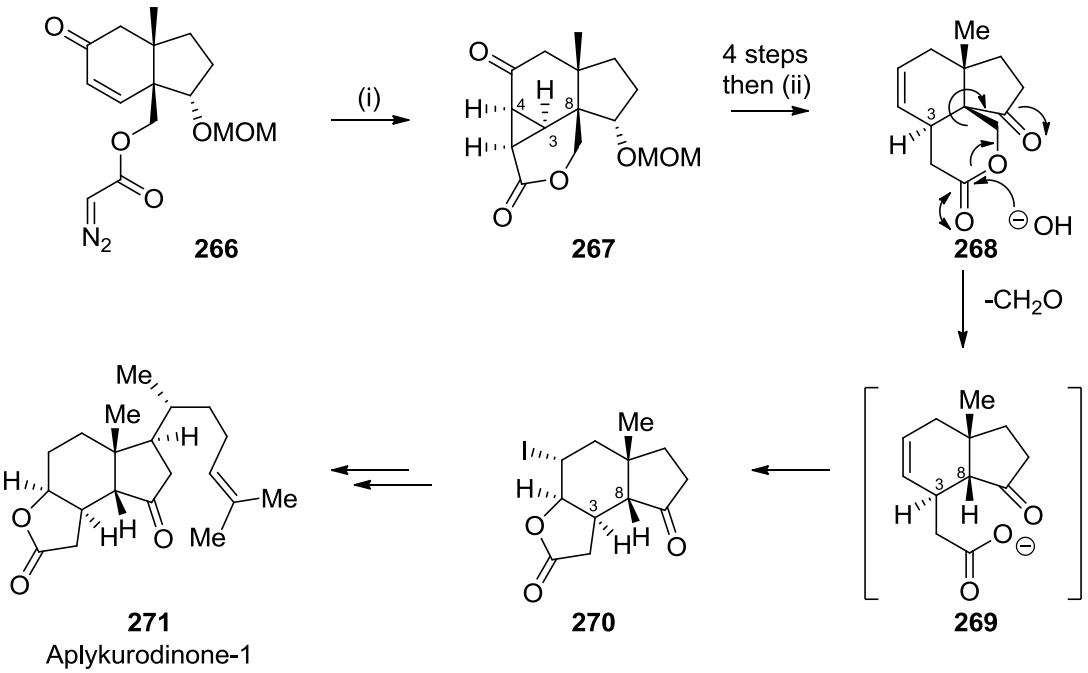
In 2000, da Silva and co-workers demonstrated the synthesis of bicyclo[6.2.1]undecane **264** from retro aldol reaction of the tricyclic intermediate **261**, which is the bicyclic core found in the furanoheliangolide class of sesquiterpene natural products such as Goyazensolide **265**. In this case,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



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

Scheme 46 Formation of the bicyclic core **264** of furanoheliangolide sesquiterpenes via retro aldol reaction of **261**

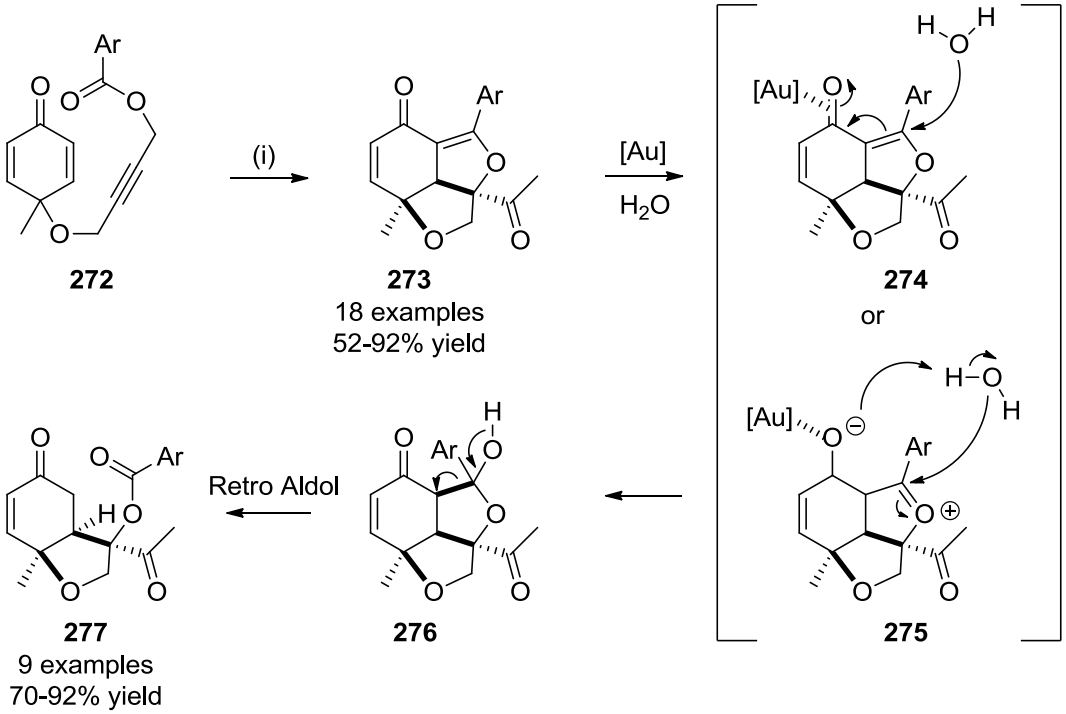
In 2010, Danishefsky and co-workers reported an elegant total synthesis of the steroidal natural product Aplykurodinone-1 **271**, involving a tandem hydrolysis/retro aldol/iodo-lactonisation sequence. They described this approach as a 'traceless stereochemical guide' that was used to secure the correct 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) Bis-(N-tert-butylsalicylaldiminato) copper(II), toluene, reflux; (ii) K_2CO_3, H_2O, 100 ˚C then NIS, CH_2Cl_2.

Scheme 47 Hydrolytic retro aldol reaction followed by iodolactonisation for the total synthesis of Aplykurodinone-1 **271**

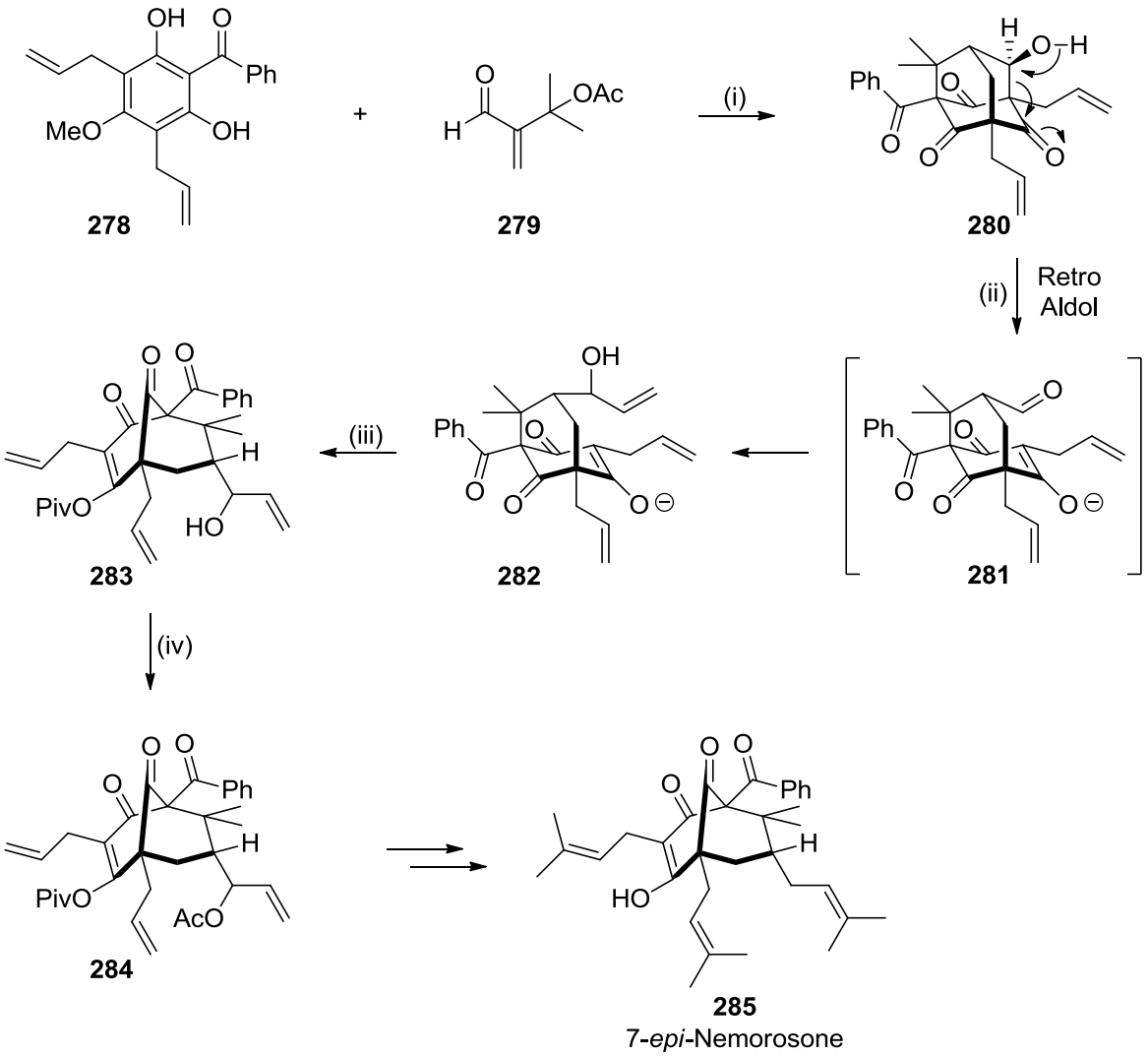
Wang and co-workers have developed a gold-catalysed cascade reaction of propargylic esters tethered to cyclohexadienones. Mechanistically, the proparglylic ester **272** undergoes a cascade of multiple bond rearrangement reactions to afford tricyclic ketone **273** in good yield. However, in the presence 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.[72]



Reagents and conditions: (i) [PPh_3AuCl]/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]

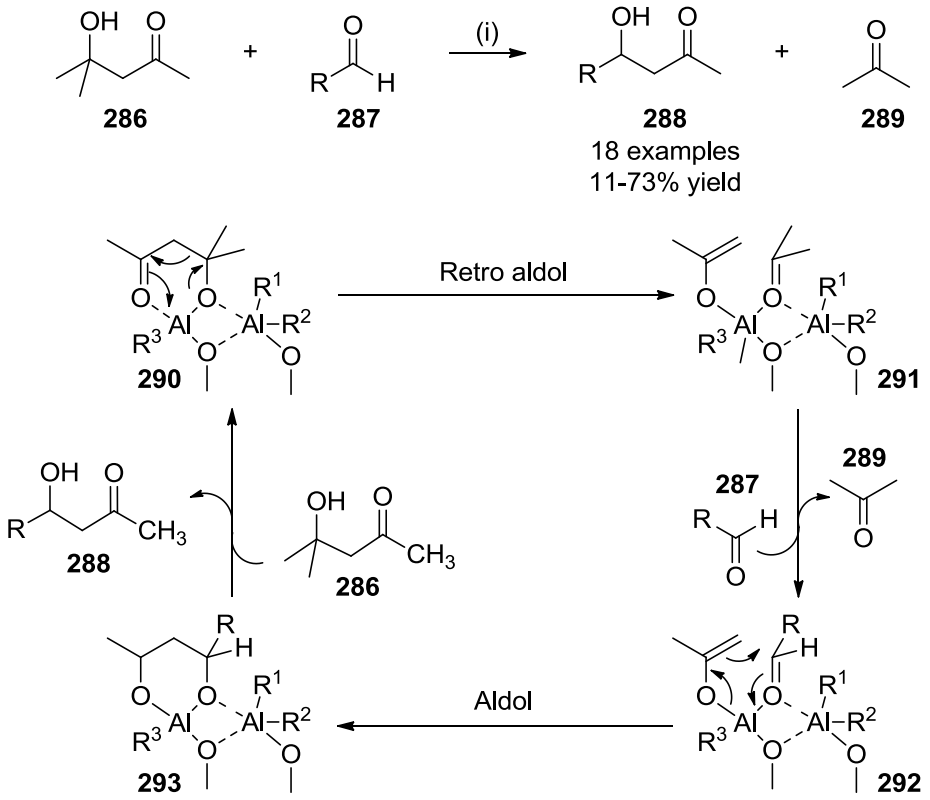


Reagents and conditions: (i) LiHMDS (2 equiv), THF, 0 ˚C to rt then conc. HCl (8 equiv), THF, 0 ˚C to rt; (ii) $CeCl_3$ (2.5 equiv), vinylmagnesium bromide (2.5 equiv), THF, -78 ˚C to -30 ˚C; (iii) Piv_2O/pyridine, DMAP (0.03 equiv), 0 ˚C to rt; (iv) DMAP, Ac_2O, NEt_3, CH_2Cl_2, 0 ˚C.

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]

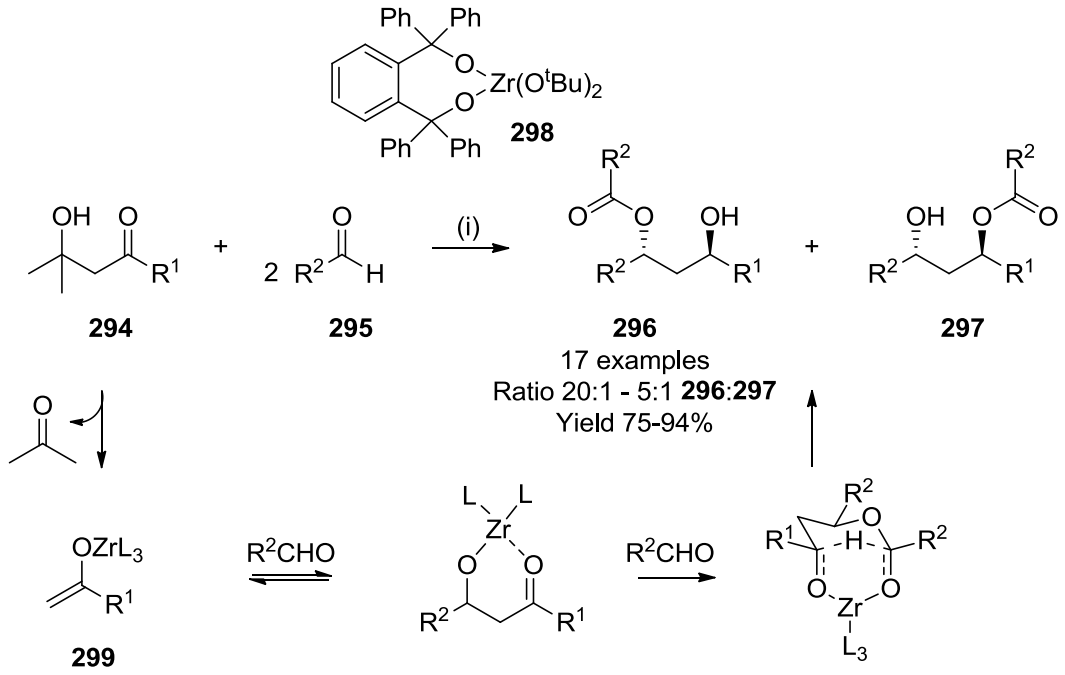


Reagents and conditions: (i) Al(III) catalyst (5-10 mol%), CH_2Cl_2, rt.

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

dichloromethane at 0 ˚C, which resulted in suppression of formation of any undesired acyl migration product **297**.[77-79]

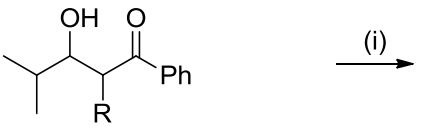


Reagents and conditions: (i) ***298*** *(10 mol%), CH_2Cl_2, 0 ˚C, 3 h.*

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

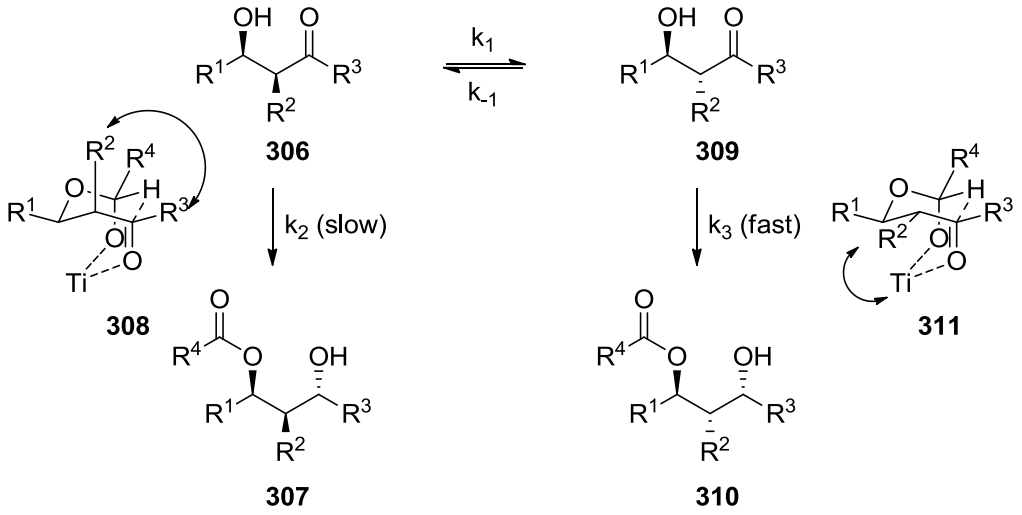
Mahrwald and co-workers also observed a retro aldol/aldol equilibrium during their investigations on a titanium catalysed aldol-Tishchenko reaction with enolizable aldehydes. They found that their reactions gave diol **304** regardless of whether the *syn*-aldol **300** or *anti*-aldol **301** diastereomers were used as a substrate. Treatment of *syn*- or *anti*-β-hydroxyketone **300**-**301** or **302**-**303** with (*R*)-BINOLTi(O^{t}Bu)$_2$/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, ^{i}Pr, the 1,3-diaxial interactions between R^2 and R^3 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]



Syn-**300** R=Et
Anti-**301** R=Et
Syn-**302** R=^{i}Pr
Anti-**303** R=^{i}Pr

304 R=Et, 53% yield 88%ee
304 R=Et, 54% yield 80% ee
305 R=^{i}Pr, 48% yield 83%ee
305 R=^{i}Pr 52% yield 81%ee

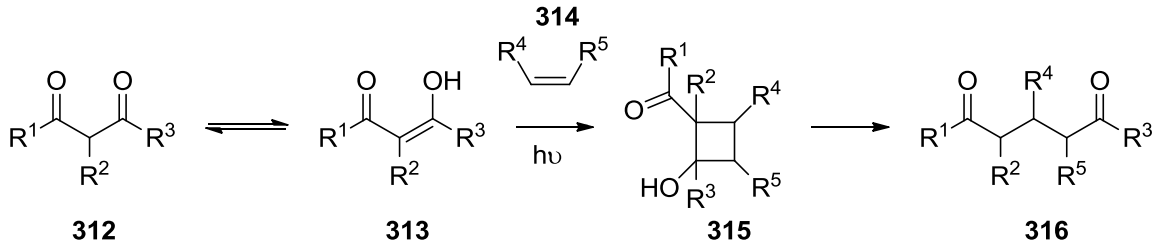


Reagents and conditions: (i) ^{i}Pr-CHO, (R)-BINOLTi($O^{t}Bu)_2$/cinchonine then OH^-.

Scheme 52 Retro aldol equilibrium for titanium catalysed asymmetric aldol-Tishchenko reaction

1.9 De Mayo Reactions

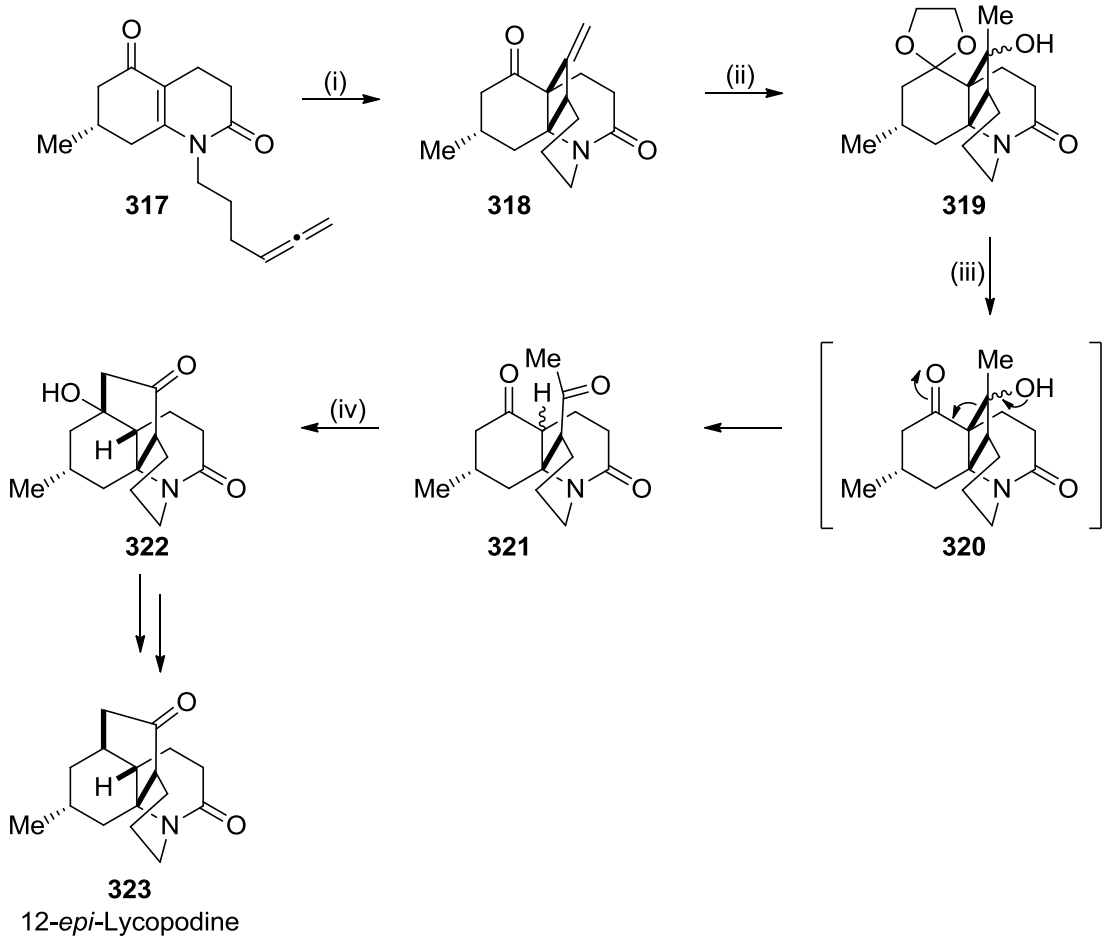
The de Mayo reaction was first demonstrated in 1971 by Paul de Mayo,[81] involving photochemical [2+2] cycloaddition between an enol **313** and an alkene **314**, to afford a cyclobutanol **315** which is often then followed by spontaneous retro aldol collapse to generate a 1,5-diketone **316**.[82]



Scheme 53 General de Mayo photocycloaddition followed by spontaneous retro aldol reaction

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.[82] 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.[83] Therefore, only selected highlights of this methodology with respect to retro aldol fragmentation are reviewed in this section.

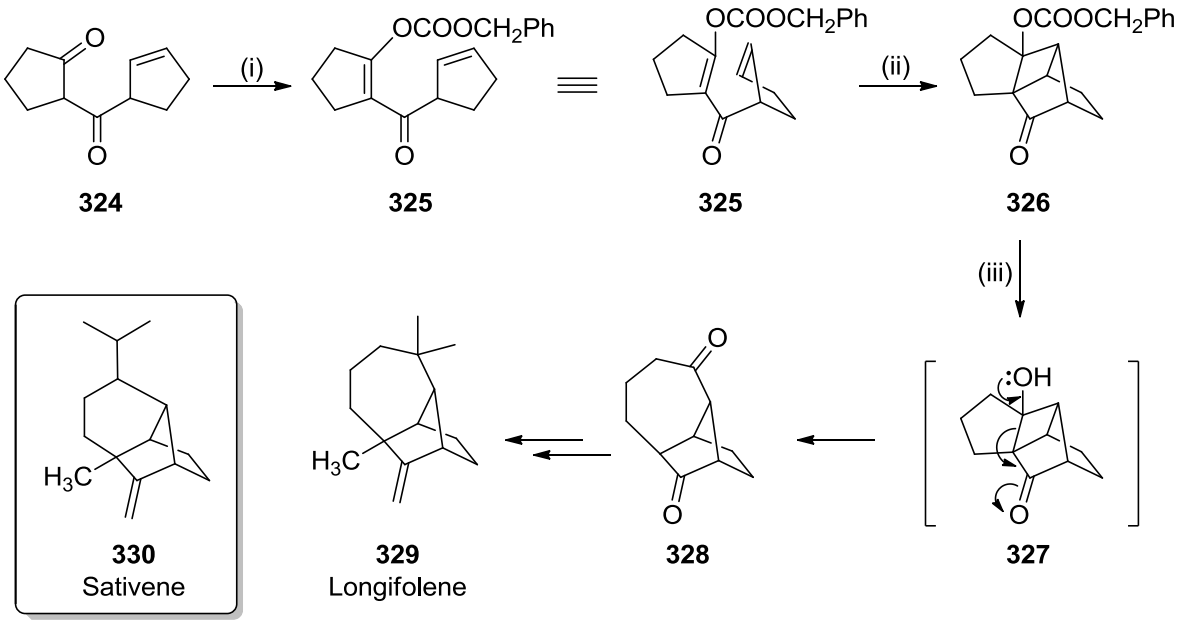
In 1967, Wiesner and co-workers used a modified de Mayo procedure in their total synthesis of 12-*epi*-lycopodine. Precursor **317** underwent intramolecular photocycloaddition to afford **318** in 70% yield. The ketone group was acetal protected, followed by epoxidation of the exocyclic alkene and subsequent 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**.[84-85]



Reagents and conditions: (i) hv, THF, -70 ˚C; (ii) 1. $(CH_2OH)_2$, 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_2O, 45 min; (iv) NaOH (0.6% in H_2O), MeOH, 36 h.

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

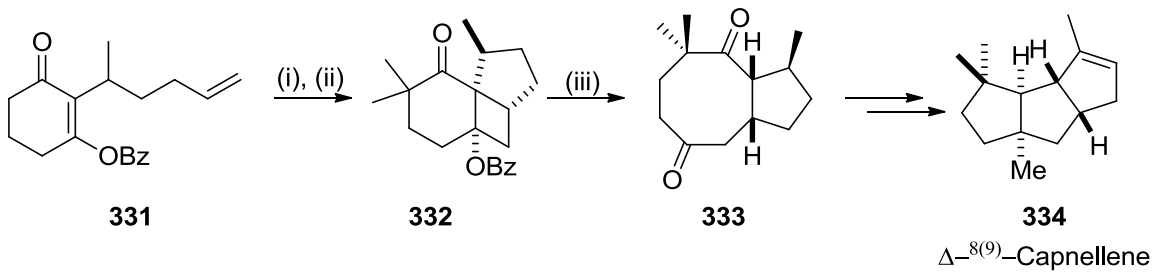
In 1978, Oppolzer and co-workers demonstrated a total synthesis of Longifolene **329** using a de Mayo fragmentation strategy. 1,3-Diketone **324** was converted into a benzyloxycarbonyl derivative **325**, which was then irradiated to trigger an intramolecular de Mayo reaction to afford **326** as a 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**.[86] This methodology was also employed in the total synthesis of Sativene **330**.[87]



Reagents and conditions: (i) Benzyloxychloroformate (2.7 equiv), pyridine, 5 ˚C, 8 h; (ii) hv, cyclohexane, pyrex, 15-30 ˚C; (iii) H_2 (3atm) Pd/C (10 mol%), HOAc, 25 ˚C.

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

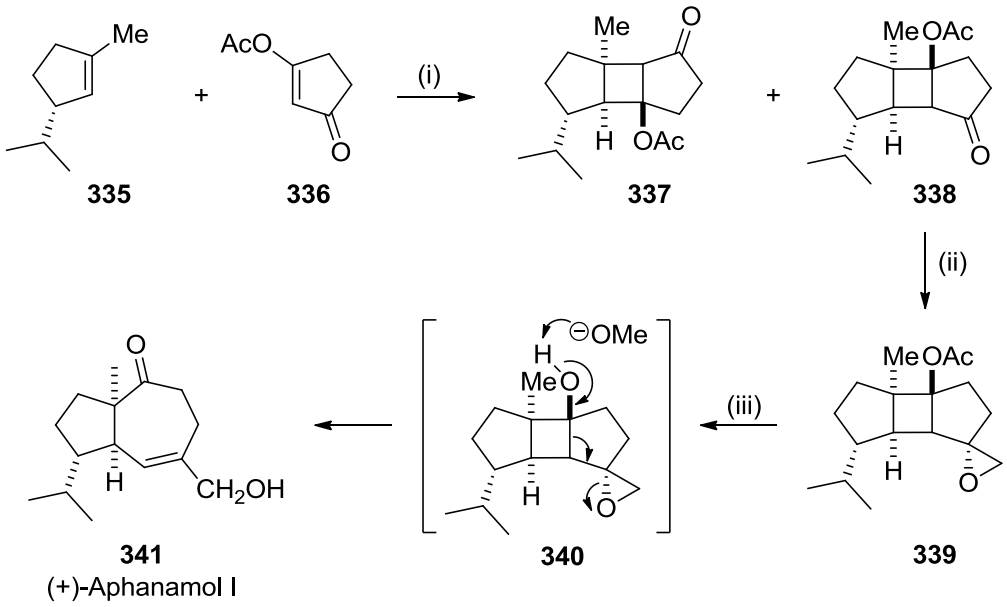
In 1983, Pattenden and co-workers reported a total synthesis of Δ-$^{8(9)}$-Capnellene **334** using a de Mayo reaction. The precursor **331** was irradiated to afford a tricyclic adduct, which was then bis-alkylated via treatment with LiHMDS and methyl iodide to afford geminal dimethyl adduct **332**. 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**.[88]



Reagents and conditions: (i) hv, hexane, 6 h, rt; (ii) LiHMDS, MeI, THF, -70 ˚C, 3.5 h; (iii) KOH, DMSO-H_2O.

Scheme 56 Total synthesis of Δ-$^{8(9)}$-Capnellene **334** using de Mayo strategy

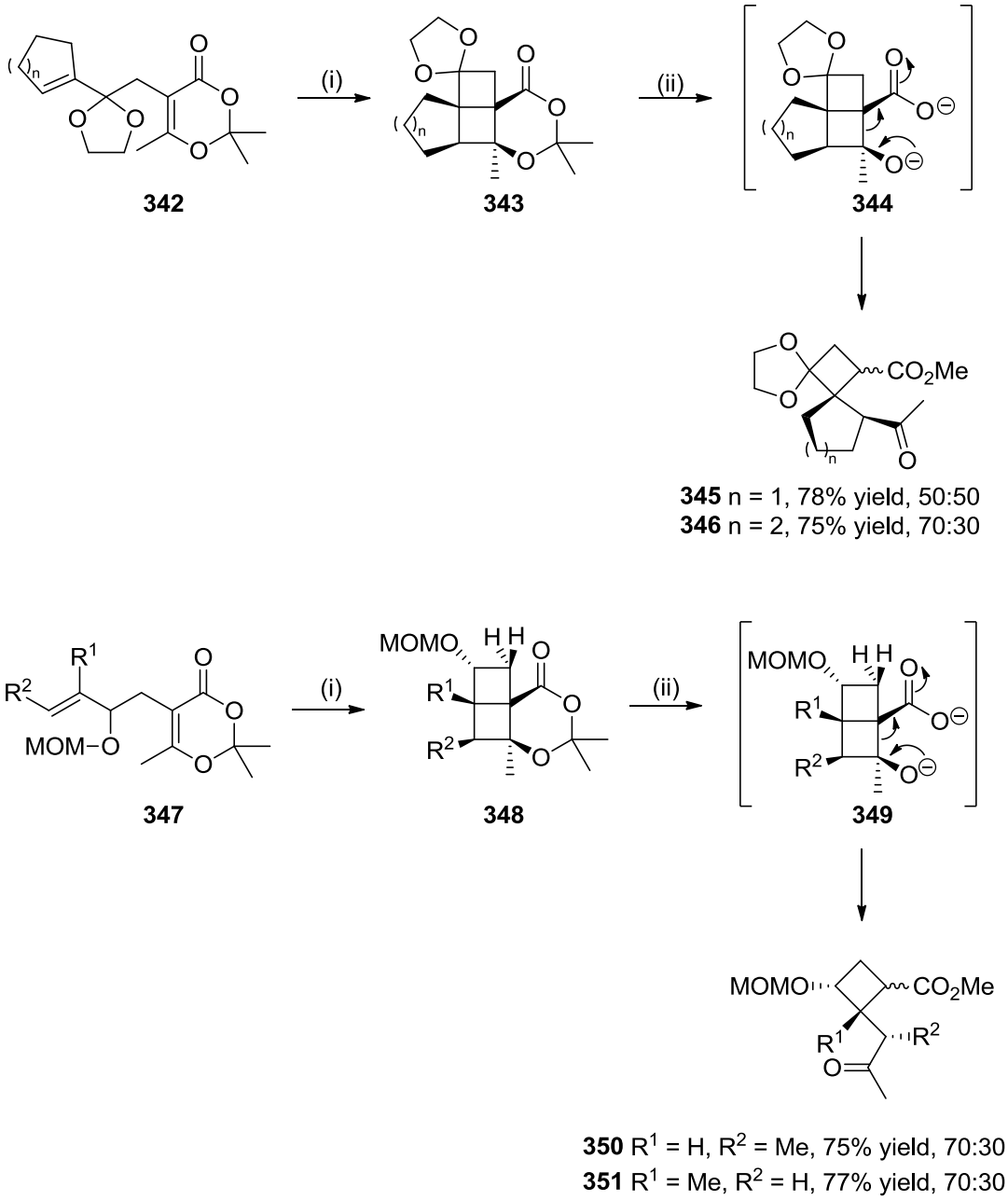
In 1992, Wickberg and co-workers utilised a de Mayo strategy in their total synthesis of (+)-Aphanamol I **341**. Photoaddition of alkene **335** to α,β-unsaturated ketone **336** produced a mixture of regioisomers **337** and **338** in 20% and 23% yield respectively. Treatment of **338** with dimethyloxosulfonium 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.[89] This type of ring expansion methodology has also been demonstrated by Weedon and co-workers in their total synthesis of Hirsutene.[90]



Reagents and conditions: (i) hv, MeCN, 12 h; (ii) $Me_2S(O)=CH_2$, THF, 3.5 h; (iii) LiOMe, MeOH, reflux, 1 h.

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]

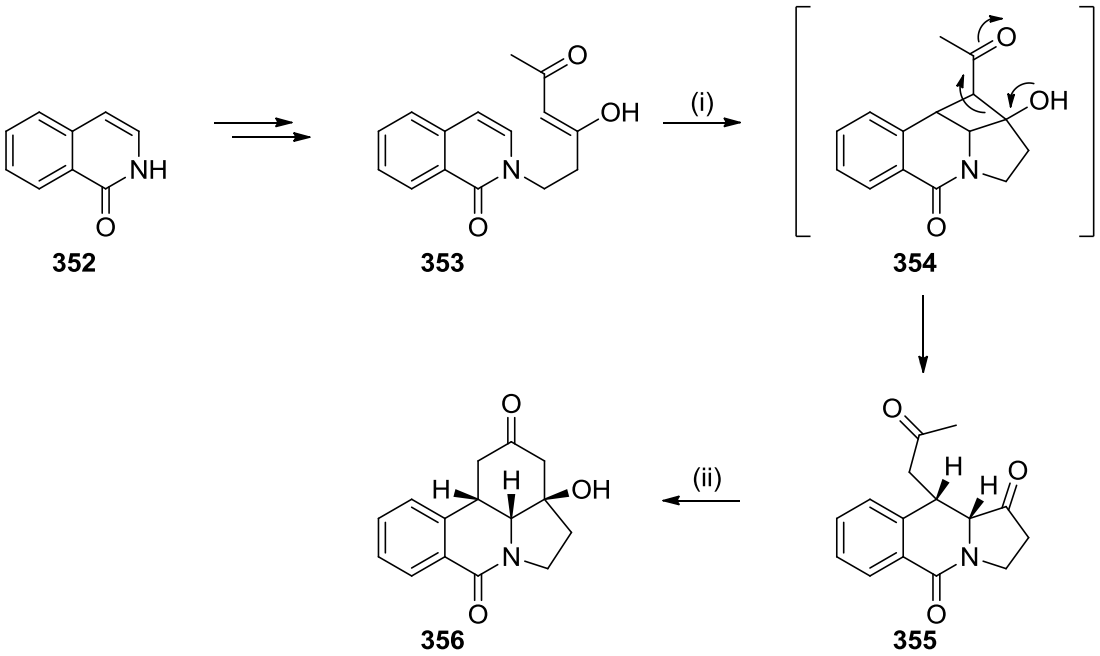


Reagents and conditions: (i) hν, MeCN/acetone; (ii) KOH, dioxane/H_2O; CH_2N_2, MeOH.

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**,

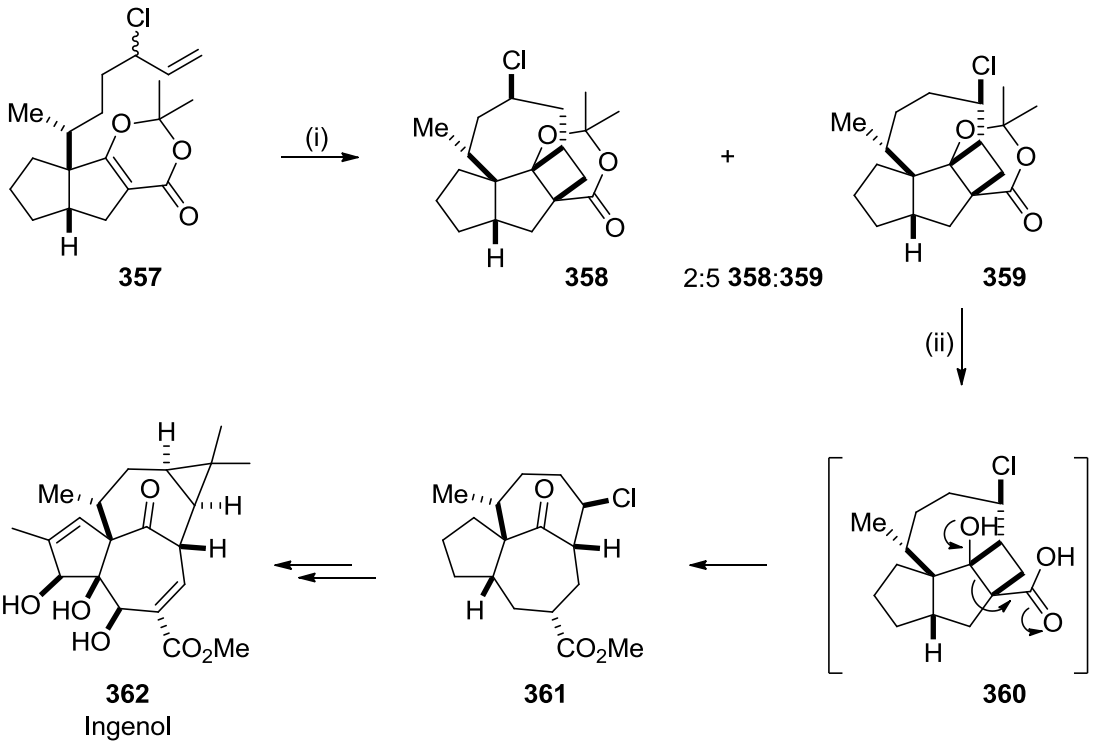
which underwent a subsequent retro aldol sequence to afford **355** as a single product in 70% yield. Treatment of **355** with piperidine then initiated a base catalysed aldol reaction to afford the desired tetracycle skeleton of **356** in 78% yield.[92]



Reagents and conditions: (i) hv, 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_2CO_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]



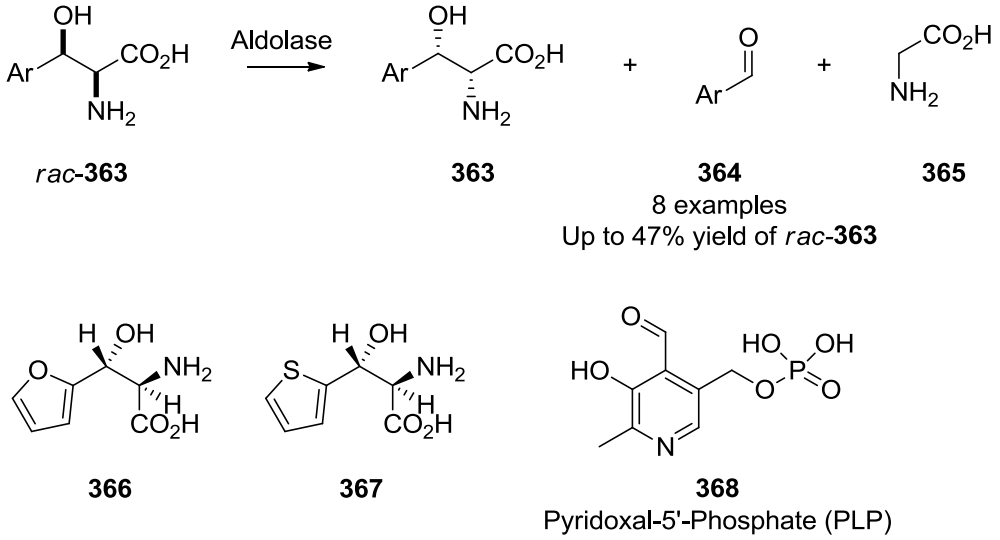
Reagents and conditions: (i) hv (pyrex); (ii) K_2CO_3, MeOH.

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

1.10 Aldolase Enzymes

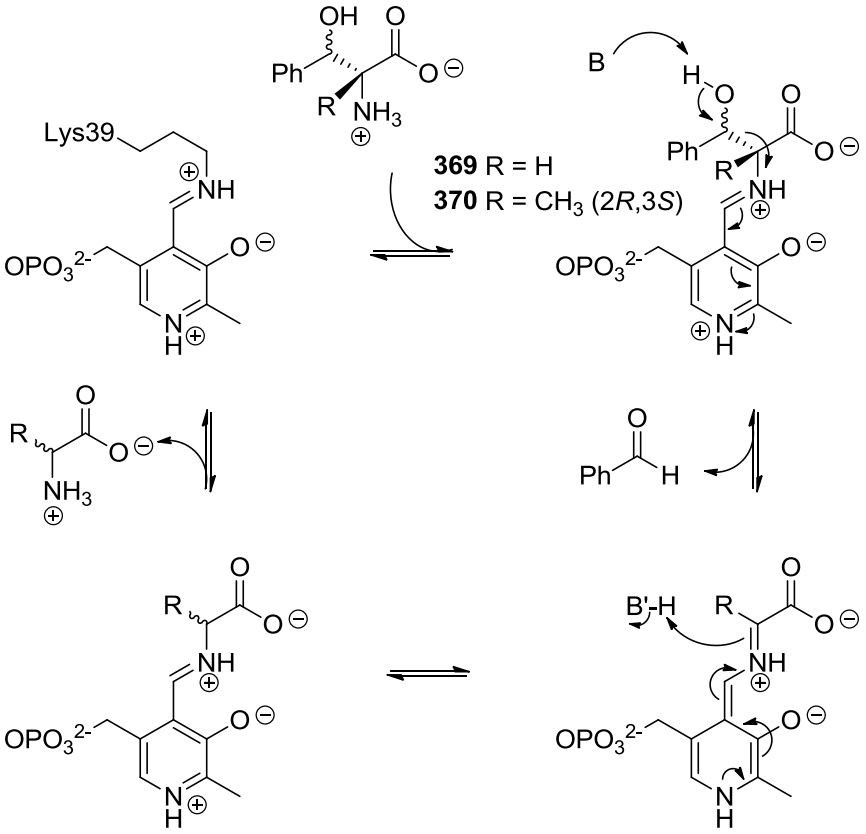
Aldolase enzymes are capable of catalysing both the aldol reaction and its reverse process with good substrate specificity and in high stereoselectivity.[96] Aldolase enzymes are divided into two main classes according to the mechanism by which they operate. Class I aldolases utilise lysine residues 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 (2*S*,3*R*) 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) **368** 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 (2*S*,3*R*)-aromatic amino acids including (2*R*,3*R*)-3-(2-furyl)serine **366** and (2*R*,3*R*)-3-(2-thienyl)serine **367**, in good yield and above 95% ee.[100]



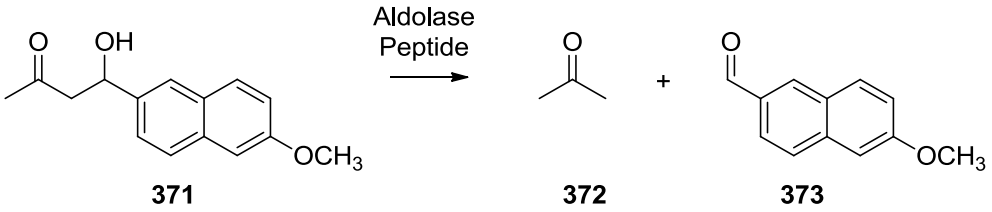
Scheme 61 Enzymatic resolution of *rac*-arylserine **363** catalysed by Streptomyces aldolase

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 *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 α-substituted β-phenylserine **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.[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 α-carbon configuration but low selectivity at the β-carbon of α-substituted β-phenylserine **370**.[102]



Scheme 62 Mechanism of alrY265A catalysed retro aldol for α-substituted β-phenyl serine **369** and **370**

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]



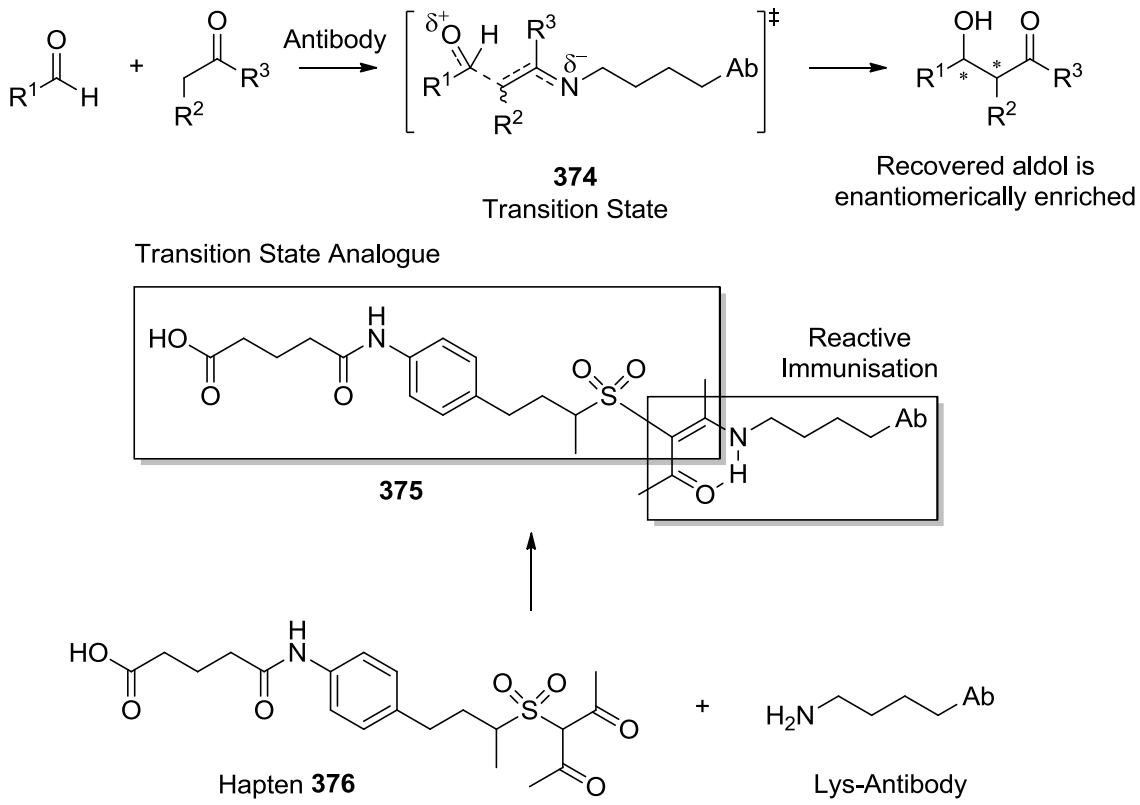
371 **372** **373**

Scheme 63 Retro aldol reaction catalysed by small designer retro aldolase peptides

1.11 Aldolase Antibodies

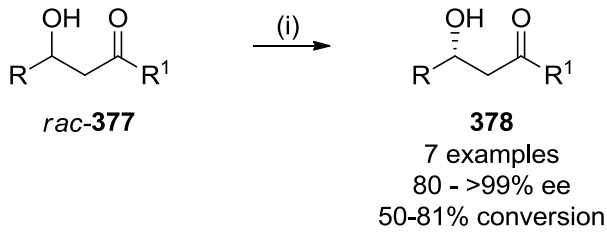
Antibodies that catalyse enantioselective retro aldol reactions have received a large amount of attention in recent years. These antibodies are generated by reactive immunisation and generally have a much broader substrate scope than aldolase enzymes.[104] Mechanistically, the retro aldol reaction proceeds through an enamine mechanism[105] catalysed by an uncharged ε-amino group of a reactive lysine residue in the active site, similar to the catalytic cycle observed for natural class I aldolases.[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.[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.[110-112] Therefore, only selected highlights will be included in this section.

Reactive immunisation[113] is a process whereby mice are exposed to a hapten, a molecule specifically designed to resemble the transition state of a chemical reaction.[114] In the case of aldolase antibodies, the hapten is usually a 1,3-diketones[115] or contains a phosphinate residue.[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.[106] The antibodies are then isolated from the immunised mice and purified for use in synthetic reactions.[113] For example, in 1999 Barbas III, Lerner and co-workers designed a β-diketo sulphone hapten **376** for the generation of new aldolase antibodies. The tetrahedral geometry of the sulphone unit mimics the transition state **374** of the carbon-carbon bond formation in the aldol reaction.[114]



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

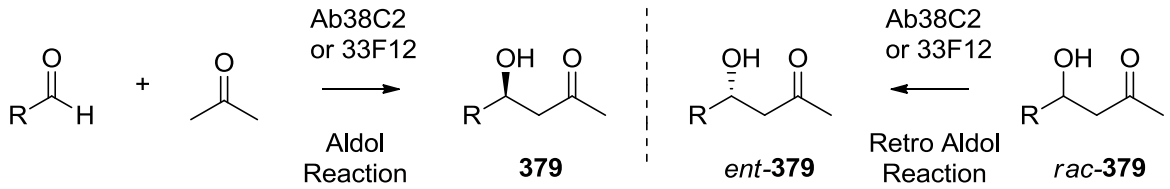
In 1998, Barbas III, Lerner and co-workers employed a catalytic antibody to mediate kinetic resolution of simple β-hydroxyketones using an enantioselective retro aldol reaction, with these reactions reaching ~50% conversion after four hours, and the unreacted aldol being recovered in high enantiomeric excess.[117]



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

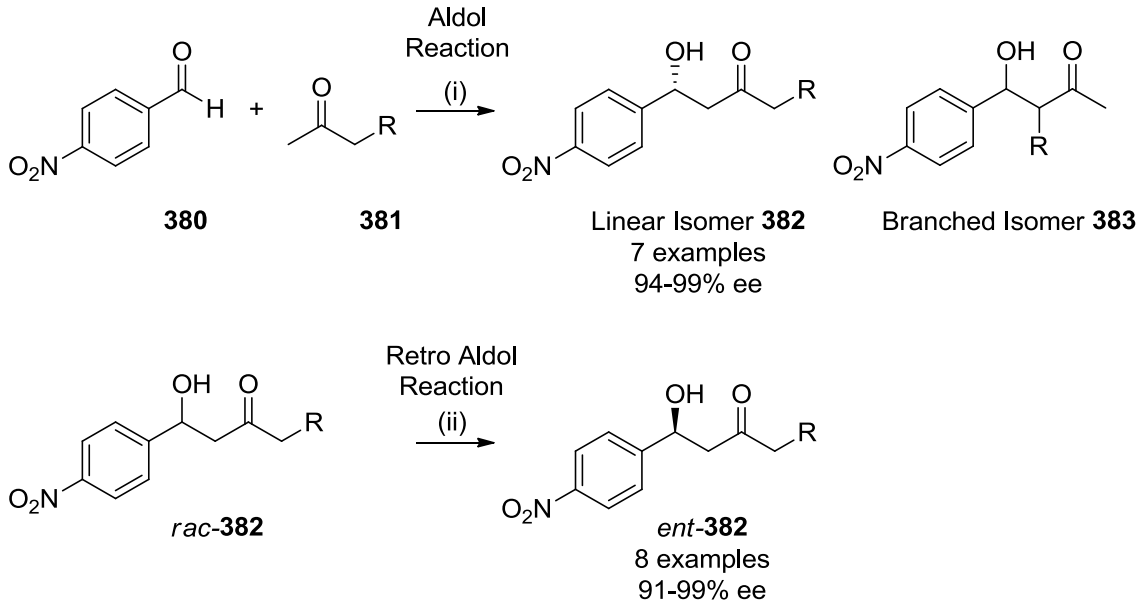
Scheme 65 Kinetic resolution of β-hydroxyketones using antibody 38C2

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.[117]



Scheme 66 Preparation of both enantiomers of aldol **379** using a single antibody

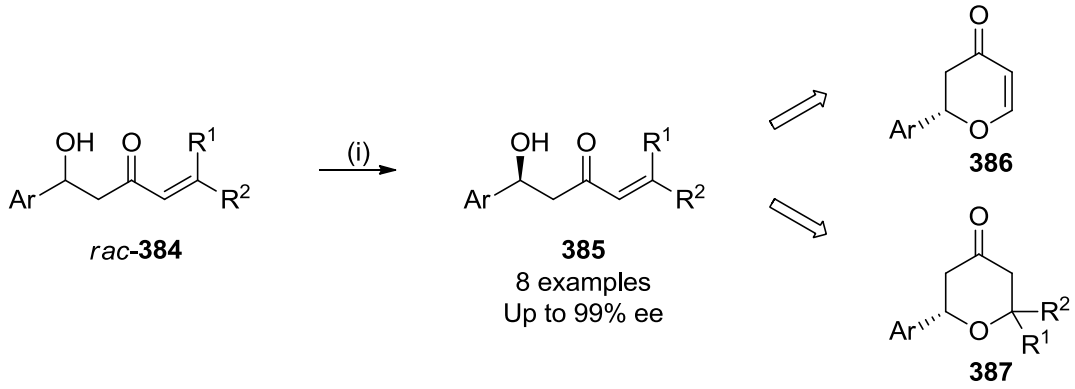
Gouverneur and co-workers have demonstrated an unusual reversal of regioselectivity in aldolase antibody mediated aldol and retro reactions using unsymmetrical methyl ketones **381** as enolate partners. In the uncatalysed aldol addition of methyl ketone **381** with *para*-nitrobenzaldehyde **380**, a branched regioisomer **383** is produced. However, when aldolase antibody 84G3 is employed the linear regioisomer **382** is favoured, with carbon-carbon bond formation taking place on the least substituted carbon, even when α-heteroatoms were present, thus showing that the antibody could differentiate between the reactive sites of an unsymmetrical methyl ketone **381**. Both aldol enantiomers **382** could be selectively accessed by carrying out either aldol or retro aldol reactions with antibody 84G3 in good conversions and excellent enantioselectivity.[118-119]



Reagents and conditions: (i) Antibody 84G3 (25 mol%), PBS, pH 7.4, 0 ˚C; (ii) Antibody 84G3 (4 mol%), PBS, pH 7.4.

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

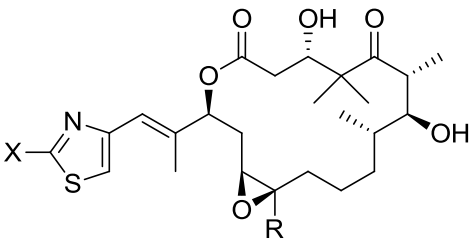
Gouverneur and co-workers have also demonstrated kinetic resolution of β-hydroxyenones **384** using aldolase antibodies in a novel approach to the synthesis of formal hetero Diels-Alder adducts. The resolution process led to highly enantiomerically enriched α,β-unsaturated methyl ketones **385** in 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 R^2 substituents, which limited the overall scope of the strategy.[120]



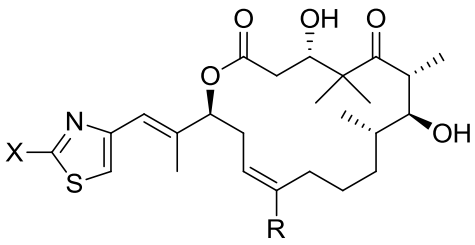
Reagents and conditions: (i) Antibody 84G3 or 93F3 (4-10 mol%), 9:1 PBS:MeCN, pH 7.4, rt

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]



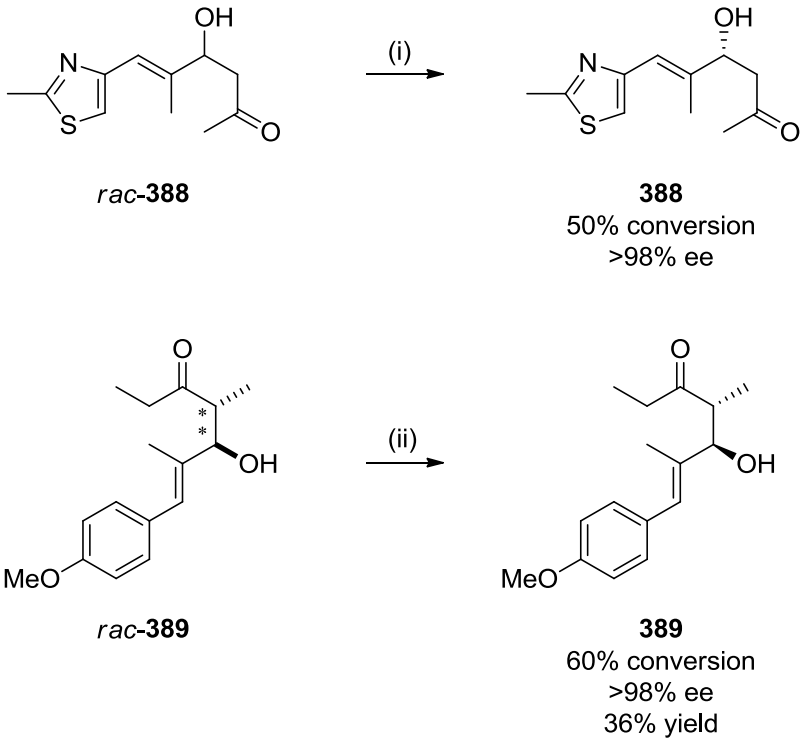
Epothilone A, R = H, X = Me
Epothilone B, R = Me, X = Me
Epothilone E, R = H, X = CH_2OH
Epothilone F, R = Me, X = CH_2OH



Epothilone C, R = H, X = Me
Epothilone D, R = Me, X = Me
Deoxyepothilone E, R = H, X = CH_2OH
Deoxyepothilone F, R = Me, X = CH_2OH

Figure 2 Structures of Epothilone A-F

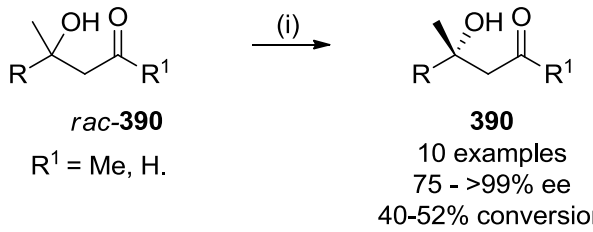
Two key precursors were synthesised via kinetic resolution of racemic β-hydroxy ketones *rac*-**389** and *rac*-**390**, using antibodies generated against a β-diketone hapten via reactive immunisation. The best results were obtained for kinetic resolution of *rac*-thiazole aldol **388** using antibody 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]



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**

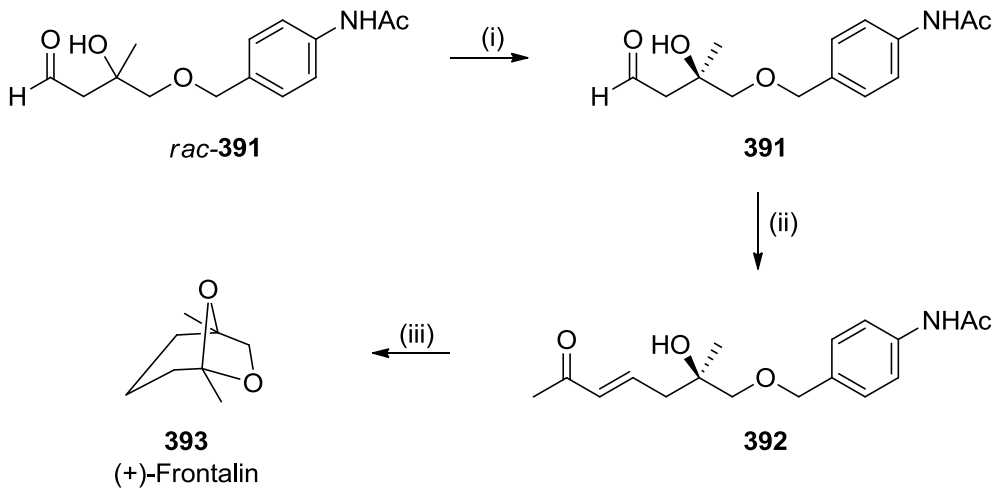
Barbas III, Lerner and co-workers also reported kinetic resolution of tertiary β-hydroxy ketones *rac*-**390** with catalytic antibodies, providing a route to ketol products containing hydroxyl substituted quaternary β-stereocentres. These kinetic resolutions did not proceed past 50% conversion, suggesting that they are highly enantioselective, with the majority of aldol products being obtained in excellent enantioelectivities.[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[124] and for the total synthesis of a series of Brevicomin natural products with a related bicyclic skeleton to (+)-Frontalin **393**.[125]



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

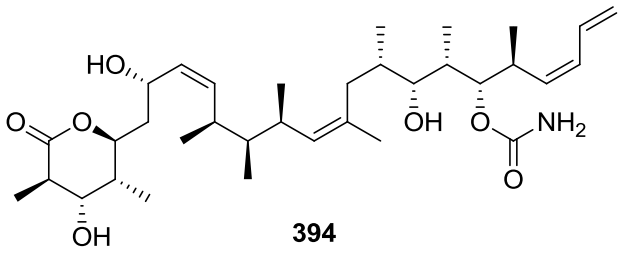
In summary, it is hoped that this review has demonstrated that the retro aldol reaction can be extremely useful for many synthetic applications. This reversible process can potentially be utilised to unmask useful aldehyde and enolate functionality, which can then be elaborated further to afford synthetically 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

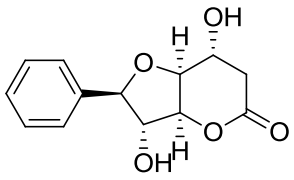
Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocentres

2.1 Introduction

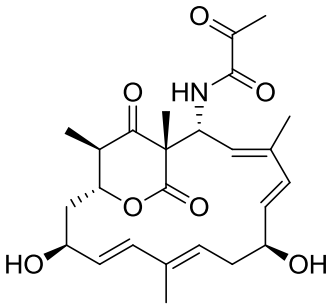
Substituted δ-lactones are exceptionally widespread in Nature and have a broad range of applications.[126] The δ-lactone motif is found in many natural products isolated from fungi and marine organisms, where they often form parts of attractants and pheromones.[127] δ-Lactones are also shunt metabolites of prematurely terminated polyketide syntheses.[128] δ-Lactones display a broad range of potent pharmacological activities including antitumour,[129] antimicrobial,[130] and immunosuppressive activity.[131] For example, the polyketide (+)-Discodermolide **394** is an inhibitor of tumour cell growth,[132] (-)-Goniofupyrone **395** is cytotoxic against human tumours[133] and the macrocycle Lankacidin C **396** is an antibiotic and antitumour agent.[134] 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*.[135]



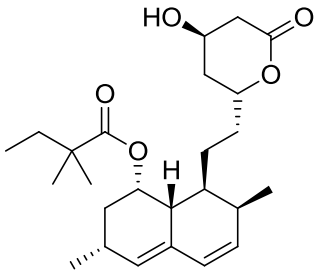
394
(+)-Discodermolide



395
(-)-Goniofupyrone



396
Lankacidin C



397
Zocor (Simvastatin)

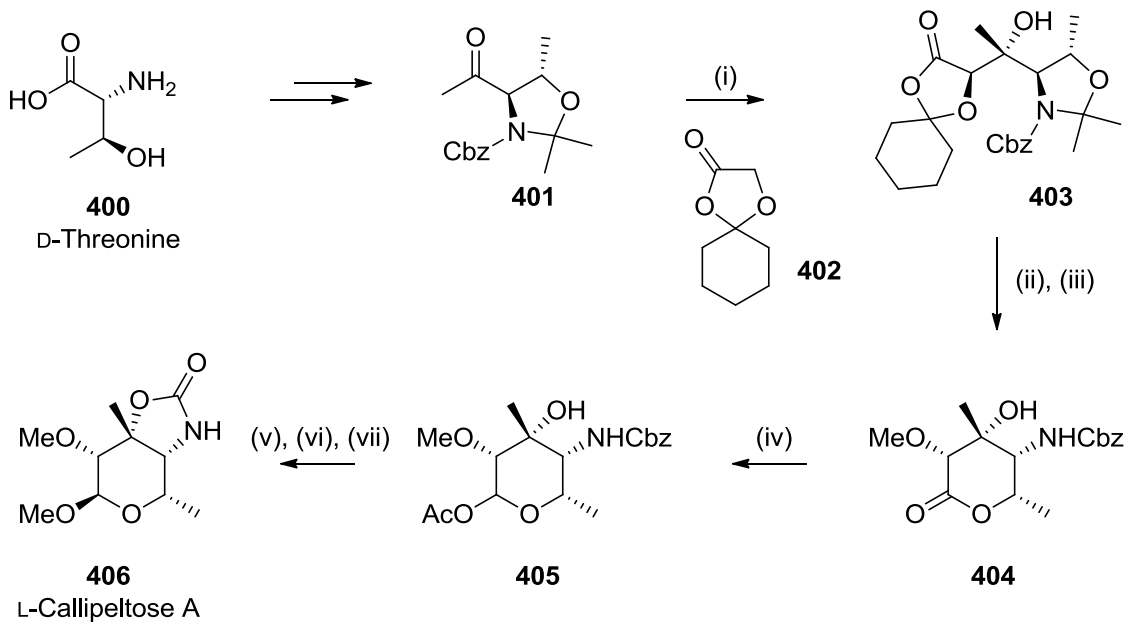
Figure 3 Examples of biologically active δ-lactones found in natural products

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.

398 **399**

Figure 4 δ-Lactone natural products found in food

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 D-threonine **400** to afford *N*-Cbz-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]



*Reagents and conditions: (i) LDA, then **402**; (ii) AcOH, H_2O; (iii) $Me_3O.BF_3$, 2,6-di-tert-butyl-4-methylpyridine; (iv) DIBAL then Ac_2O, pyridine, DMAP; (v) NaH, THF; (vi) DBU, Cl_3CCN; (vii) MeOH, TMS-OTf, CH_2Cl_2.*

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

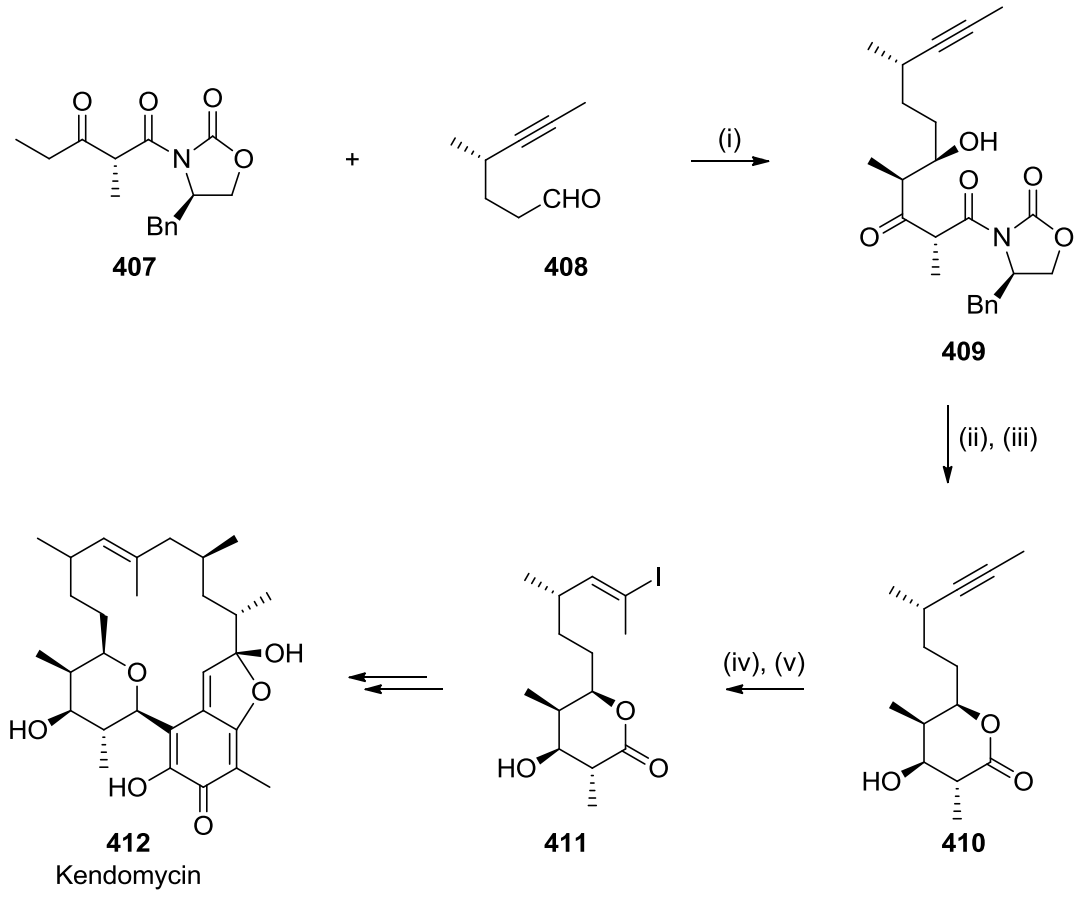
2.2 Synthesis of δ-Lactones with Multiple Contiguous Stereocentres

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.[139-142] Furthermore, highly substituted δ-lactones can perform as useful building blocks in the synthesis of polyketide natural products containing stereotetrads.[143] Many strategies have been developed for the synthesis of precursors containing four or more contiguous stereocentres for natural product synthesis.[144-146]

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),[147-149] or the electrophile (using enantiopure aldehydes).[128,140,150-152]

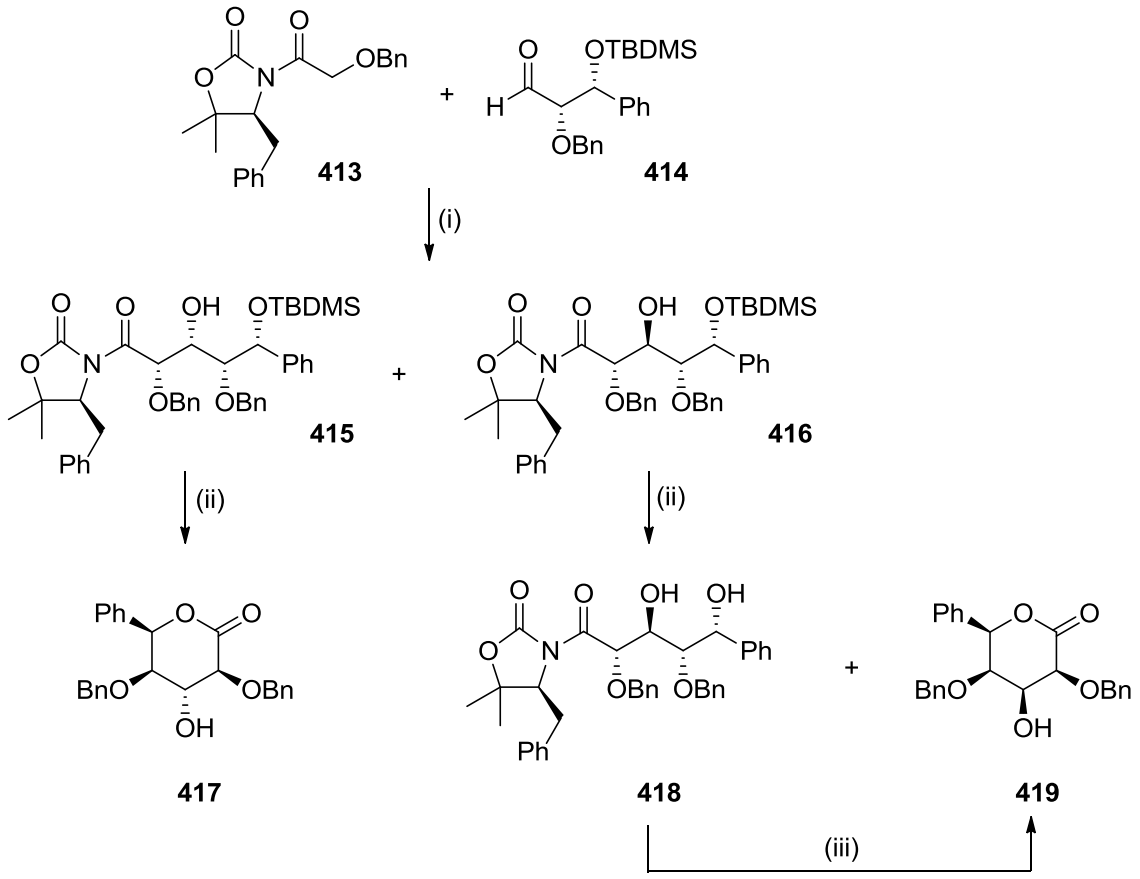
For example, Lee and co-workers employed β-keto-*N*-acyl-oxazolidin-2-one **407** in a tin promoted Evans' aldol reaction with aldehyde **408** to afford aldol **409** in 82% yield. This subsequently underwent a reduction-lactonisation sequence to afford highly substituted δ-lactone **410**, which was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



Reagents and conditions: (i) $Sn(OTf)_2$, NEt_3, CH_2Cl_2, -78 ˚C; (ii) $NaBH(OAc)_3$, AcOH, 5 ˚C; (iii) DBU, CH_2Cl_2; (iv) $Pd(OAc)_2$, PCy_3, n-Bu_3SnH, Hexane-THF; (v) I_2, CH_2Cl_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]

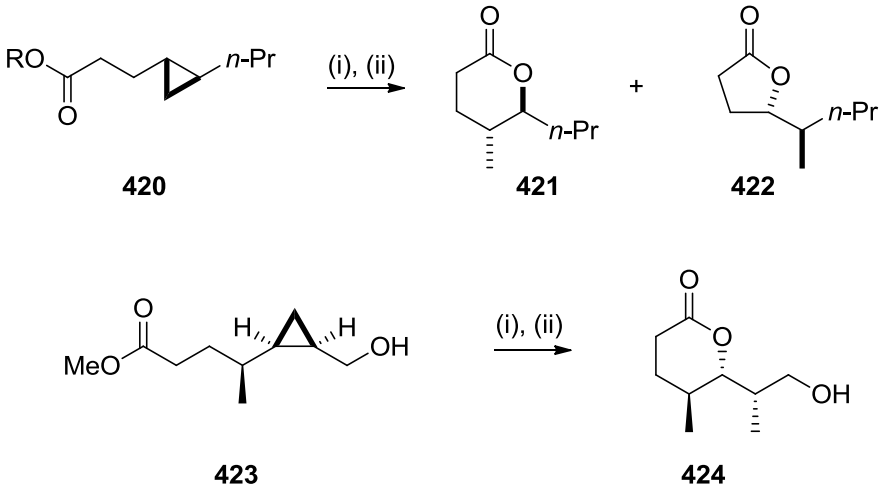


Reagents and conditions: (i) Et_2BOTf, $N(^iPr)_2Et$, CH_2Cl_2, -78 ˚C to 0 ˚C; (ii) TBAF, AcOH, THF, rt; (iii) Toluene, Δ.

Scheme 74 Synthesis of δ-lactones **417** and **419** from SuperQuat auxiliary

2.3 Literature Precedent and Previous Work

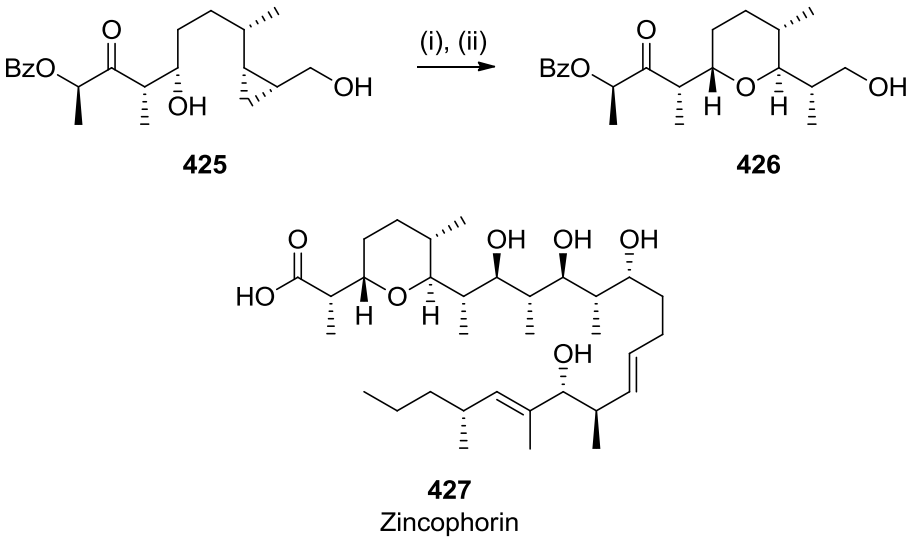
The mercury(II) mediated cyclopropylcarbinol ring opening reaction is well documented and has been previously employed for the synthesis of oxygen heterocycles.[153-155] For example, Collum and co-workers have reported that disubstituted δ-lactones can be synthesised from cyclopropane **420** in a mercury 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**.[153-154] Cossy and co-workers have also utilised this highly regio- and stereoselective transformation to produce disubstituted δ-lactone **424** from **423** in 66% yield.[153]



Reagent and conditions (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt then saturated KBr; (ii) n-Bu_3SnH, 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).[156-157]



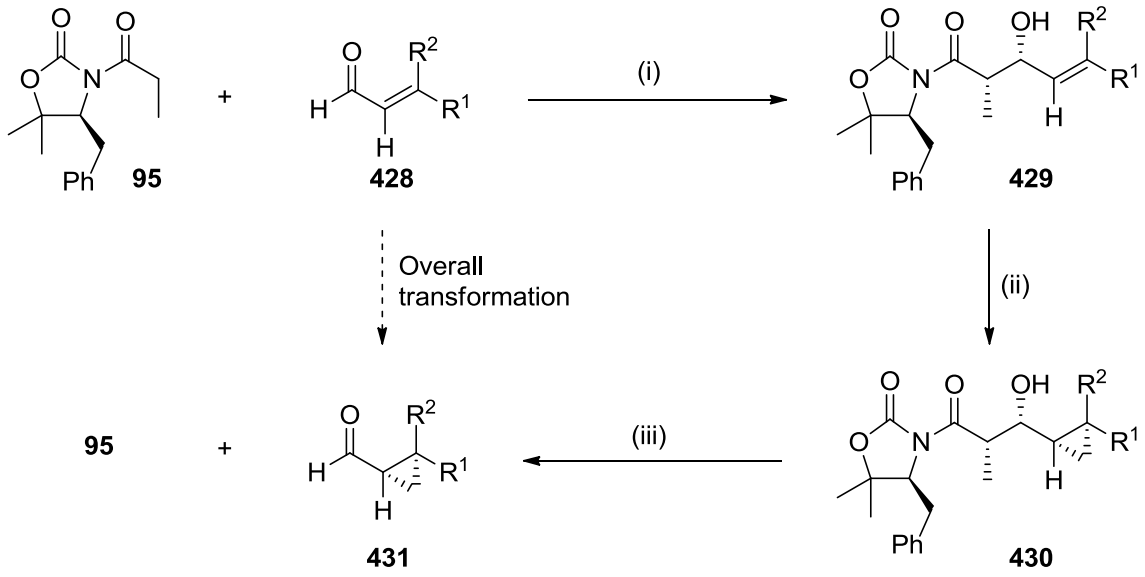
425 **426**

427
Zincophorin

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt then aq. KBr; (ii) n-Bu_3SnH, 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,[40] which has been applied to the synthesis of the natural products Grenadamide[158] and Cascarillic acid.[42] 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.

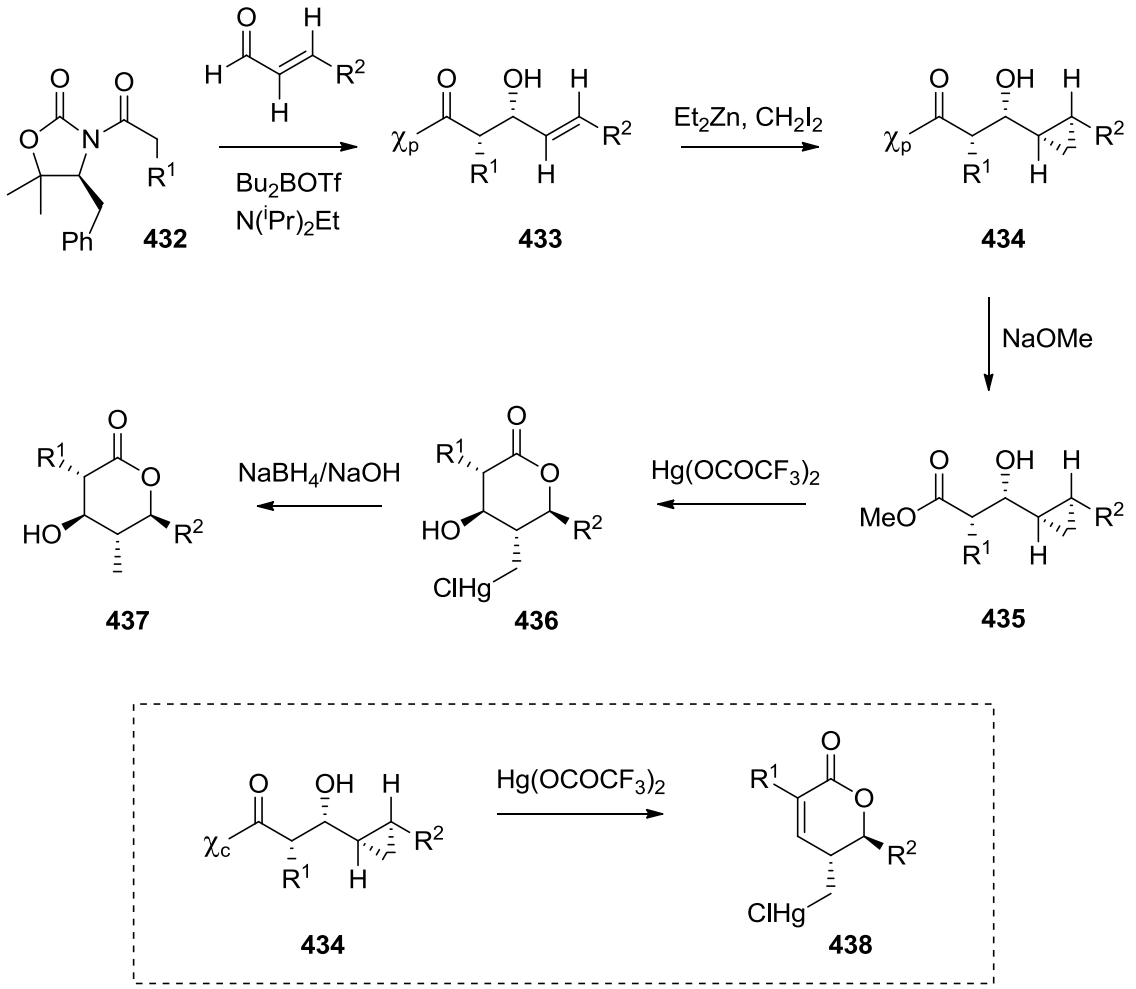


Reagents and conditions: (i) 9-BBN-OTf , N(^{i}Pr$_2$)Et, CH_2Cl_2, -78 to 0 ˚C; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0 ˚C; (iii) LiHMDS (1.1 equiv), toluene.

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**.

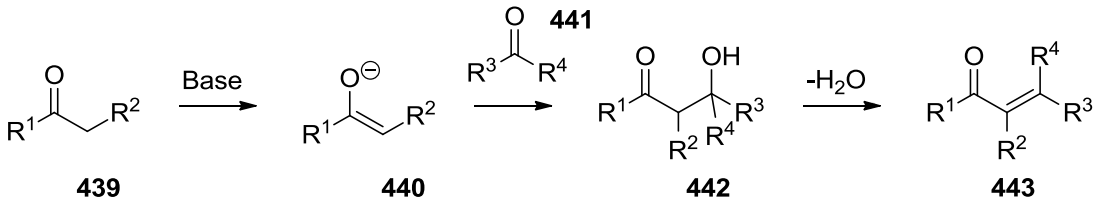


Scheme 78 Novel methodology for the synthesis of highly substituted δ-lactones **437**

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

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]

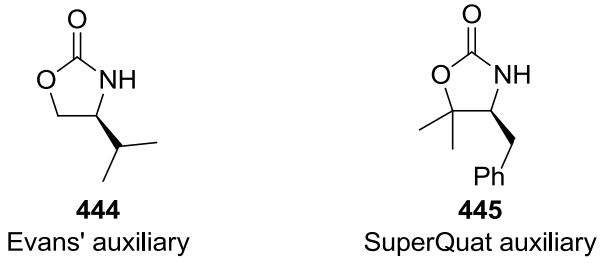
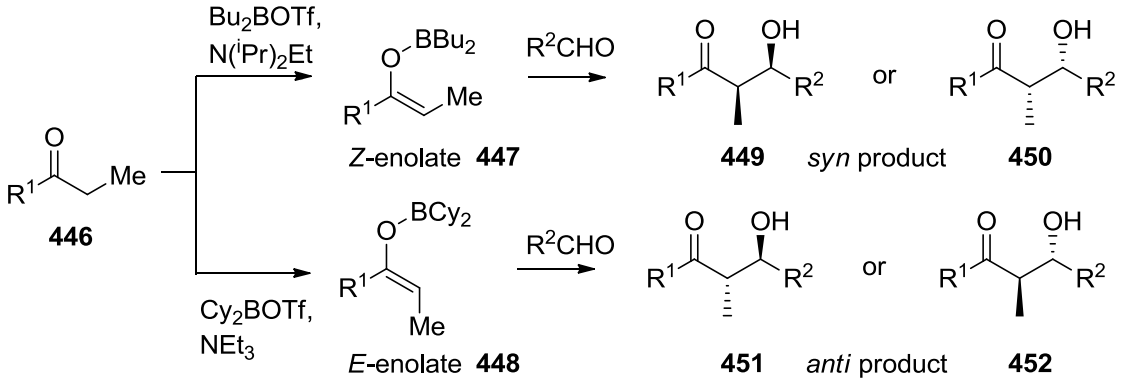


Figure 5 Chiral oxazolidinone auxiliaries

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.

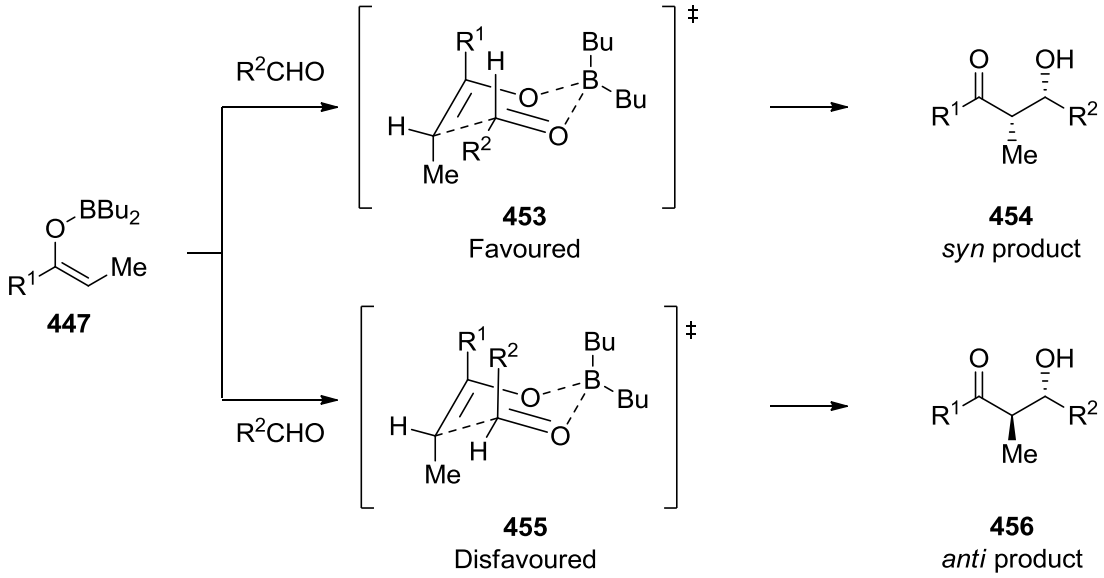
Boron reagents are often employed in directed aldol additions to generate the desired enolate geometry. Bulky boron substituents such as cyclohexyl groups result in *E* enolates **448**, whereas substitutents that are less sterically demanding, such as butyl groups or 9-BBN (9-borabicyclononane), result 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 *syn* product **449**-**450**, whereas the *E* enolate **448** provides the *anti* product **451**-**452**.



Scheme 80 Diastereoselectivity in the aldol reaction is determined by enolate geometry

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

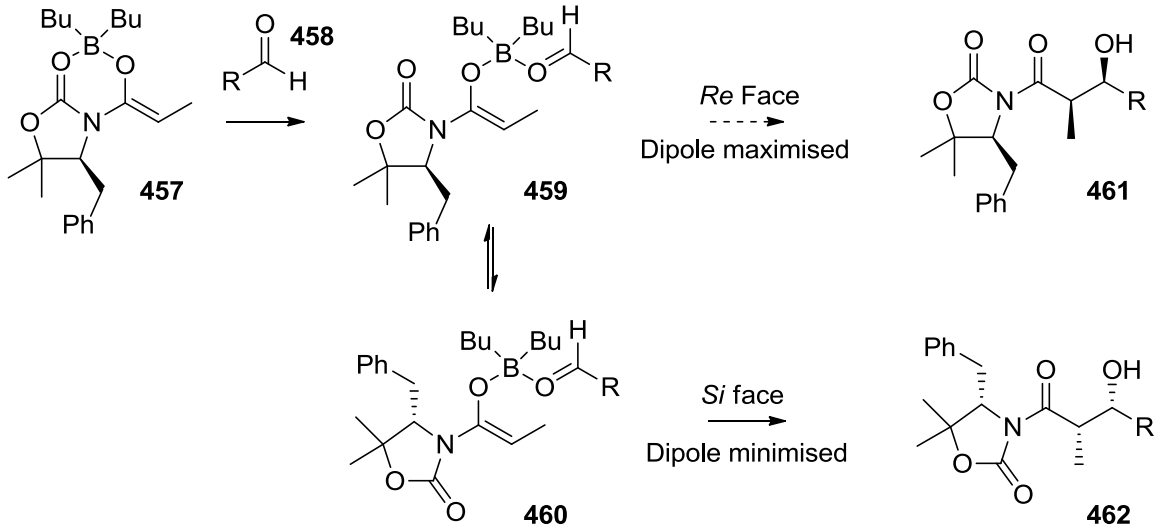
the enolate and the R^2 group of the aldehyde (**455**). Therefore, the reaction proceeds through the transition state in which the R^2 group is equatorial to minimise steric interactions (**453**) to afford the *syn* product **454**. Therefore, enolate geometry controls the overall diastereoselectivity, but not the enantioselectivity so a racemic mixture is obtained.[161-162]



Scheme 81 Zimmerman-Traxler transition states for a *Z* boron enolate **447**

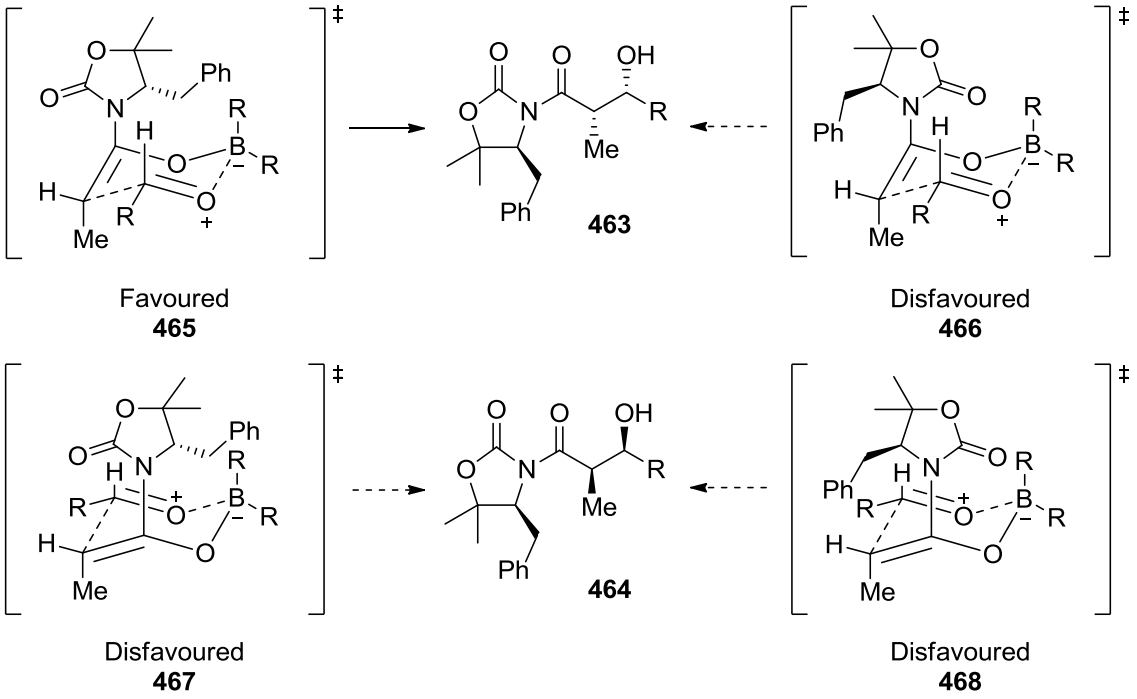
The absolute stereochemistry of the aldol reaction can be controlled using chiral auxiliaries such as the SuperQuat auxiliary **445**. The chiral auxiliary is used to control which *syn* enantiomer is produced when a *Z* boron enolate is used in the aldol reaction.[163] The Lewis acidic boron coordinates 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 *Re* face where the dipole is minimised resulting in *syn* enantiomer **462**.[159,164-165]



Scheme 82 Minimisation of adverse dipole-dipole interactions in the aldol reaction favours formation of *syn*-aldol **462**

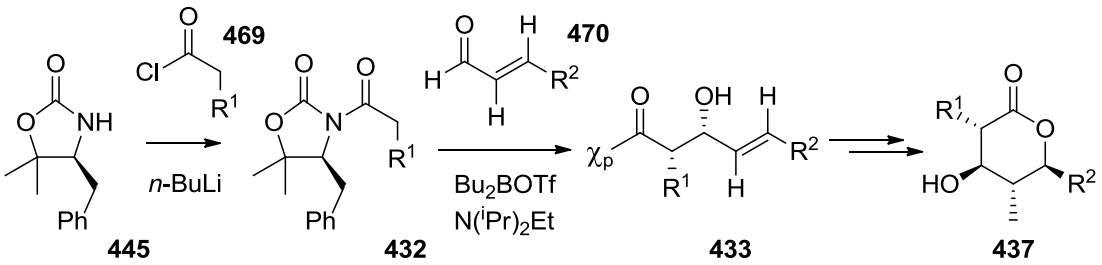
The absolute stereochemical outcome can also be explained using Zimmerman-Traxler transition states.[159] The boron coordinates to the incoming aldehyde creating four possible transition states (**465-468**). The R group of the aldehyde must adopt a pseudo equatorial position to minimise the 1,3-diaxial 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 *syn* product **463**.[163]



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

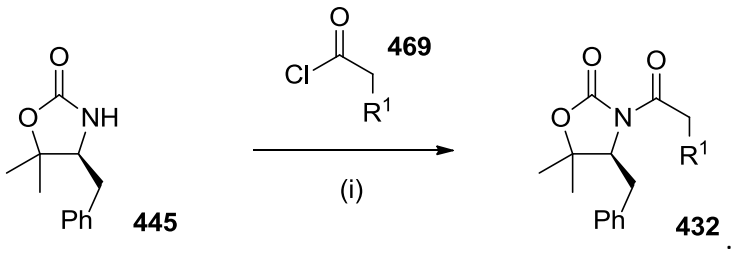
2.4.2 Asymmetric Synthesis of Unsaturated syn-Aldol Products

Our novel strategy for the synthesis of highly substituted δ-lactones **437** allows for variation at two of the substituents, R^1 and R^2 (Scheme 84). Structural variation at R^1 could be introduced by employment of different acid chlorides **469** in the auxiliary *N*-acylation step. The R^2 substituent would then be varied by using different aldehydes **470** in the asymmetric aldol reaction.



Scheme 84 Variation of substituents R^1 and R^2 on δ-lactone **437** framework

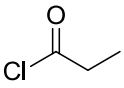
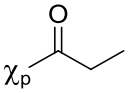
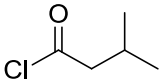
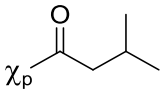
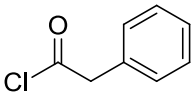
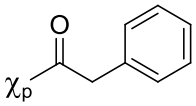
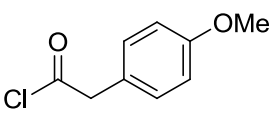
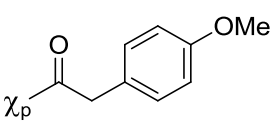
A range of *N*-acylated oxazolidin-2-ones were synthesised to investigate the scope of this methodology. SuperQuat auxiliary **445** in THF was treated with *n*-butyl lithium (2.5 M in hexane) at -78 ˚C followed by the addition of the appropriate acid chloride **469**. The resulting solution was allowed 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.



Reagents and conditions: (i) n-BuLi (1.1 equiv), THF, -78 ˚C, 30 min, ***469*** *(1 equiv), -78 ˚C, 2 h.*

Scheme 85 Synthesis of *N*-acylated SuperQuat auxiliary products **432**

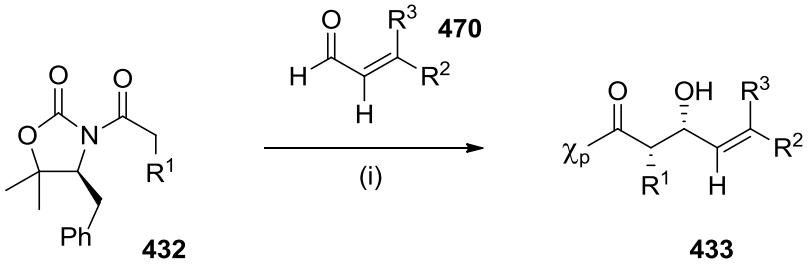
The following acylated SuperQuat auxiliary products were synthesised in high yield using the methodology described (Table 1).

Entry	*Acid Chloride*	*Acylated Auxiliary*[a]	*Product*	*Yield*[b]
1			**95**	92%
2			**471**	72%
3			**472**	76%
4			**473**	78%

[a]χ_p refers to SuperQuat auxiliary; [b]isolated yield after column chromatography

Table 1 *N*-Acylated oxazolidin-2-one products **432**

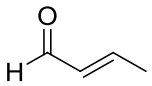
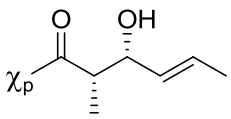
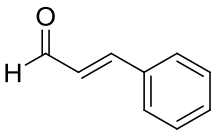
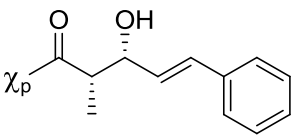
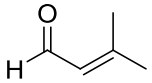
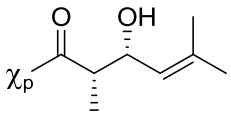
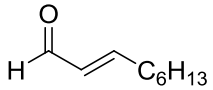
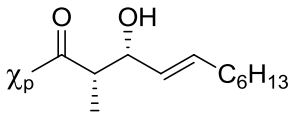
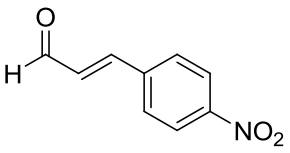
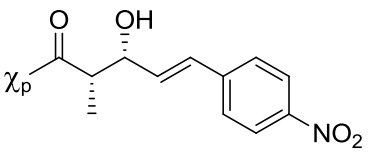
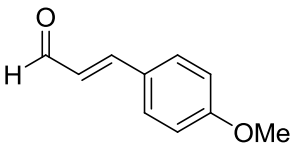
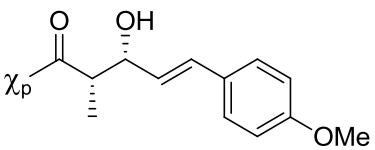
The *N*-acylated auxiliary products in Table 1 were then used to synthesise the unsaturated *syn*-aldol products **433**. The acylated auxiliary **432** was treated with dibutylboron triflate (1.1 equiv) followed by diisopropylethylamine (1.3 equiv) in dichloromethane at 0 ˚C. After 30 minutes, the solution 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) Bu_2BOTf, $N(^iPr)_2Et$, CH_2Cl_2, 0 ˚C then aldehyde **470**, -78 ˚C.*

Scheme 86 Synthesis of unsaturated *syn*-aldol products **433**

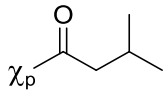
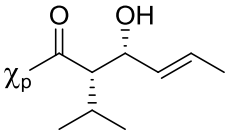
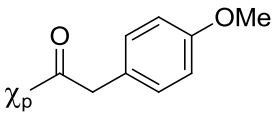
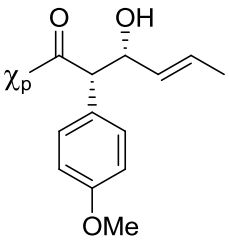
This asymmetric *syn*-aldol methodology was applied to (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one (R^1 = Me) using different aldehydes **470** as substrates to introduce variation at the R^2 position. The following *syn*-aldol products were synthesised in high yield and *de* (Table 2).

Entry	*Aldehyde*	*Aldol Product*[a]	*Product*	*Yield*[b] *de*
1			**474**	95% >95%
2			**475**	86% >95%
3			**476**	81% >95%
4			**477**	66% >95%
5			**478**	66% >95%
6			**479**	56% >95%

[a]χ_p refers to SuperQuat auxiliary; [b]isolated yield after column chromatography

Table 2 Unsaturated *syn*-aldol products produced from different α,β-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).

Entry	*Acylated Auxiliary*[a]	*Aldol Product*[a]	*Product*	*Yield*[b] *de*
1			**480**	82% >95%
2			**481**	72% >95%

[a]χ_p refers to SuperQuat auxiliary; [b]isolated yield after column chromatography

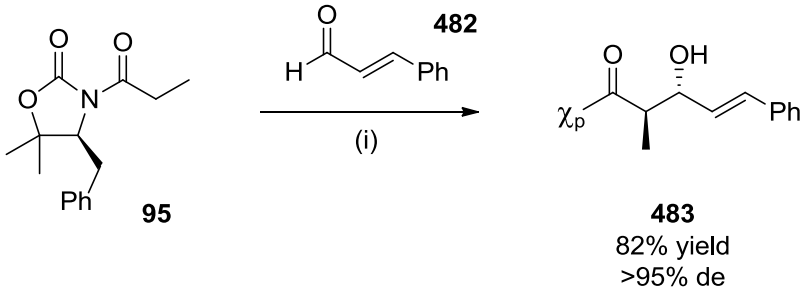
Table 3 Unsaturated *syn*-aldol products prepared using different *N*-acylated auxiliaries

An asymmetric aldol reaction was attempted using *N*-acylated oxazolidin-2-one **472** where R^1 = 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 = aliphatic and 6.9-6.2 ppm when R^2 = aromatic, with a coupling constant of between 15-16 Hz indicating *E* alkene geometry.

2.5 Non-Evans' *anti*-aldol

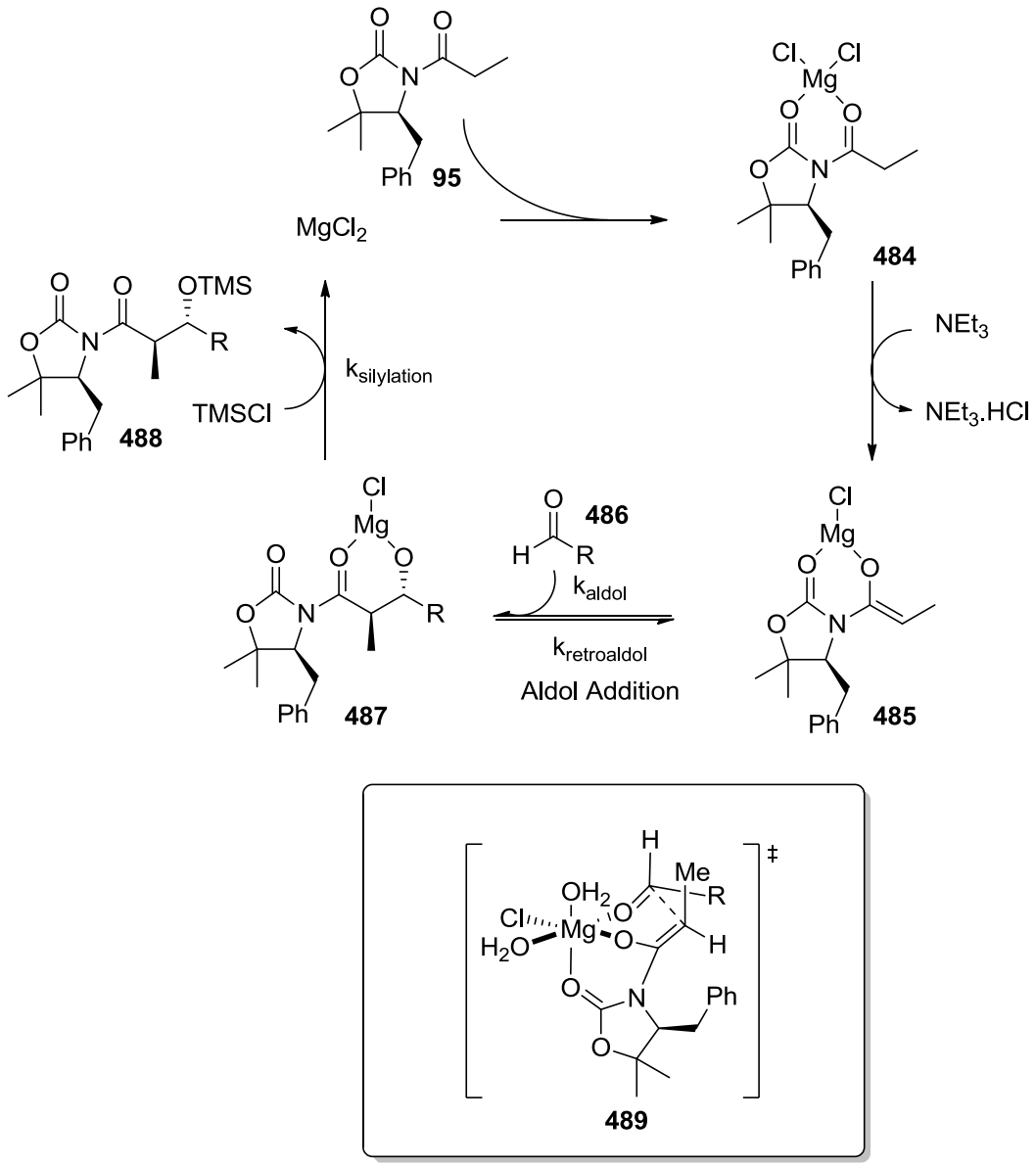
A non-Evans' *anti*-aldol product **483** was prepared to investigate the effect of using substrates with an alternative stereochemistry at the α-position. According to a literature procedure, (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** was dissolved in dry ethyl acetate along with a catalytic amount of magnesium chloride and sodium hexafluoroantimonate.[166] 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 ^{1}H and ^{13}C NMR spectra were similar to that of *syn*-aldol product **483**, although the most noticeable difference in chemical shift was that of the CH_AH_BPh 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.[166]



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.[167]



Scheme 88 Catalytic cycle for magnesium chloride catalysed *anti*-aldol reaction

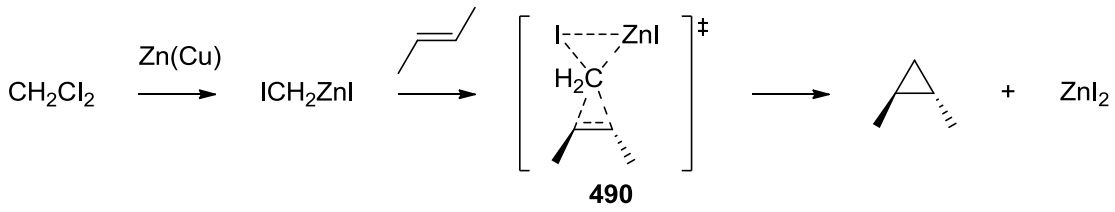
Attempts were made to synthesise other *anti*-aldol products using different aldehydes. However, these failed possibly owing to the non-general nature of this procedure, which is most successful when non-enolisable electrophiles such as aromatic and unsaturated aldehydes are employed for reaction. The *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

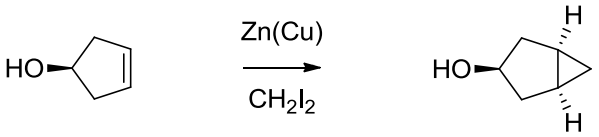
Simmons and Smith first reported the use of diiodomethane and zinc-copper couple to convert alkenes into cyclopropanes.[168-169] The reaction has been shown to proceed through a three membered 'butterfly-type' transition state **490**[170-171] in which $IZnCH_2I$ is the active cyclopropanating agent.[172] 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

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]

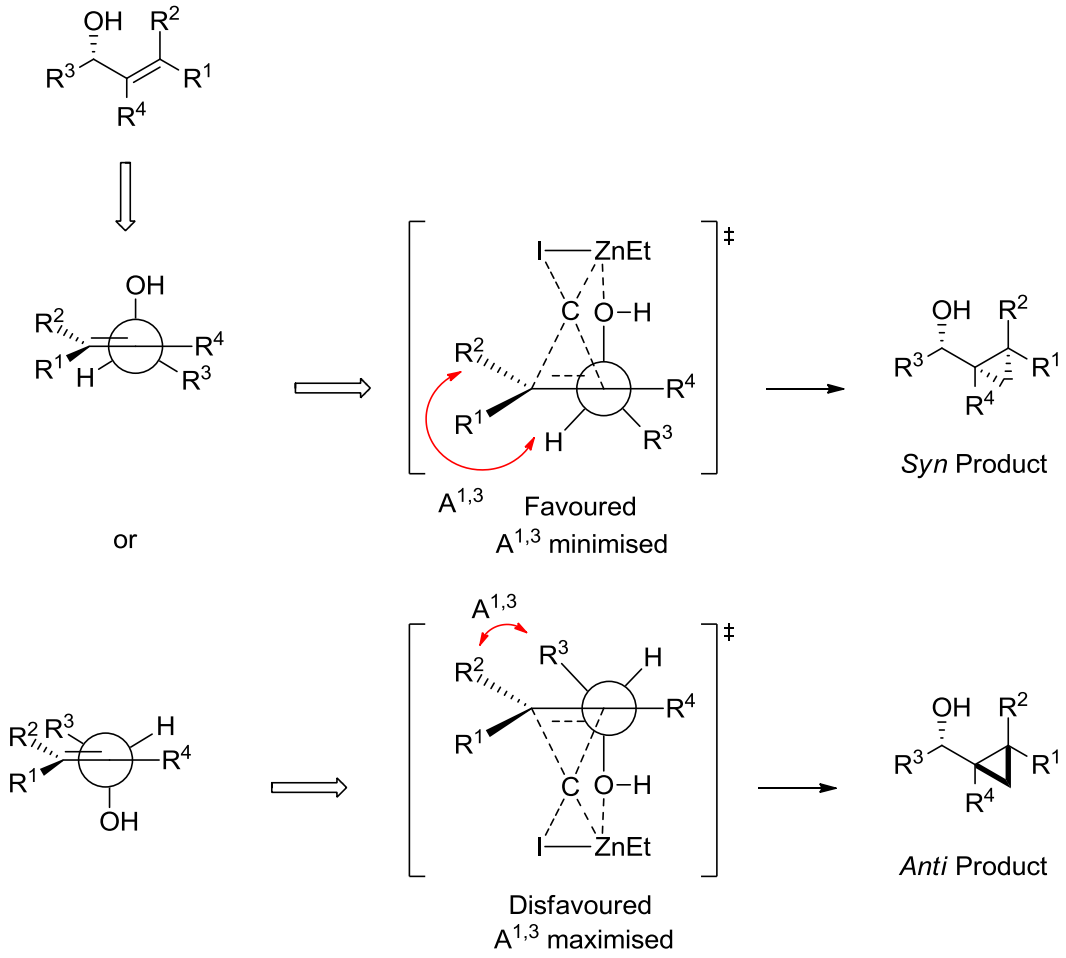
Winstein and co-workers reported the first application of a Simmons-Smith reaction to an allylic alcohol **491**. The oxygen atom coordinates to the zinc to direct the methylene group to the neighbouring alkene to afford the *syn* product **492** as a single stereoisomer in 75% yield.[178] It has also 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]



491 **492**

Scheme 90 Hydroxyl-directed Simmons-Smith cyclopropanation reaction

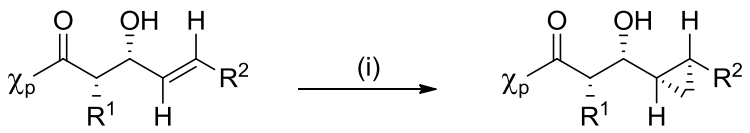
The stereoselectivity of the cycloropanation reaction with acyclic allylic alcohols can be explained using the allylic strain model. The 'staggered' model proposed by Houk considers the possible allylic conformation for the transition states in the addition of the cyclopropane carbon to the double bond.[183-184] Coordination of the active species $EtZnCH_2I$ 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]



Scheme 91 Transition states for the stereoselective cyclopropanation of allylic alcohols

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.

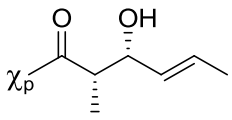
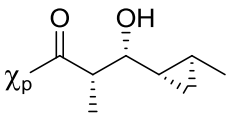
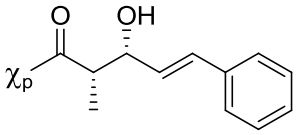
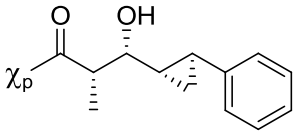
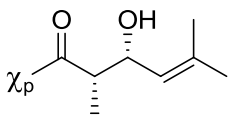
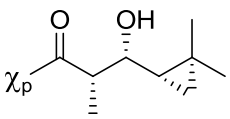
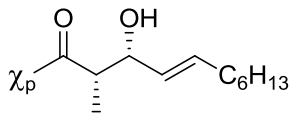
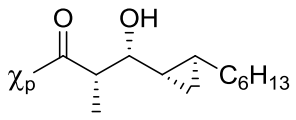


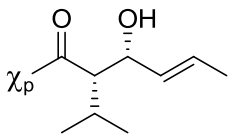
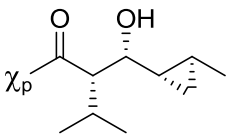
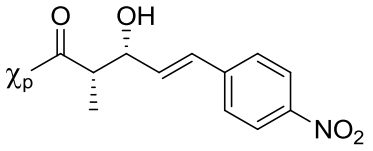
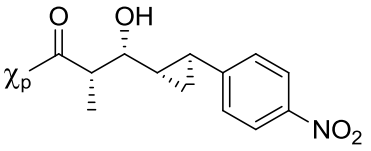
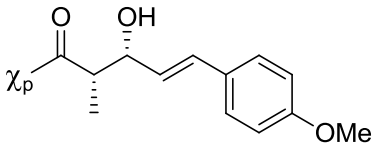
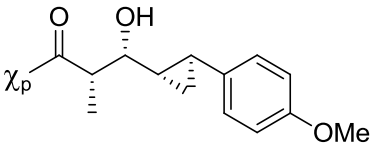
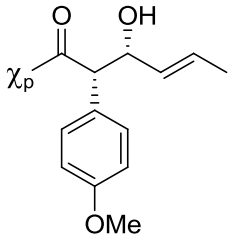
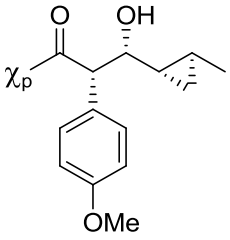
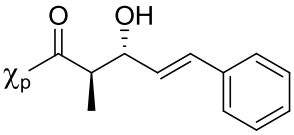
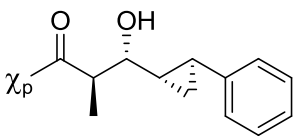
433 **434**

Reagents and conditions: (i) Et_2Zn (5 equiv), CH_2I_2 (5 equiv), CH_2Cl_2, 0 ˚C, 2 h.

Scheme 92 Synthesis of *syn*-aldol cyclopropane products **434**

The ^{1}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 α,β-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).

Entry	*Aldol Product*[a]	*Cyclopropane Product*[a]	*Product*	*Yield*[b] *De*
1			**493**	84% >95%
2			**494**	98% >95%
3			**495**	98% >95%
4			**496**	98% >95%

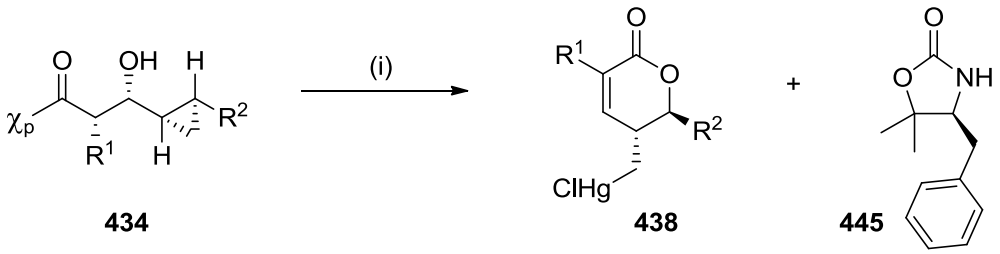
5			**497**	97% >95%
6			**498**	98% >95%
7			**499**	72% >95%
8			**500**	68% >95%
9			**501**	99% >95%

[a]χ_p 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.

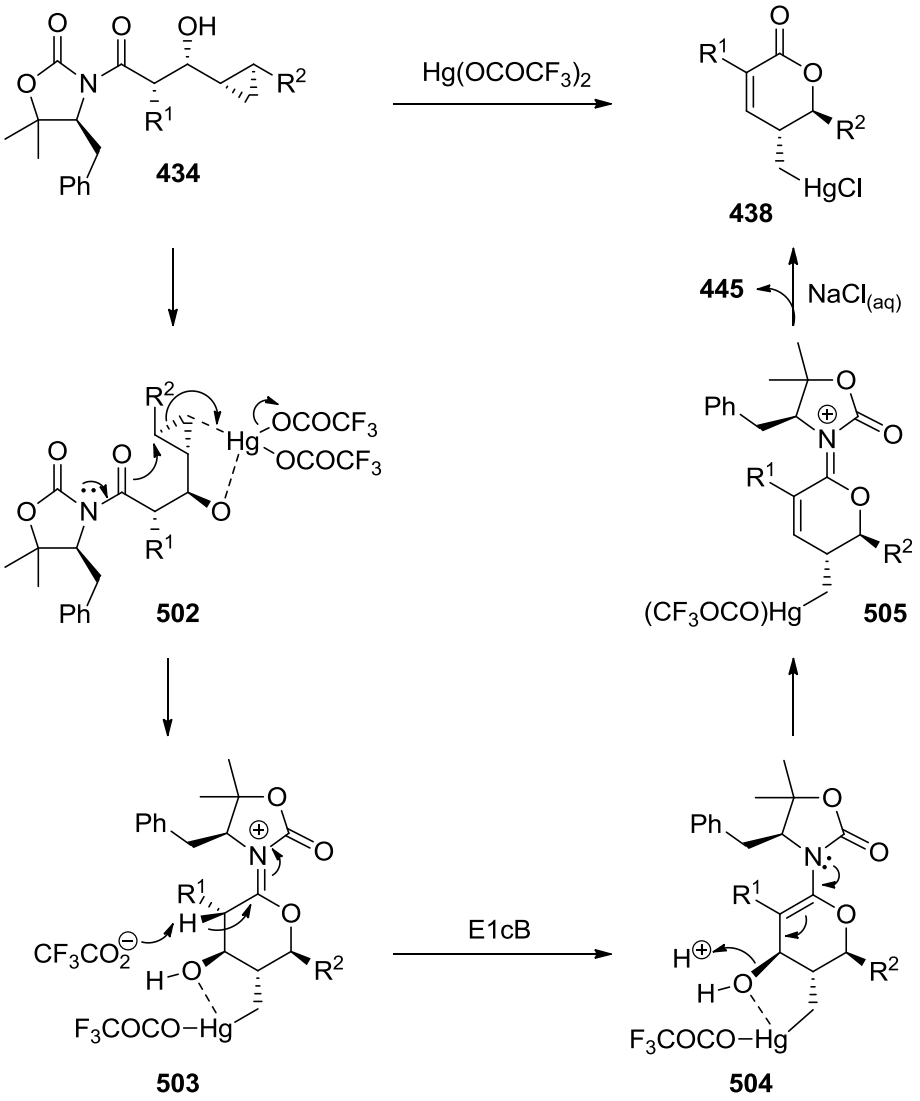


434 **438** **445**

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 24 h then aq. NaCl.

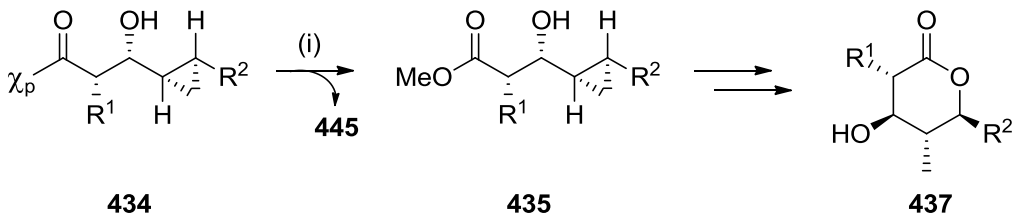
Scheme 93 Synthesis of undesired α,β-unsaturated δ-lactone **438**

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**.



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).

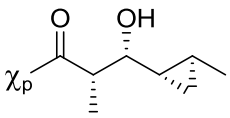
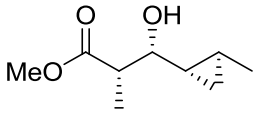
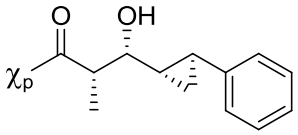
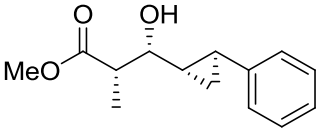
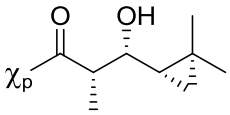
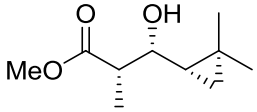
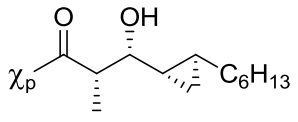
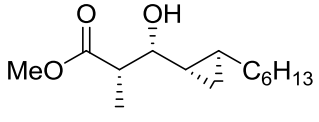
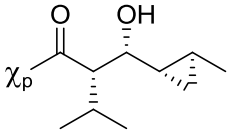
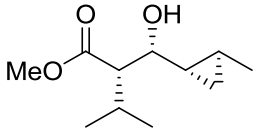


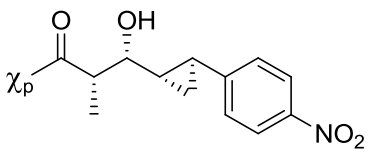
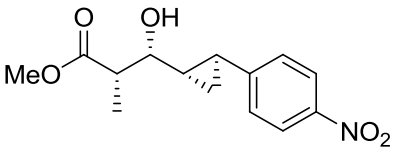
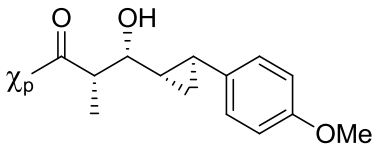
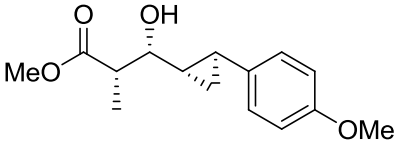
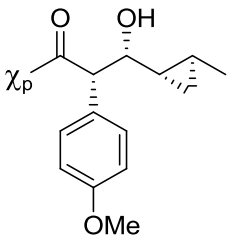
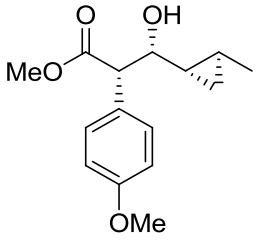
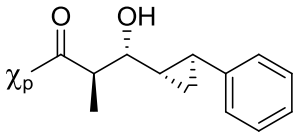
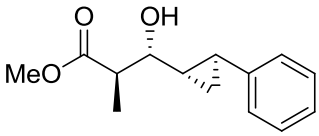
434 **435** **437**

Reagents and conditions: (i) NaOMe (1 equiv, 0.5 M in methanol), CH_2Cl_2, 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.

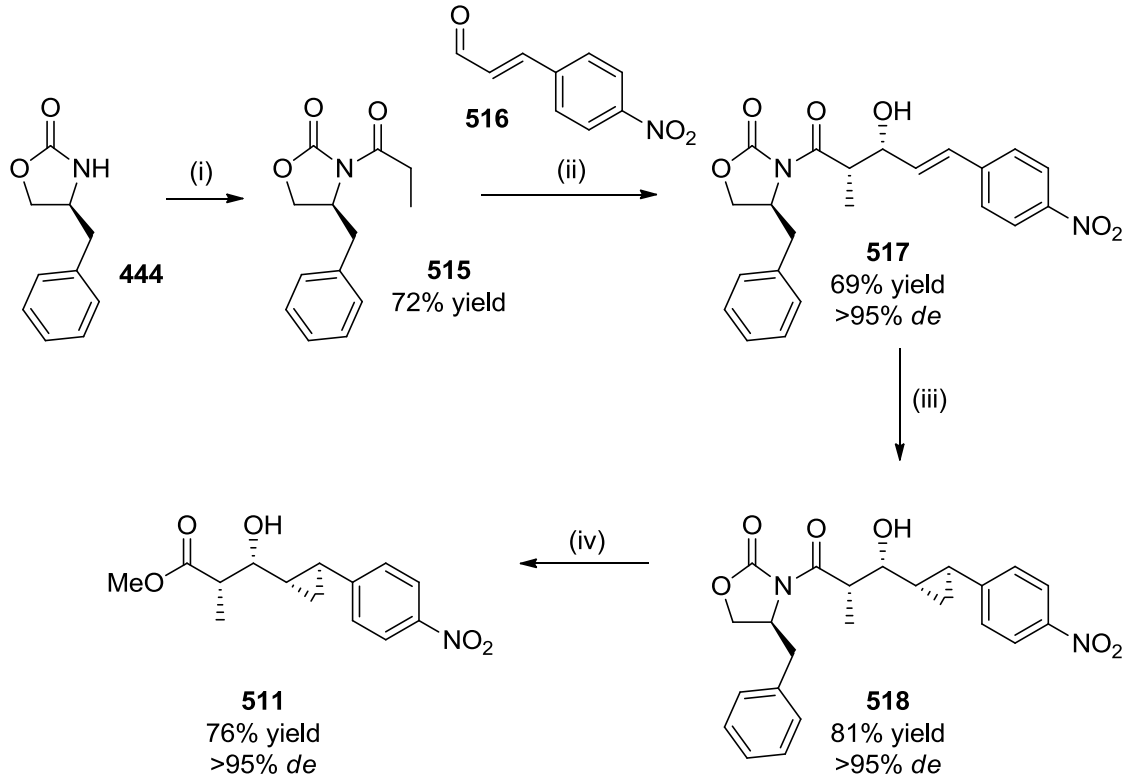
Entry	*Cyclopropane Product*[a]	*Methyl Ester Product*	*Product*	*Yield*[b]
1			**506**	76%
2			**507**	94%
3			**508**	89%
4			**509**	74%
5			**510**	82%

6			**511**	76%
7			**512**	62%
8			**513**	55%
9			**514**	78%

[a]χ_p refers to SuperQuat auxiliary; [b]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.

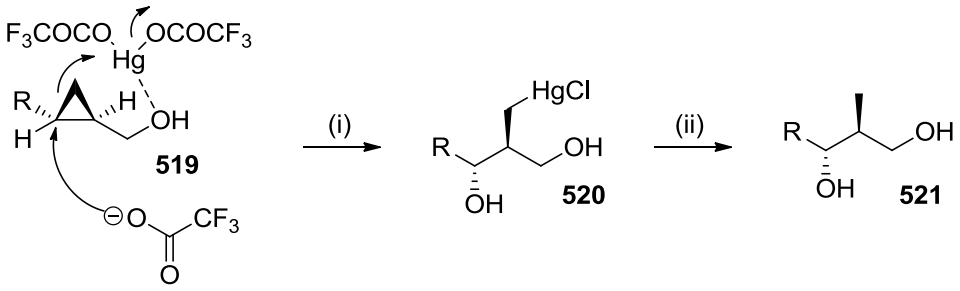


*Reagents and conditions: (i) n-BuLi (1.1 equiv),THF, -78 ˚C for 30 min, propionyl chloride (1 equiv), -78 ˚C, 2 h; (ii) Bu_2BOTf (1.1 equiv), $N(^iPr)_2Et$ (1.3 equiv), CH_2Cl_2, 0 ˚C then aldehyde **516**, -78 ˚C to rt; (iii) Et_2Zn (5 equiv), CH_2I_2 (5 equiv), CH_2Cl_2, 0 ˚C, 2 h; (iv) NaOMe (1 equiv), CH_2Cl_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.[153-155] For example, Cossy 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,[155] and this methodology has been applied by Cossy and co-workers to the synthesis of polypropionate units with up to four contiguous stereocentres.[185-186]

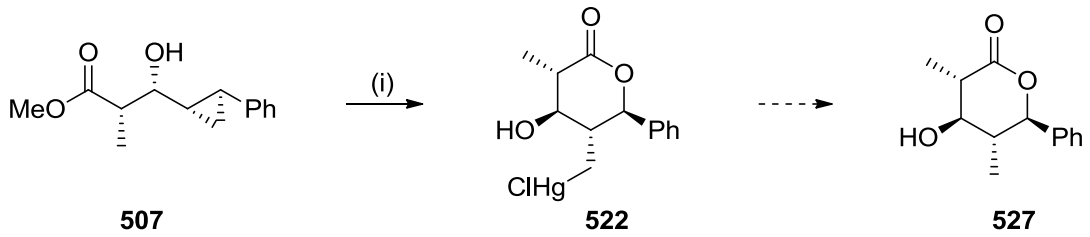


Reagent and conditions (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, then aq. NaCl; (ii) $LiAlH_4$, THF.

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.

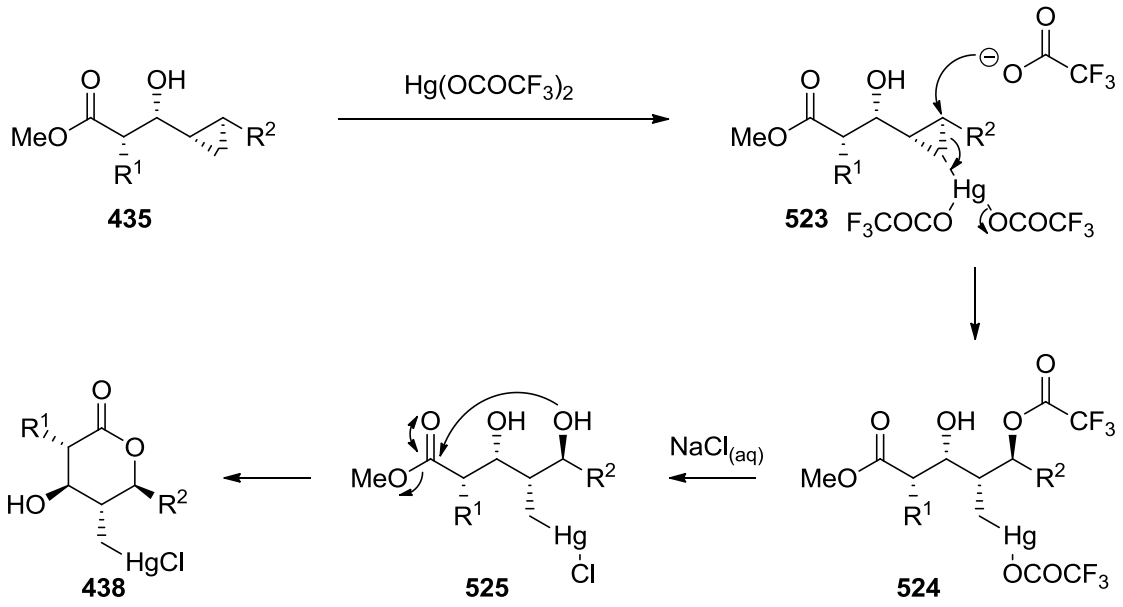


Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 24h then aq. NaCl.

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

towards nucleophilic attack by a trifluoroacetate ion in an S_N2 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 Mechanism for mercury(II) mediated lactonisation of methyl ester cyclopropyl-aldols **435**

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 (2*R*,3*R*,4*S*,5*S*), with its solution phase conformation being consistent with that of a distorted chair conformer.

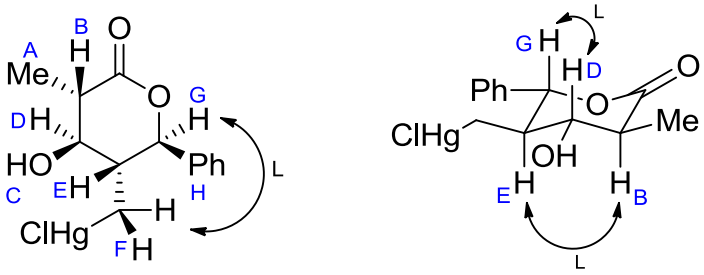
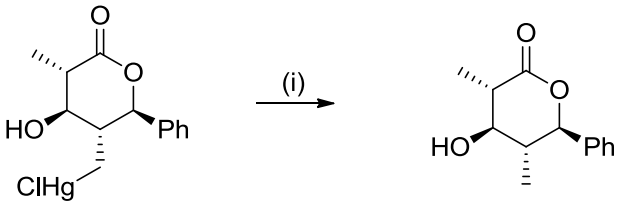


Figure 6 ^{1}H NOESY interactions between protons in δ-lactone **522**

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[186] 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.[154] 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.

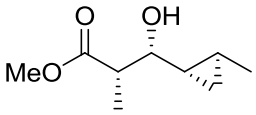
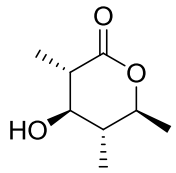
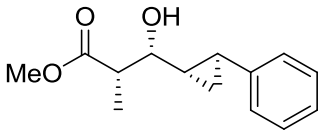
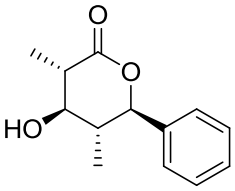
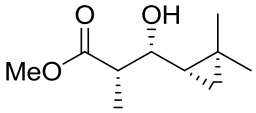
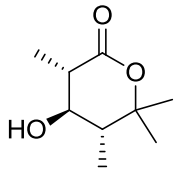
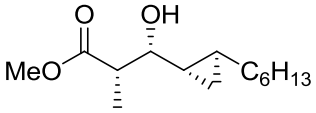
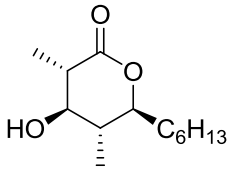
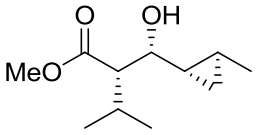
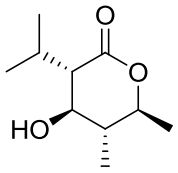


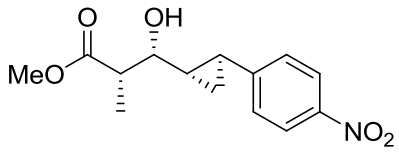
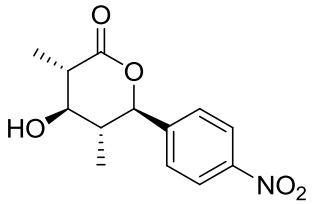
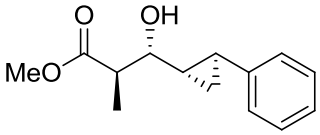
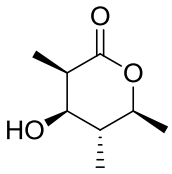
522 **527**

Reagents and conditions: (i) $NaBH_4$ (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 ($NaBH_4$/NaOH/MeOH).

Entry	*Methyl Ester Product*	*δ-Lactone Product*	*Product*	*Yield*[a] *de*
1			**526**	71% >95%
2			**527**	81% >95%
3			**528**	52% >95%
4			**529**	66% >95%
5			**530**	72% >95%

6			**531**	51% >95%
7			**532**	77% >95%

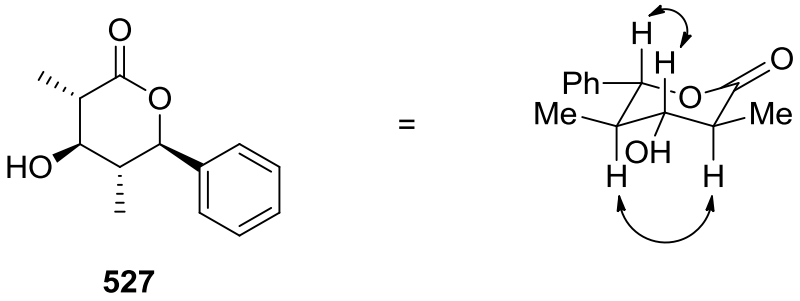
[a]Isolated yield after column chromatography

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

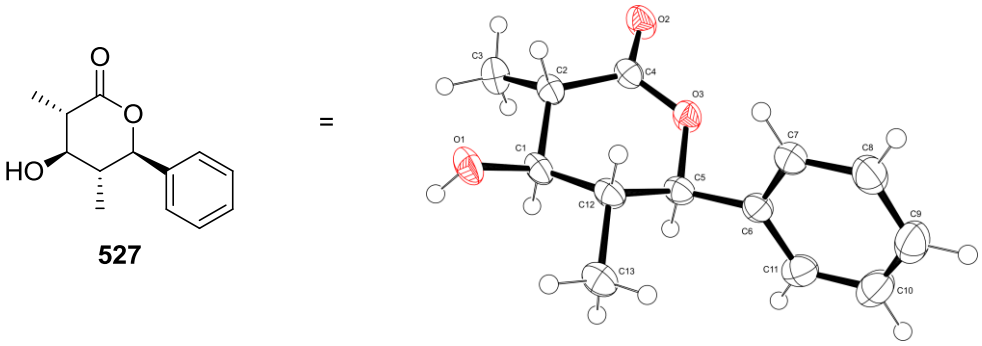
The stereochemistry of the demercurated highly substituted δ-lactone **527** was again confirmed using NOE spectroscopy. The ^{1}H NOE spectrum revealed strong interactions between both sets of axial protons on either side of the chair conformation. Furthermore, there were no interactions observed between protons with a *trans* relationship on the ring. This confirms the *cis* relationship of the axial protons, thus establishing the stereochemistry as (3*S*,4*R*,5*R*,6*R*).



527

Figure 7 ^{1}H NOE interactions in δ-lactone **527**

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.



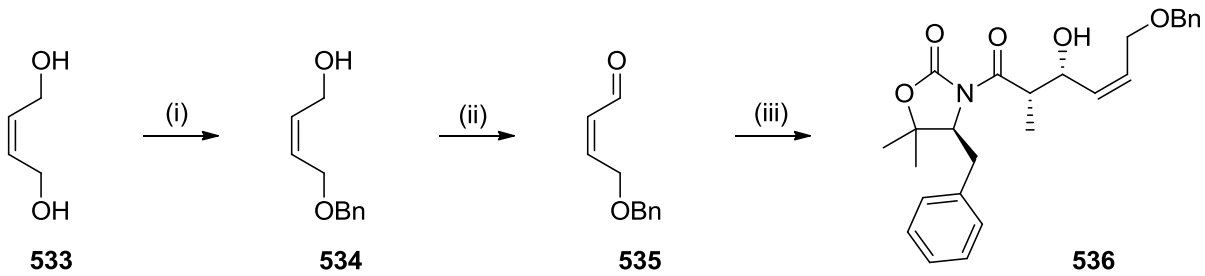
527

Figure 8 X-Ray crystal structure of δ-lactone **527**

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 R^2 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.

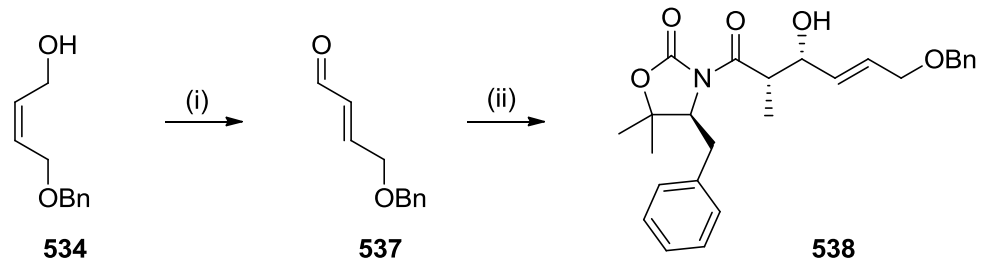
The proposed synthesis began with the synthesis of aldehyde **535** (Scheme 101), which would subsequently be used in an asymmetric aldol reaction. A literature procedure developed by Anderson and co-workers was followed for the synthesis.[187] The starting material was commercially available (*Z*)-but-2-ene-1,4-diol **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 H_2O; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, -55 ˚C, 15 min then NEt_3, 15 min then H_2O; (iii) ***95****, Bu_2BOTf, NEt_3, CH_2Cl_2, -10 ˚C, 30 min then -78 ˚C, aldehyde* ***535****, 45 min, then 0 ˚C, 3 h.*

Scheme 101 Synthesis of *cis*-aldol product **536**

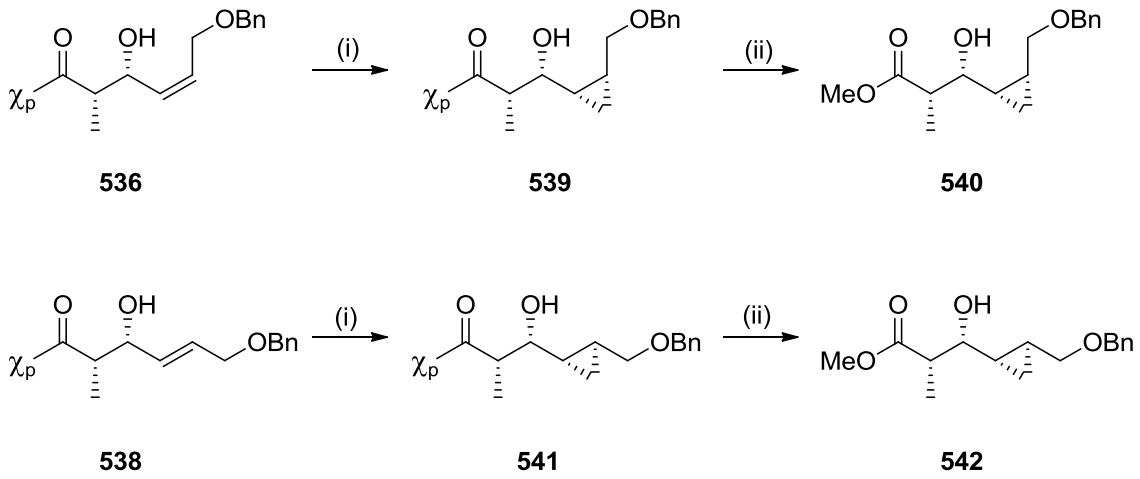
It was also discovered that the *trans* isomer **537** could be obtained in a 99:1 ratio by stirring *cis*-aldehyde **535** overnight at room temperature in dichloromethane (1 mL) with a catalytic quantity of *para*-toluenesulphonic acid. This was subsequently used as a substrate in a *syn*-aldol reaction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



Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, -55 ˚C, 15 min then NEt_3, 15 min then H_2O. Stir at room temperature in CH_2Cl_2 with p-TSA (cat.) overnight; (iii) ***95****, Bu_2BOTf, NEt_3, CH_2Cl_2, -10 ˚C, 30 min then -78 ˚C, aldehyde* ***537****, 45 min, then 0 ˚C, 3 h.*

Scheme 102 Synthesis of *trans*-aldol product **537**

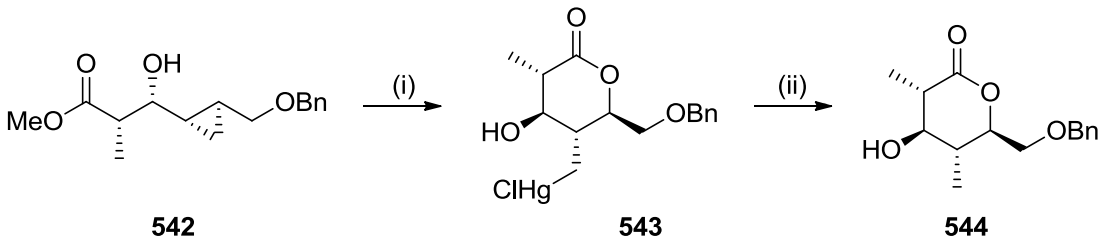
Aldol products **536** and **538** underwent cyclopropanation in 89% and 95% yield respectively to afford *syn*-aldol cyclopropane products **539** and **541**, which were then transesterified with sodium methoxide to furnish methyl esters **540** and **542** in high yield.



Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 ˚C, 2 h.; (ii) NaOMe, CH_2Cl_2, 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.

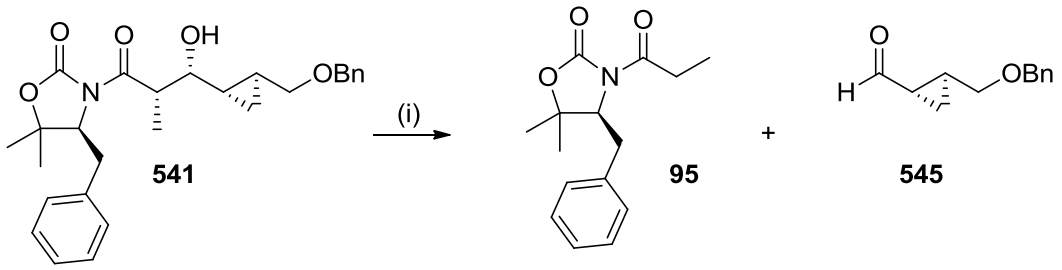


Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 72h; (ii) $NaBH_4$, NaOH (3.5 M), MeOH, rt, 1 h then 1 M HCl.

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 γ-amino acid **549**,[188] which has applications in foldamer science.* Initially, *syn*-cyclopropyl aldol **541** was treated with LiHMDS in toluene at 0 ˚C for three hours to afford chiral cyclopropane-carboxaldhyde **545** in 92% yield.

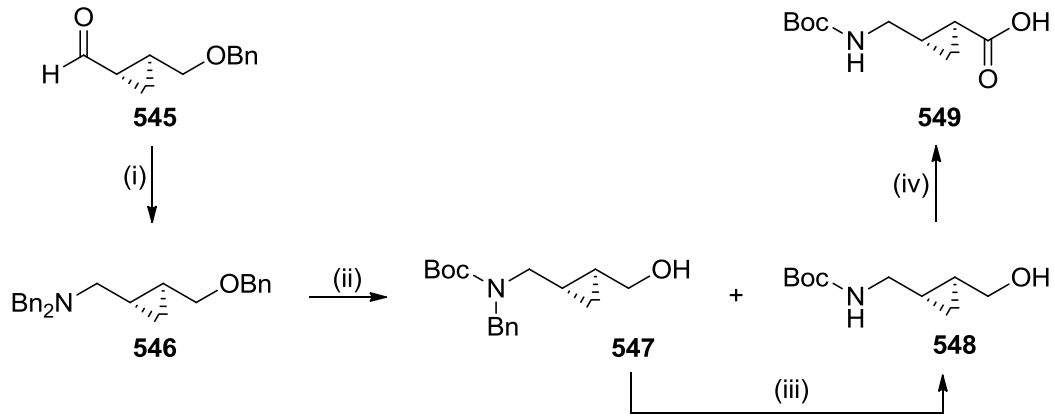


Reagents and conditions: (i) LiHMDS (2.2 equiv), toluene, 0 ˚C, 3h.

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.[189] 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 $Pd(OH)_2$ in THF under a hydrogen atmosphere produced the desired compound **548** in quantitative yield. Finally, alcohol **548** underwent Jones' oxidation to afford the desired γ-amino acid **549** in 63% yield.

* Work completed in collaboration with Prof. D.J. Aitken and co-workers.



*Reagents and conditions: (i) $NaBH(OAc)_3$, Bn_2NH, **545**, DCE, 4Å MS, rt, 4 h; (ii) Pd/C (10%), **546**, HCO_2H, MeOH, rt, 16 h then Boc_2O, 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.*

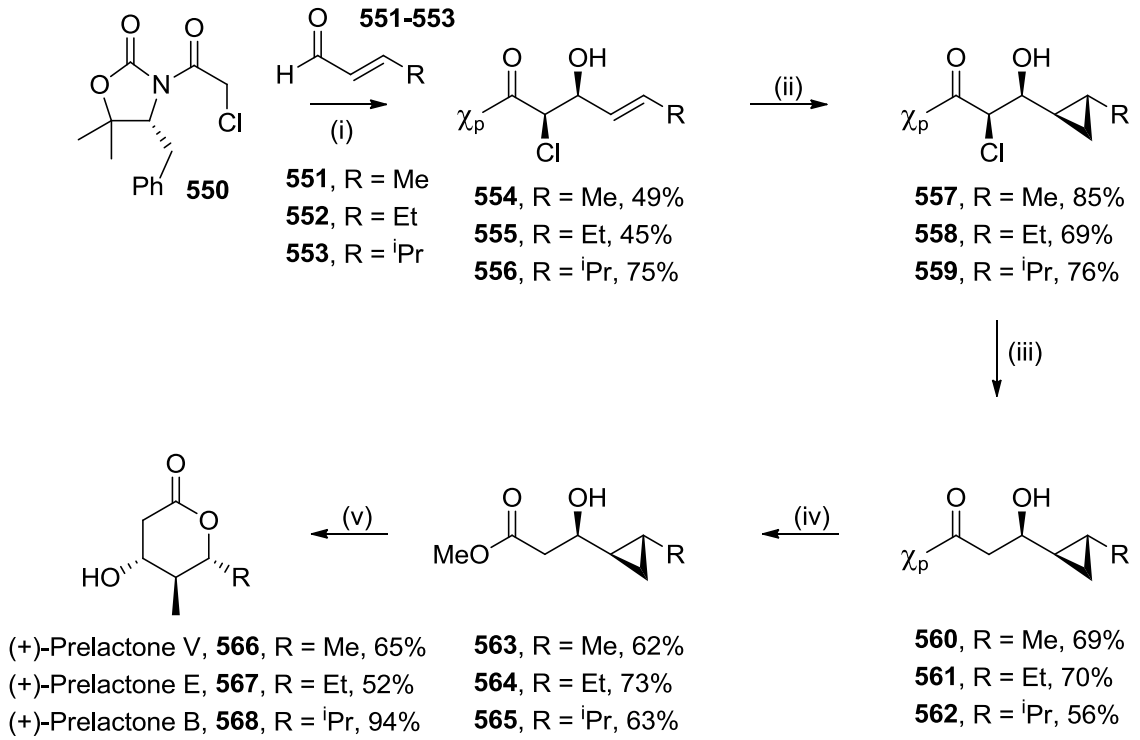
Scheme 106 Synthesis of *N*-protected (*S*,*S*)-2-aminomethyl-1-cyclopropanecarboxylic acid **549**

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 griseu*.[190-191] 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.[192] Many total syntheses have been reported.[192-194]

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.[195] Therefore, an α-chloro substituent was employed to increase the stereoselectivity of the asymmetric *syn*-aldol addition[196] that could be removed at a later stage.[197]

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 $Hg(OCOCF_3)_2/NaCl_{(aq)}$, followed by reductive demercuration with $NaBH_4$/NaOH/MeOH, to furnish (+)-Prelactone B, E and V **566-568** in acceptable yields and excellent diastereoselectivity of >95%.

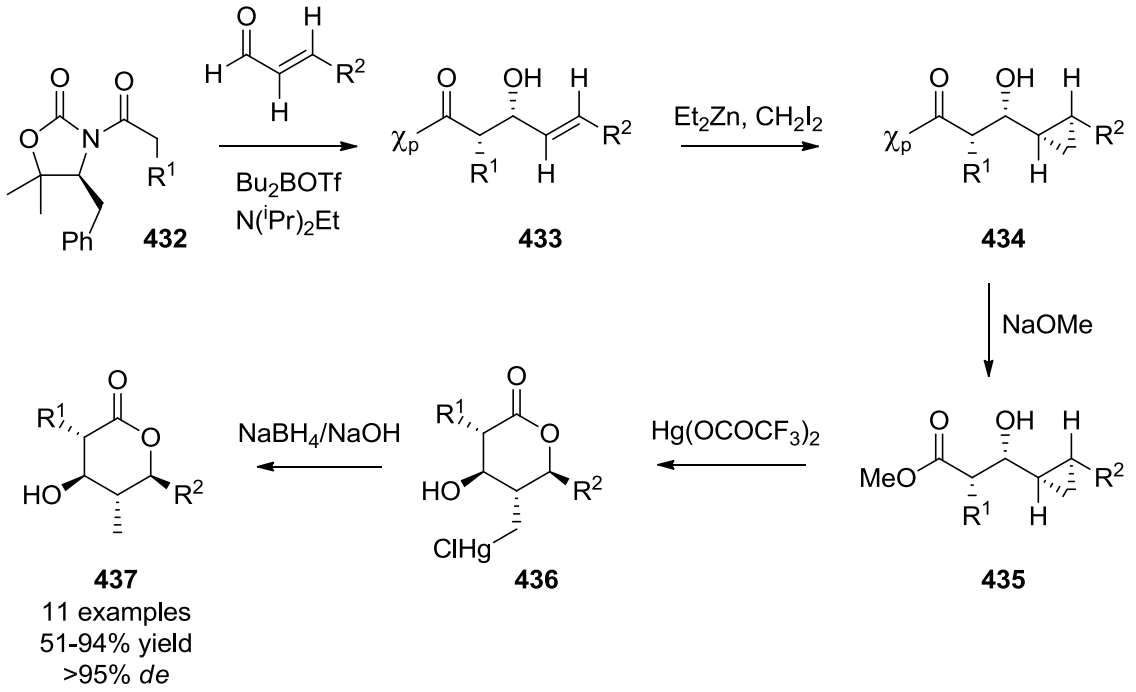


*Reagents and conditions: (i) 9-BBNOTf or Bu_2OTf, $N(^iPr)_2Et$, CH_2Cl_2, 0 ˚C, **551-553**, -78 ˚C to rt; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 ˚C, 2 h; (iii) Zn, NH_4Cl, MeOH, rt; (iv) NaOMe (0.5 M in MeOH) CH_2Cl_2, rt, 5 min; (v) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 24h then aq. NaCl then $NaBH_4$, NaOH (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 stereocentres 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**.



Scheme 108 Asymmetric synthesis of chiral δ-lactones containing multiple contiguous stereocentres

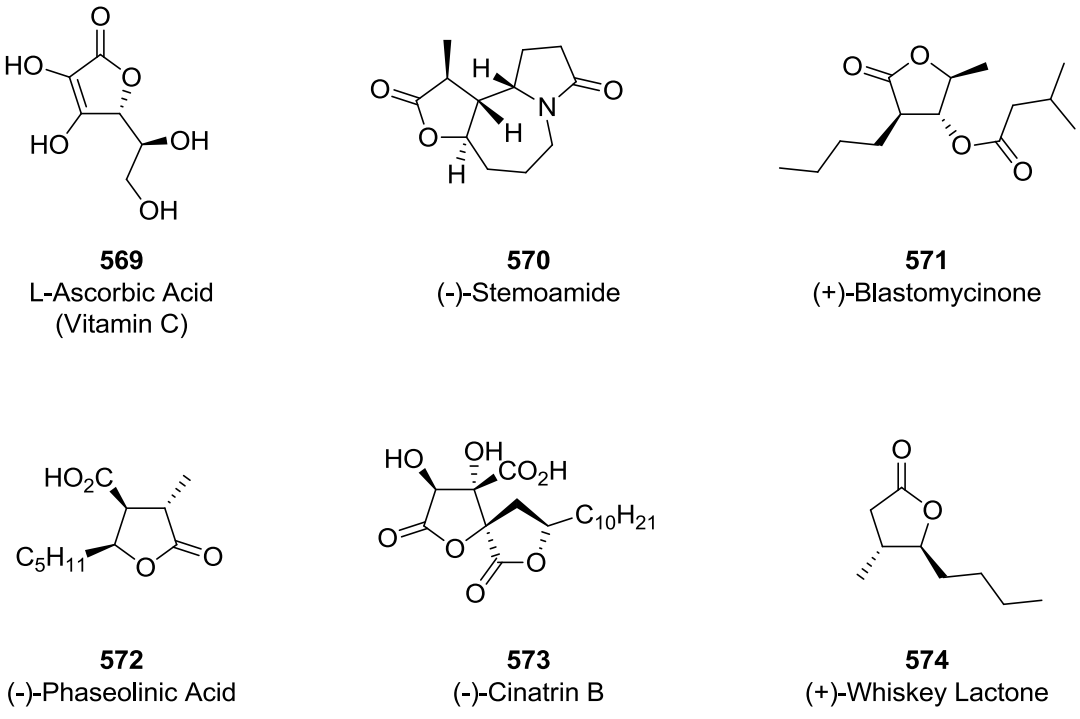
The scope of the novel methodology has been investigated, with variation at the R^1 and R^2 substituents. A highly substituted δ-lactone with an *O*-benzyl synthetic handle has also been successfully synthesised for use as a building block for natural product synthesis. This novel methodology has also 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,[199-201] antifungal,[202-203] anti-inflammatory[204] and cytotoxic[205-206] 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.[207-208] Substituted γ-butyrolactones are also responsible for the distinctive flavours of many alcoholic drinks such as whiskey, cognac and wine.[209]



569 L-Ascorbic Acid (Vitamin C)

570 (-)-Stemoamide

571 (+)-Blastomycinone

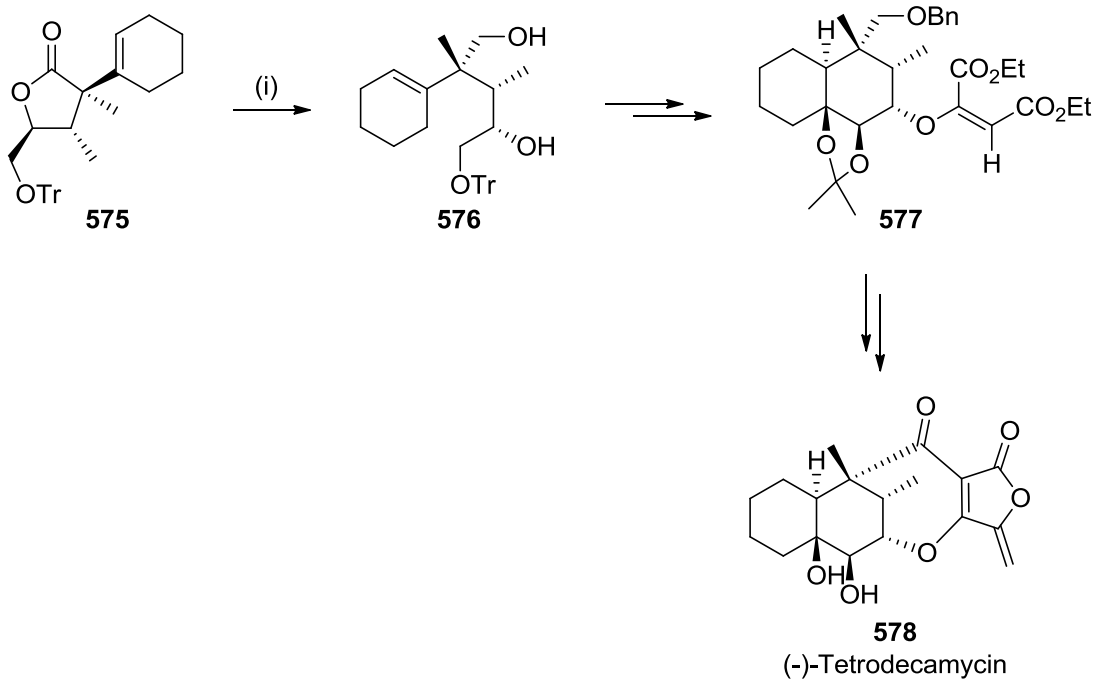
572 (-)-Phaseolinic Acid

573 (-)-Cinatrin B

574 (+)-Whiskey Lactone

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.[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 **578**. Enantiomerically pure lactone **575** was reduced with lithium borohydride to afford straight chain diol **576** in high yield. This underwent a series of well established synthetic procedures to furnish intermediate **577**, which was used to complete the first total synthesis of the natural product (-)-Tetrodecamycin **578**.[217]



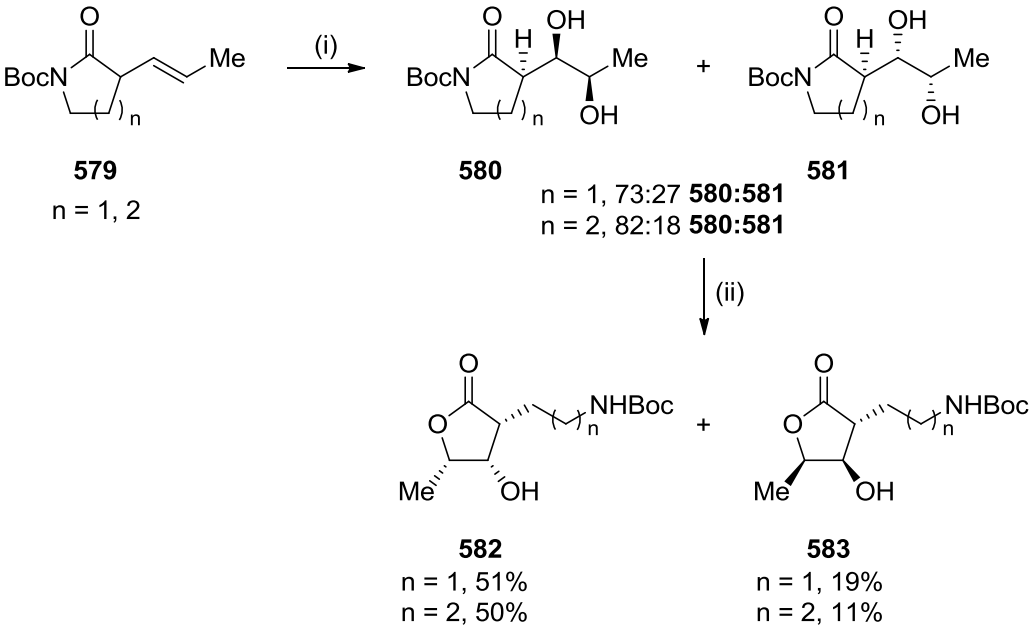
Reagents and conditions: (i) $LiBH_4$, THF, 65 ˚C, 38 h.

Scheme 109 Highly substituted γ-butyrolactone **575** as a precursor for the synthesis of (-)-Tetrodecamycin **578**

The ubiquitous nature of trisubtituted 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.[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.[226-235] Many of these strategies rely on diastereoselective addition of an enolate to an appropriately substituted electrophile.[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.[236-241] 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 OsO_4 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**.[236]



579
n = 1, 2

580 **581**
n = 1, 73:27 **580:581**
n = 2, 82:18 **580:581**

582
n = 1, 51%
n = 2, 50%

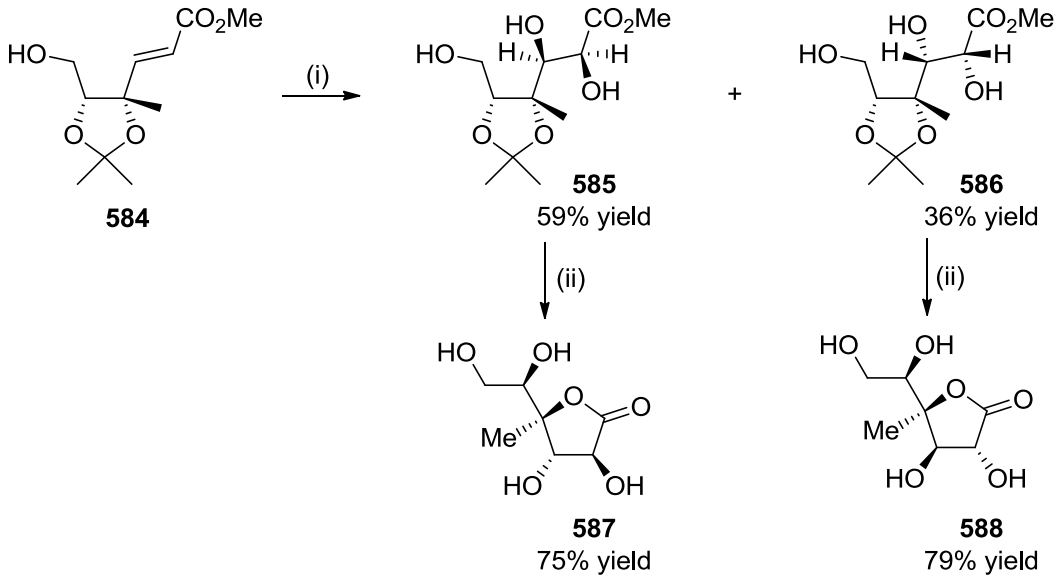
583
n = 1, 19%
n = 2, 11%

Reagents and conditions: (i) cat. OsO_4, NMO, quinuclidine, CH_2Cl_2, 0 ˚C; (ii) p-TsOH·H_2O, C_6H_6, 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

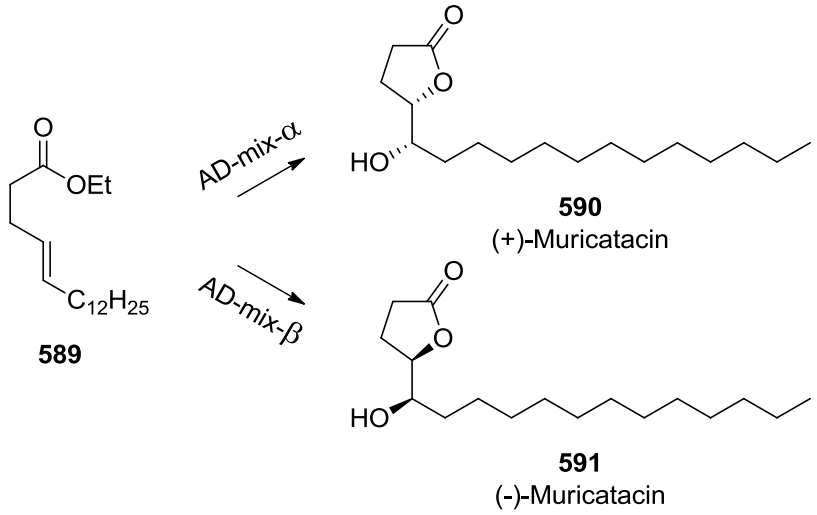
catalysed acetal deprotection and subsequent lactonisation to afford **587** and **588** in good yields.[237]



Reagents and conditions: (i) K_2OsO_4, NMO, H_2O, ^tBuOH, tartaric acid; (ii) Dowex (50W X8, H^+), H_2O.

Scheme 111 Synthesis of branched sugar lactones via dihydroxylation methodology

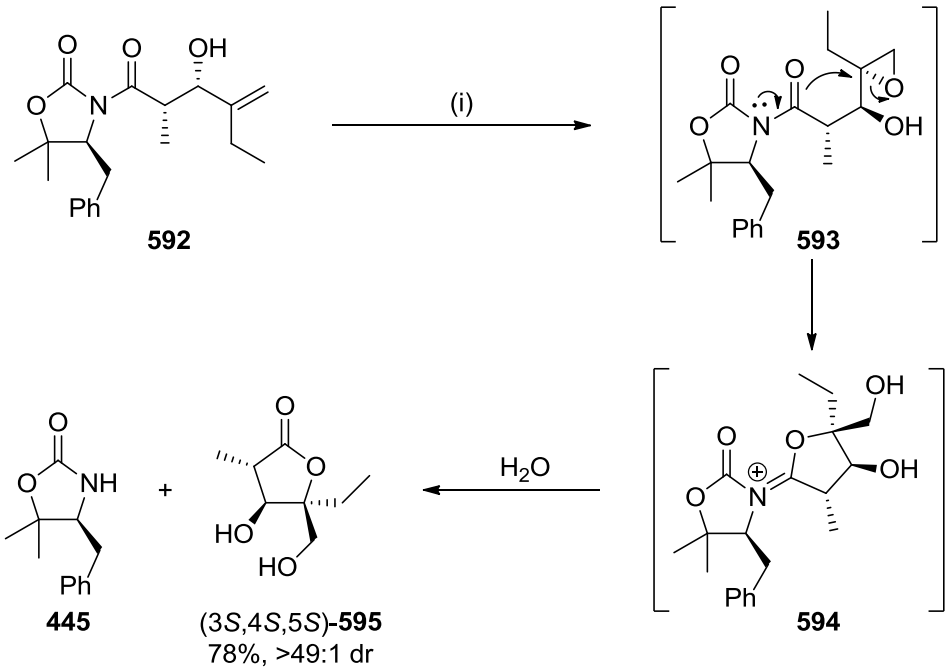
Sharpless and co-workers completed a stereoselective synthesis of both enantiomers of Muricatacin using dihydroxylation methodology. Treatment of **589** with AD-mix-α afforded lactone **590** in 84% yield, whilst AD-mix-β afforded **591** in 82% yield, both in >95% ee.[238]



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 β,γ-alkenyl-β-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-γ-butyrolactone **595**. Initially, the epoxidation reaction proceeds with high levels of diastereocontrol 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-γ-butyrolatone **595** in high yield and diastereoselectivity with release of the SuperQuat auxiliary **445**.[242-243]

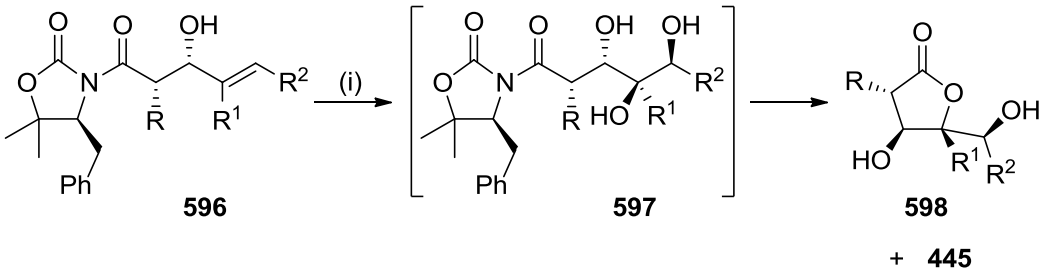


Reagents and conditions: (i) $VO(acac)_2$ (10 mol%), ^tBuOOH, benzene, rt, 12h.

Scheme 113 Epoxidation/lactonisation sequence to afford hydroxy-γ-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-γ-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 β-hydroxyl

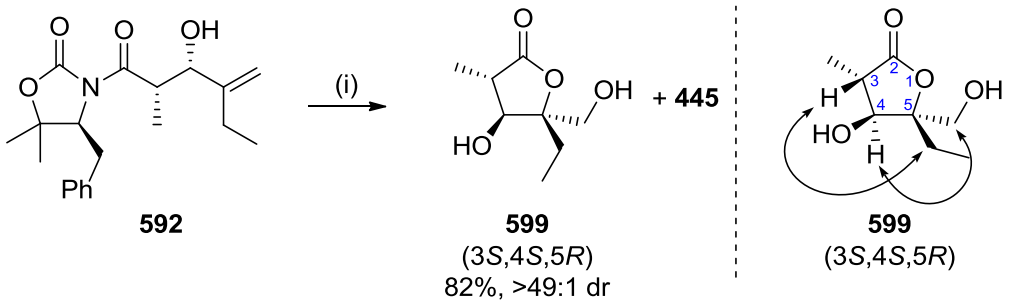
group to afford unstable triol **597**, which would spontaneously lactonise to furnish diastereomeric hydroxy-γ-butyrolactone **598** and SuperQuat auxiliary **445**.[243]



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

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 (3*S*,4*S*,5*S*) 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% OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) in acetone:H_2O (8:1) at room temperature to afford a *new* hydroxy-γ-butyrolactone **599** in 69% yield and in >49:1 dr.



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

Scheme 115 Dihydroxylation/lactonisation sequence of unsaturated aldol **592** to afford hydroxy-γ-butyrolactone **599** with strong ^{1}H NOE interactions in **599** confirming stereochemistry

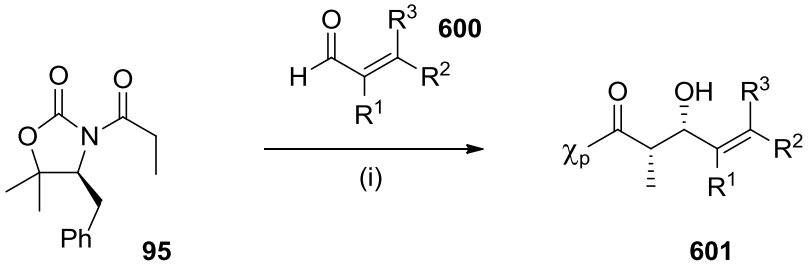
^{1}H NOE spectroscopic analysis was used to assign the stereochemical configuration of the *new* hydroxy-γ-butyrolactone **599**. This revealed a strong interaction between the C-3 proton and the methylene protons of the C-5 ethyl group, as well as a strong interaction between the C-4 proton and the C-5 CH_2OH methylene protons, indicating a (3*S*,4*S*,5*R*) 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 (3*S*,4*S*,5*S*)-hydroxy-γ-butyrolactone **595**. However, application of the dihydroxylation/lactoniation methodology to the same unsaturated aldol product **592** leads to (3*S*,4*S*,5*R*)-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

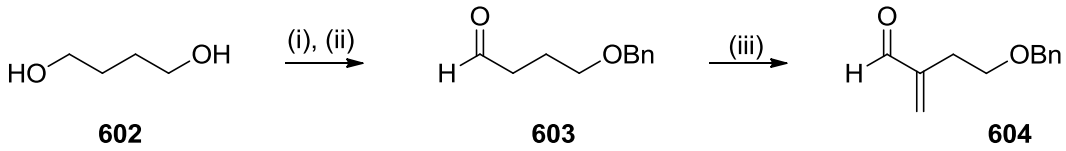
A series of aldol products was prepared according to the methodology previously described in Chapter 2. The alkene geometry of the unsaturated aldol products was varied using the same substitutents in order to investigate the effect of the alkene substitution pattern on the stereochemical outcome of the dihydroxylation/lactonisation reaction. The CH_2OBn 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.[143]



*Reagents and conditions: (i) Bu_2BOTf/ 9-BBNOTf, $N(^iPr)_2Et/NEt_3$, CH_2Cl_2, 0 ˚C then aldehyde **600**, -78 ˚C.*

Scheme 116 Synthesis of α,β-unsaturated *syn*-aldol products **601**

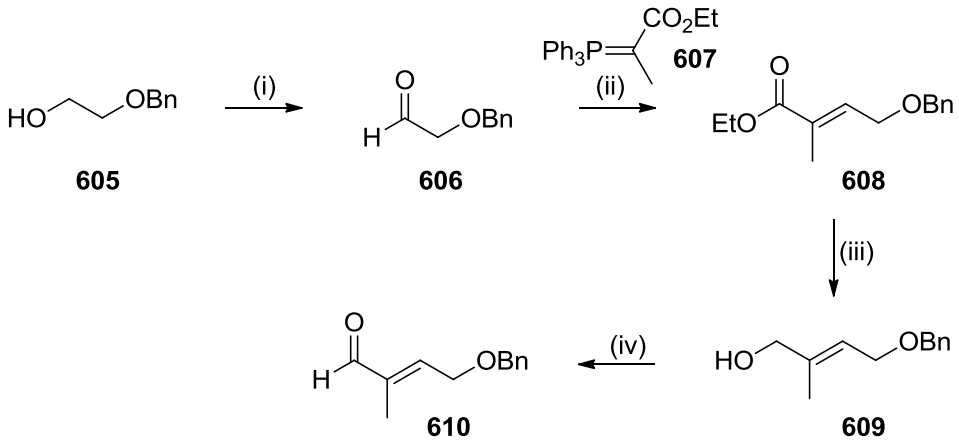
The synthesis of non-commercially available aldehydes was carried out using established literature procedures. Aldehyde **604** was synthesised in three steps from butane-1,4-diol **602**. Mono-benzyl protection of **602** followed by Swern oxidation, produced aldehyde **603** in 75% yield. This was treated with 37% aqueous formaldehyde solution and dimethylamine hydrochloride in a Mannich/elimination type reaction to furnish 4-(benzyloxy)-2-methylenebutanal **604** in 78% yield.[245]



Reagents and conditions: (i) NaH, BnBr, THF, reflux then H_2O; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, -55 ˚C, 15 min then NEt_3, 15 min then H_2O; (iii) CH_2O (37% solution in H_2O), $NEt_2H{\cdot}HCl$, 70 ˚C, 24 h.

Scheme 117 Synthesis of aldehyde **604**

Aldehyde **610** was synthesised from 2-(benzyloxy)ethanol **605** in four steps following a literature procedure.[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.

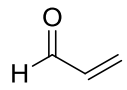
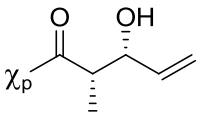
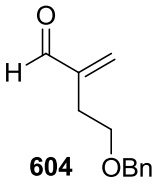
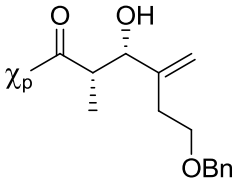
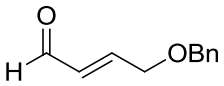
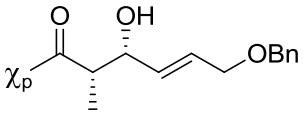
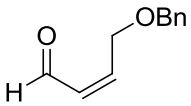
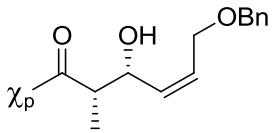
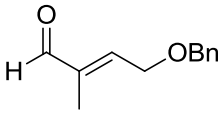
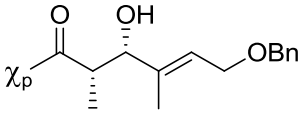
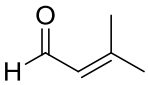
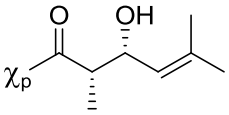


605 **606** **608** **609** **610**

Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, -55 ˚C, 15 min then NEt_3, 15 min then H_2O; (ii) ***607****, CH_2Cl_2, 0 ˚C, 30 min; (iii) DIBAL, Et_2O, -78 ˚C, 1 h then 0 ˚C, 1 h; (iv) $(COCl)_2$, DMSO, CH_2Cl_2, -55 ˚C, 15 min then NEt_3, 15 min then H_2O.*

Scheme 118 Synthesis of aldehyde **610**

The synthesis of (*E*)-4-(benzyloxy)but-2-enal **537** and (*Z*)-4-(benzyloxy)but-2-enal **535**[187] and their aldol products **536** and **538** have previously been described in Chapter 2.

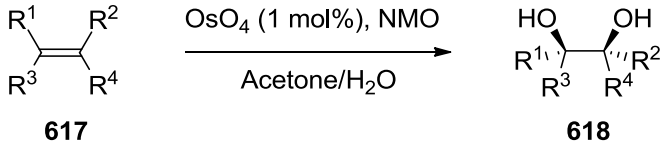
Entry	*Aldehyde*	*Aldol Product*[a]	*Product*	*Yield*[b] *de*
1	 **611**		**613**	53% >95%
2	 **604** OBn		**614**	78% >95%
3	 **537**		**538**	89% >95%
4	 **535**		**536**	88% >95%
5	 **610**		**615**	46% >95%
6	 **612**		**616**	92% >95%

[a]χ_p refers to SuperQuat auxiliary; [b]isolated yield after column chromatography

Table 7 Unsaturated *syn*-aldol products with variation of alkene geometry

3.5 Upjohn Dihydroxylation

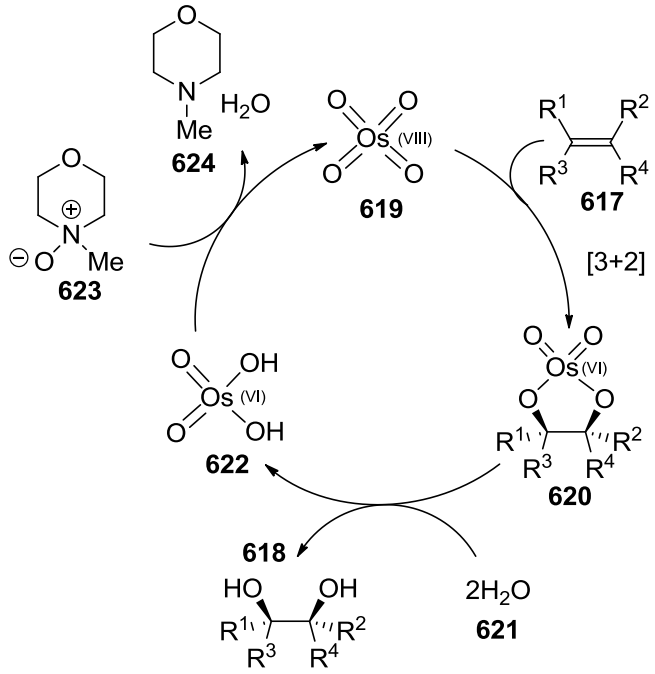
The Upjohn dihydroxylation reaction was first reported in 1976 for the preparation of *cis*-1,2-diols from alkenes using catalytic osmium tetroxide and stoichiometric *N*-methyl-morpholine-*N*-oxide (NMO) as the re-oxidant. It was developed as an alternative to using stoichiometric quantities of toxic, volatile and expensive osmium tetroxide.[244] It is one of the most widely used reactions in organic synthesis due to its mildness, generality and specificity.[247]



Scheme 119 General Upjohn dihydroxylation

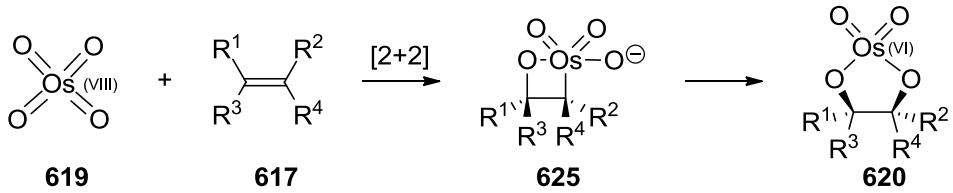
3.5.1 Mechanism of Upjohn Dihydroxylation

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

The mechanism of the reaction is controversial and has been the subject of intense investigation.[247] 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 **620**.[248] 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 **625**, which subsequently rearranges to produce the five membered cyclic osmate ester **620** in the rate determining step.[249]



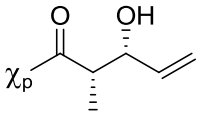
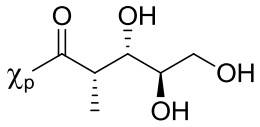
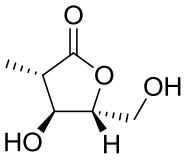
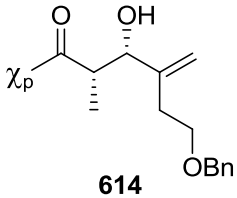
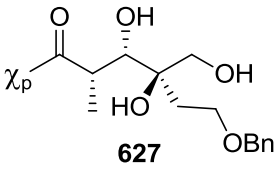
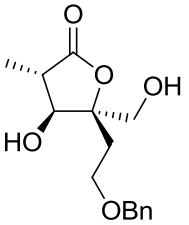
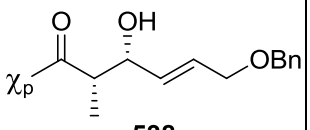
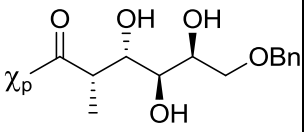
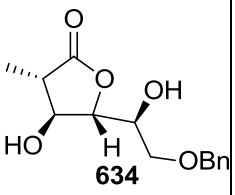
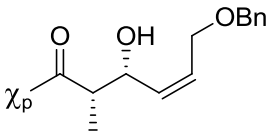
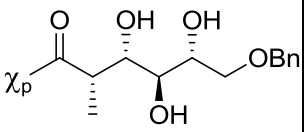
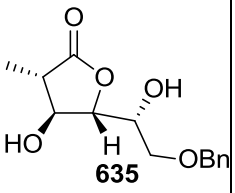
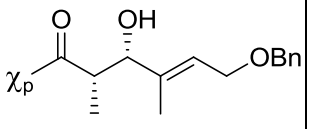
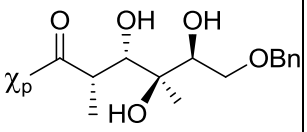
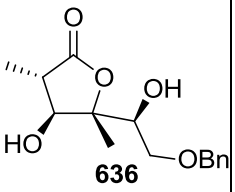
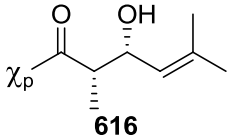
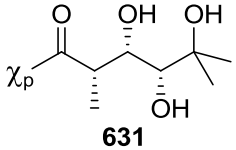
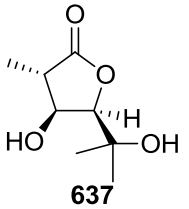
619 **617** **625** **620**

Scheme 121 Proposed [2+2] cycloaddition pathway of Upjohn dihydroxylation

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,[250-252] with this conclusion being supported by computational modelling[253] and experimental kinetic isotope effects.[254]

3.5.2 Synthesis of Highly Substituted Hydroxy-γ-Butyrolactones

Unsaturated *syn*-aldol products **613-616**, **536**, **538** 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-γ-butyrolactones **632-637** in good yield and generally high diastereoselectivity (Table 8).

Entry	*Aldol (**613-616**, **536**, **538**)*[a]	*Triol (**626-631**) (not isolated)*[b]	*Lactone (**632-637**)*[b,c]	*dr*[d]	*Yield*[e]
1	 **613** 53%, >95% de	 **626**	 **632**	3:1	79%
2	 **614** 78%, >95% de	 **627**	 **633**	10:1	93%
3	 **538** 89%, >95% de	 **628**	 **634**	4:1	77%
4	 **536** 88%, >95% de	 **629**	 **635**	2:1	74%
5	 **615** 46%, >95% de	 **630**	 **636**	>49:1	93%
6	 **616** 92%, >95% de	 **631**	 **637**	5:1	41%

[a] χ_p refers to SuperQuat auxiliary. [b] Major diastereoisomer formed. [c] Configuration of hydroxy-γ-butyrolactones confirmed by ^{1}H NOE spectroscopic analysis. [d] Determined by analysis of the crude ^{1}H NMR spectra. [e] Isolated yields after purification by column chromatography.

Table 8 Dihydroxylation of aldols **613-616**, **536**, **538** to afford hydroxy-γ-butyrolactones **632-637**

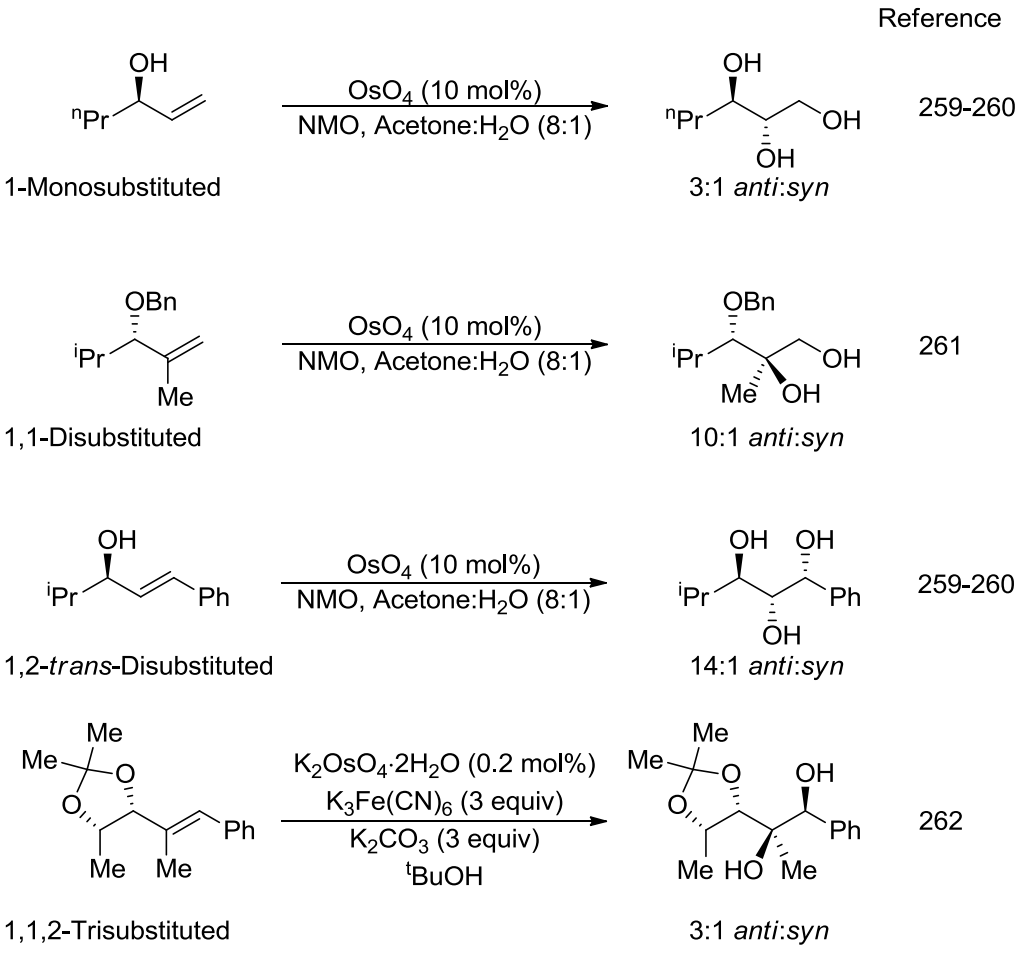
The stereochemical configuration of each of the hydroxy-γ-butyrolactones **632-637** was determined by ^{1}H NOE spectroscopic analysis and X-ray crystallography, as well as by comparison with literature precedent for each of the alkene substitution patterns. In depth analysis of how the configuration 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-butryolactone **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 diastereocontrol 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 (3*S*,4*S*,5*R*)-hydroxy-γ-butyrolactone **637** in 41% yield.

3.6 Assignment of Stereochemistry of Hydroxy-γ-Butyrolactones

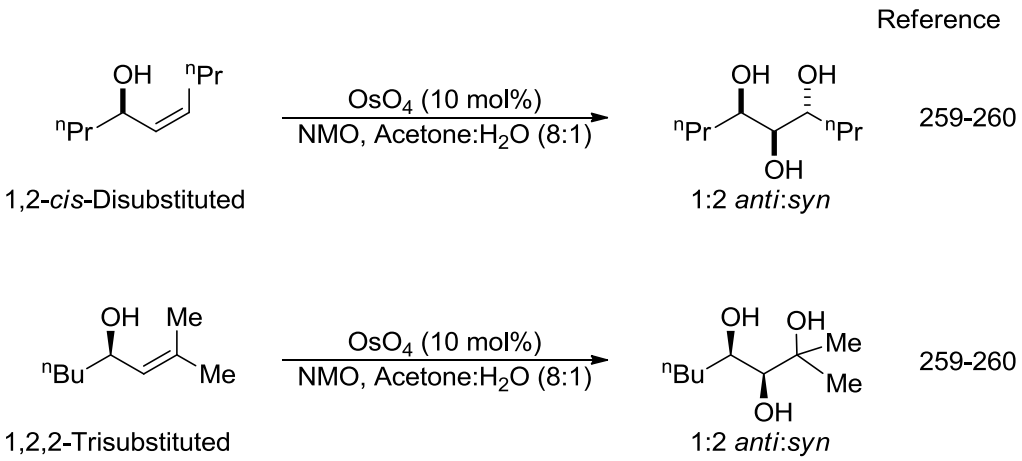
3.6.1 Literature Examples

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



Scheme 122 Literature examples of Upjohn dihydroxylation reactions of allylic alcohols with different alkene substitution patterns giving *anti*-diastereoselectivity

However, 1,2-*cis*-disubstituted[259-260] and 1,2,2-trisubstituted[259-260] alkene systems have been shown to undergo dihydroxylation with modest levels of *syn*-diastereoselectivity.



Scheme 123 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.[261,263] These include models described by Kishi,[264-265] Houk[184,266-268] and Vedejs.[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.[263]

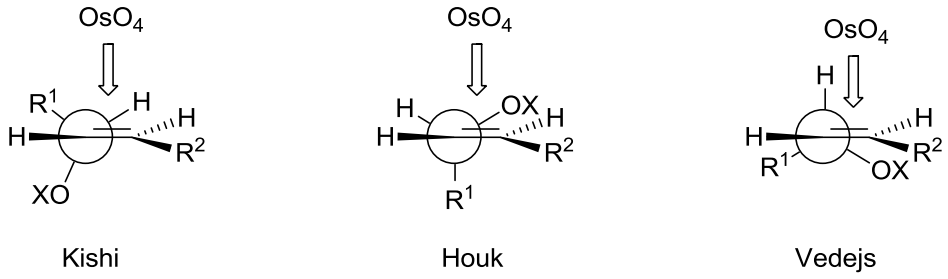
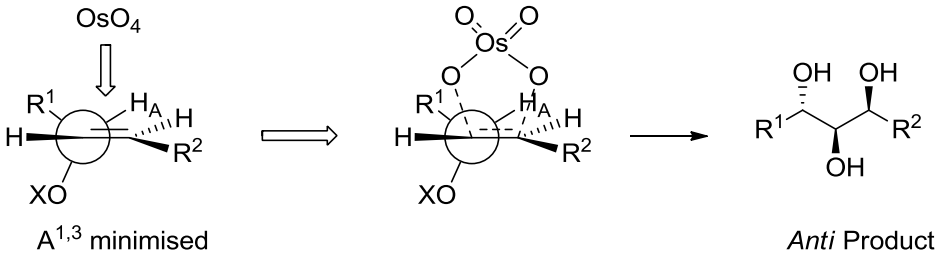


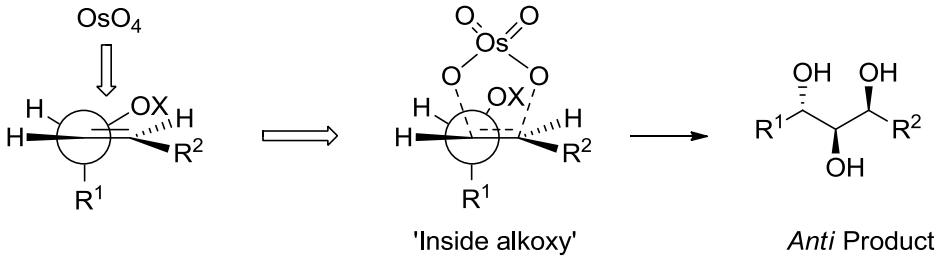
Figure 10 Proposed stereochemical models for *anti*-diastereoselectivity in OsO_4 dihydroxylation

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_A) 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]



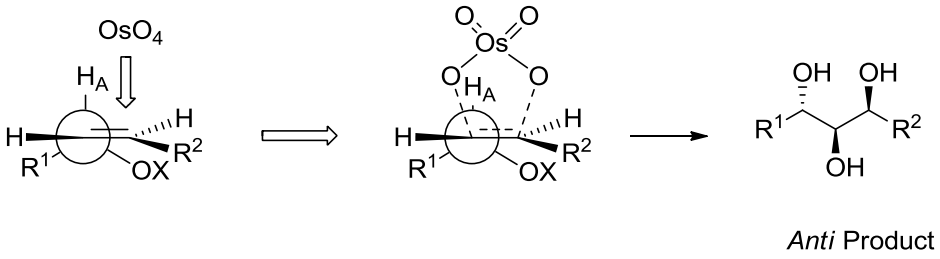
Scheme 124 Kishi model for *anti*-diastereoselectivity in dihydroxylation of allylic alcohols

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 substitutent 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 σ/π 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

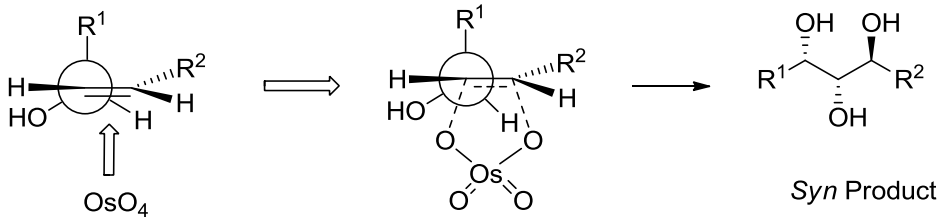
Vedejs suggested that steric interactions between the substrate and the oxidant are dominant in determining the diastereoselectivity. The favoured transition state positions the smallest substituent (H_A) perpendicular to the alkene diastereoface undergoing dihydroxylation. The large alkyl substitutent R^1 is placed on the opposite face of OsO_4 attack to minimise steric hindrance. The stereogenic proton (H_A) minimises steric interactions with the incoming OsO_4 and consequently this model also predicts *anti*-diastereoselectivity.[263,269-270]



Scheme 126 Vedejs model for *anti*-diastereoselectivity in dihydroxylation of allylic alcohols

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 R^1 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*-disubstitited 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 OsO_4 approaches from the same side as the free hydroxyl group. This is further enhanced if the alkyl group R^1 is large, which may allow steric interactions to override electronic factors.[260]



Scheme 127 Modified Kishi model for *syn*-diastereoselectivity in dihydroxylation of *cis*-alkenes

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.[260] 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.[263]

3.6.3 ^{1}H NOE Spectroscopic Analysis

The stereochemistry of hydroxy-γ-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.

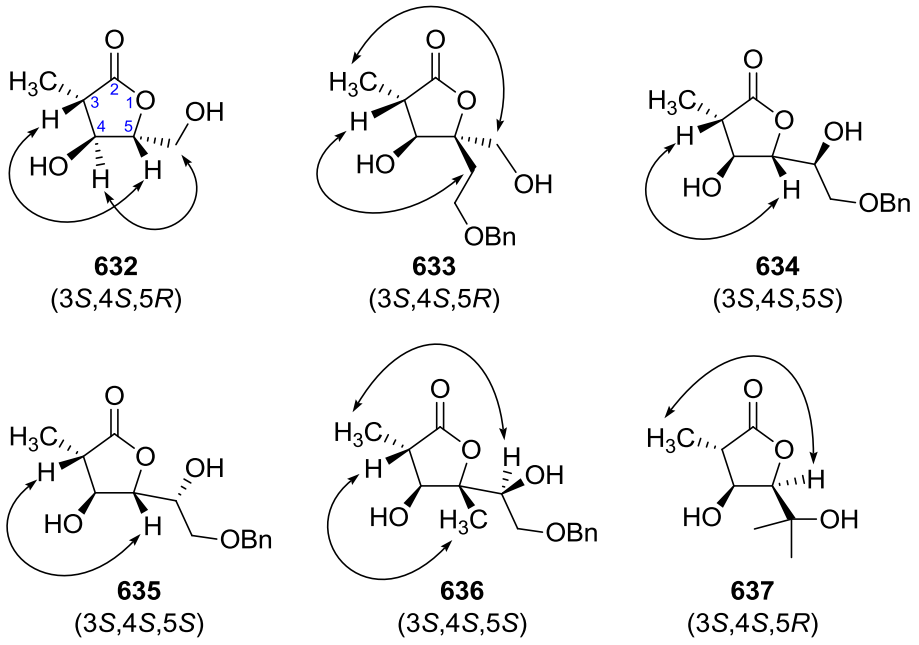


Figure 11 Strong interactions in the ^{1}H NOE spectra of the hydroxy-γ-butyrolactones (**632-637**)

The ^{1}H NOE spectrum of hydroxy-γ-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_2OH methylene protons, indicating a (3*S*,4*S*,5*R*) 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-γ-butyrolactone **633**, derived from 1,1-disubstitued aldol **614**, was unequivocally determined to be (3*S*,4*S*,5*R*) 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_2OH 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]

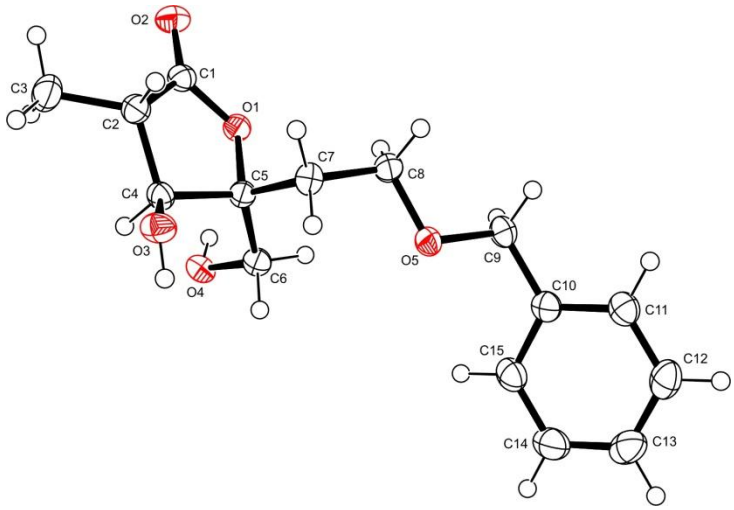


Figure 12 X-ray crystal structure of (3*S*,4*S*,5*R*)-**633**

The ^{1}H NOE spectrum of hydroxy-γ-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 (3*S*,4*S*,5*S*), which corresponds to an *anti*-diastereoselective dihydroxylation and this is supported by the literature examples reported by Donohoe and co-workers.[259-260]

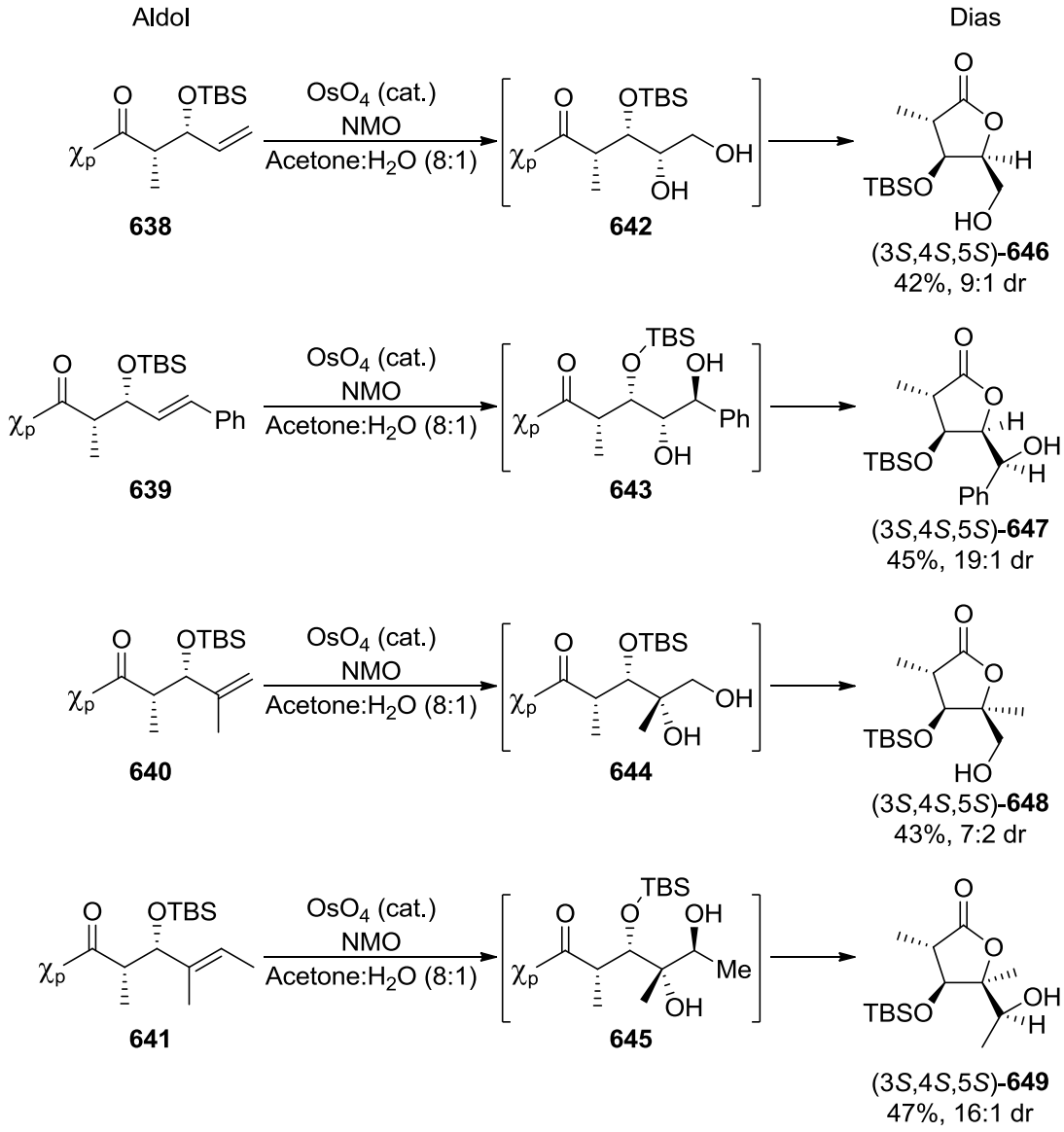
The ^{1}H NOE spectrum for the major diastereomer **635** from the dihydroxylation/lactonisation of 1,2-*cis*-disubstituted alkene **536** revealed a strong interaction between the C-3 proton and C-5 proton, proving that these protons are on the same face of the lactone. Therefore, the stereochemistry was assigned as (3*S*,4*S*,5*S*), which corresponds to *anti*-diasteroselectivity. 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.[259-260] 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.[259-260]

The ^{1}H NOE spectrum of hydroxy-γ-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 C*H*OH proton, leading to a stereochemical assignment of (3*S*,4*S*,5*S*) 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.[262]

The stereochemistry of the major diastereomer **637** of the dihydroxylation/lactonisation reaction of 1,2,2-trisubstituted aldol **616** was determined as (3*S*,4*S*,5*R*), 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.[259-260] The ^{1}H NMR spectrum of the major diastereomer revealed a vicinal coupling constant between protons on C-4 and C-5 of ^{3}J = 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 ^{3}J = 4.0 Hz, which is consistent with an *anti*-relationship between these protons in this diastereoisomer.

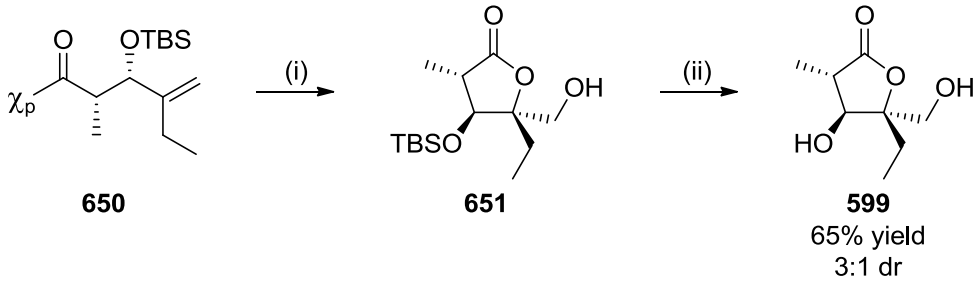
3.7 Reassignment of Literature Published by Dias and Co-workers

Dias and co-workers had previously described the dihydroxylation/lactonisation of a small series of closely related Evans derived γ-alkenyl-*O*-silyl aldol products (**638-641**).[239] Surprisingly, the configuration of the resulting *O*-silyl-γ-butyrolactones (**642-645**) was reported as (3*S*,4*S*,5*S*), 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 β-*O*-silyl hydroxyl group (Scheme 128).



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.[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 ^{1}H, ^{13}C, and NOE spectra were identical to those of the lactone we had previously formed from dihydroxylation/lactonisation of the unprotected aldol **592**.

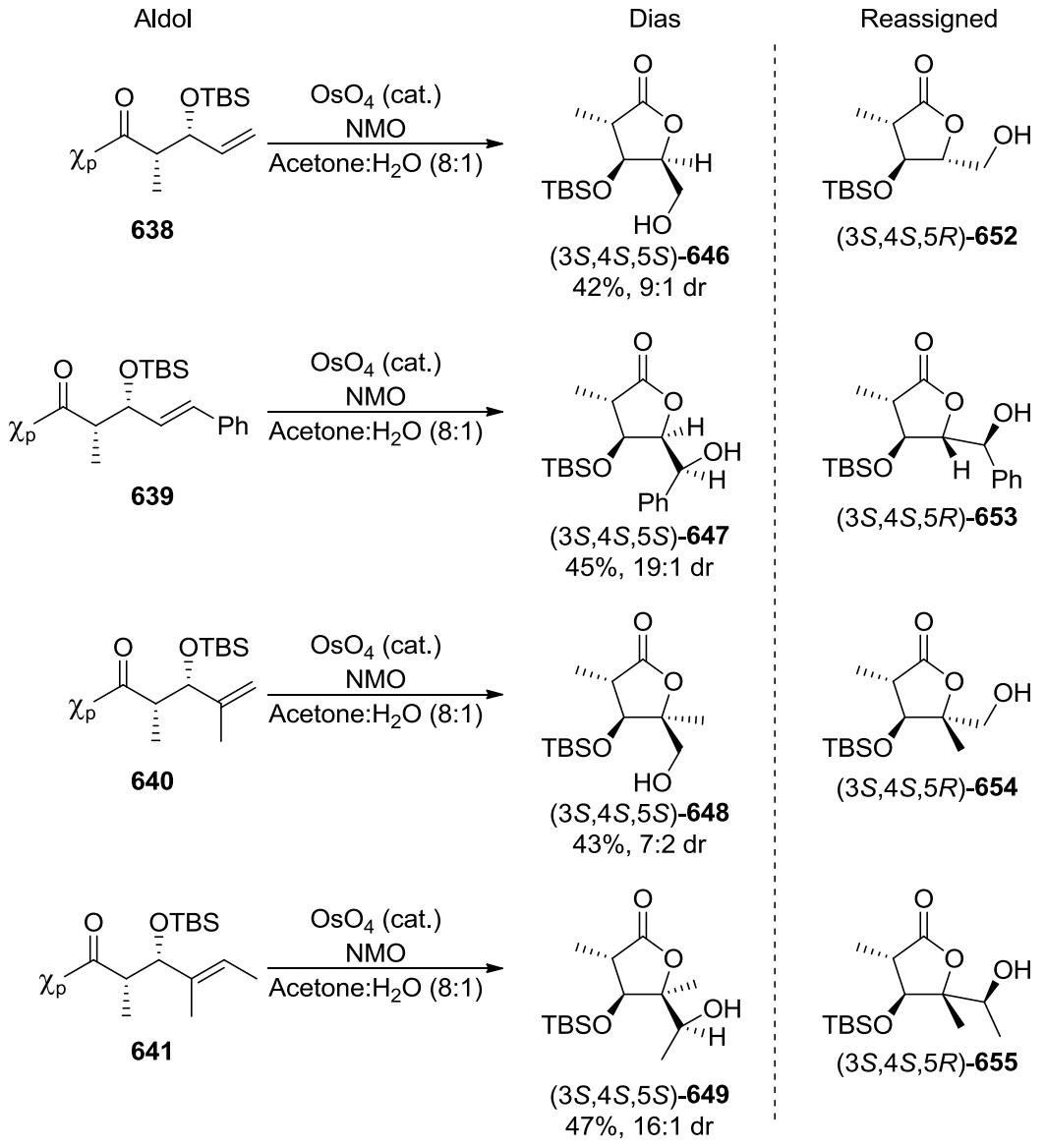


Reagents and conditions: (i) OsO_4 (10 mol%), NMO, acetone:H_2O (8:1); (ii) TBAF, CH_2Cl_2.

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 (3*S*,4*S*,5*R*)-stereochemistry for γ-butyrolactone **646** derived from the dihydroxylation/lactonisation of aldol **638**, which was used for a natural product synthesis.[272] This assignment is different to that reported in their original paper, but is consistent with our results.



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 conditions[273-274] 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 $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3 and a chiral quinine ligand. The $K_2Os_2(OH)_4$ acts as a source of OsO_4, 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, $(DHQD)_2PHAL$ **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 $(DHDQ)_2PHAL$, with a catalytic quantity of OsO_4 sometimes being added to initiate the dihydroxylation reaction.[275]

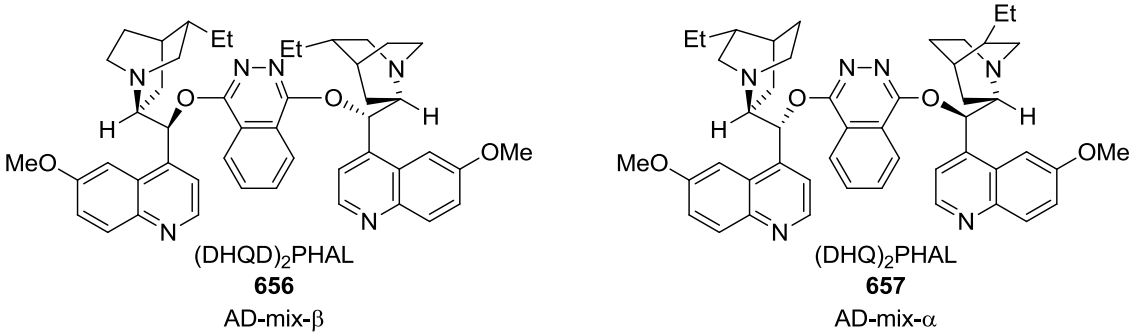
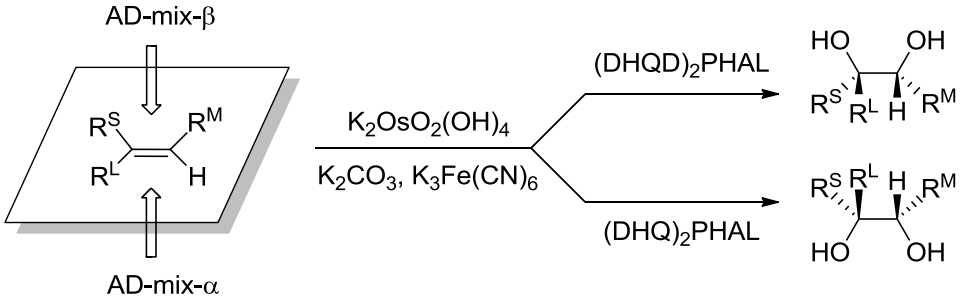


Figure 13 Chiral quinine ligands in AD-mix for Sharpless Asymmetric Dihydroxylation

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

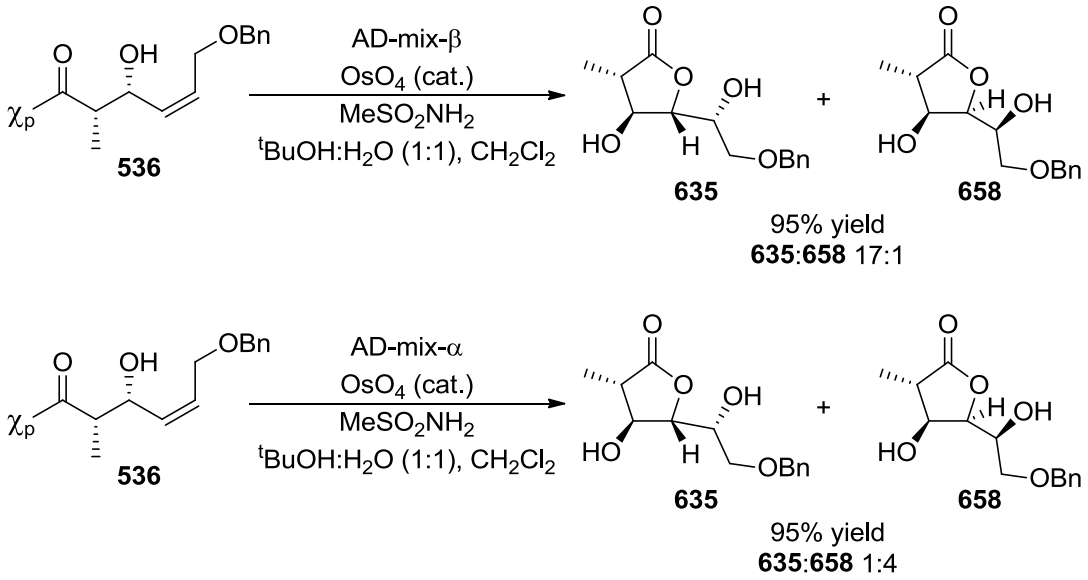
The model is best suited to predicting the enantioselectivity of dihydroxylation reactions of *trans*-alkenes, but cannot usually be used to predict the stereoselective outcome of the dihydroxylation of 1,2-*cis*-disubstituted alkenes.[256,276] Indeed, it is notoriously difficult to obtain high levels 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 enantioselection 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 β-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 OsO_4 was added.

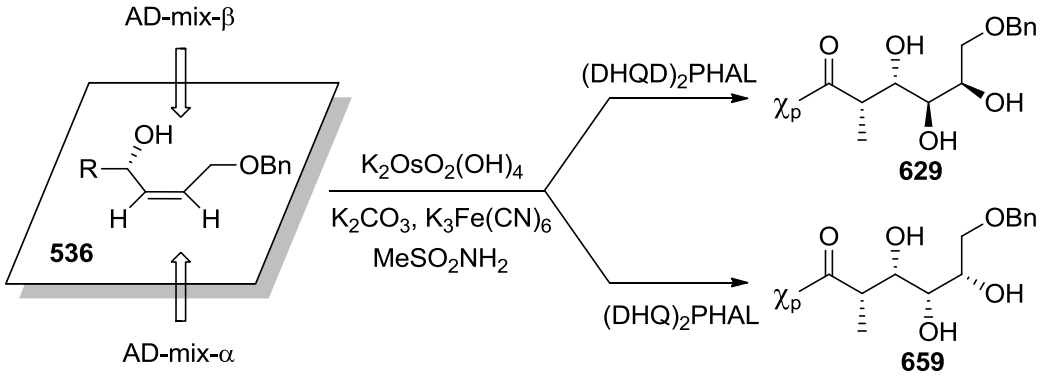
Treatment of *cis*-1,2-disubstituted aldol **536** with AD-mix-β led to an enhancement of stereochemistry observed for dihydroxylation under Upjohn conditions, to afford hydroxy-γ-butyrolactone **635** in a 17:1 mixture of diastereomers and 95% yield in favour of the *anti*-product. Pleasingly, treatment 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**.



Scheme 132 Sharpless asymmetric dihydroxylation of *cis*-1,2-disubstituted aldol **536**

These results are consistent with those obtained by Sharpless and co-workers on the dihydroxylation of a simplified (*Z*)-*O*-benzyl allylic alcohol.[277-278] 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.

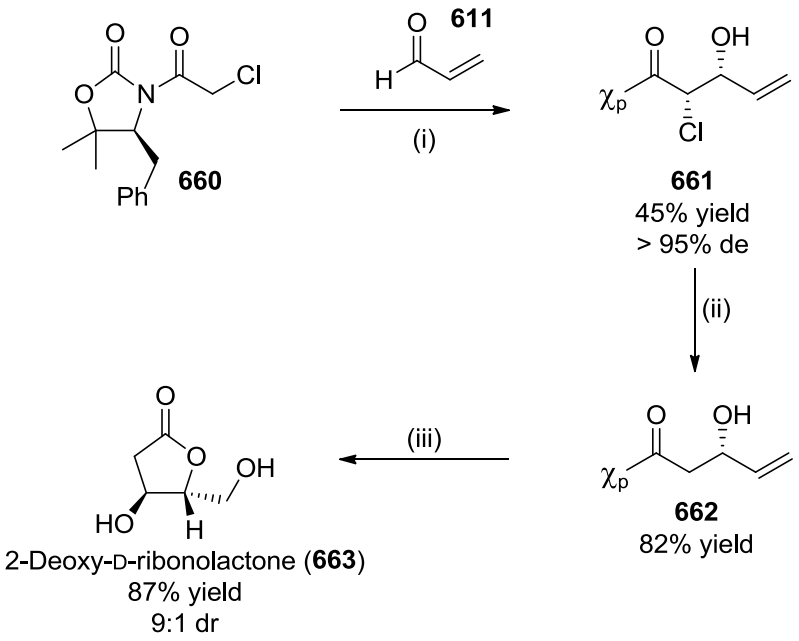


Scheme 133 Modified stereochemical mnemonic for predicting enantioselectivity of Sharpless asymmetric dihydroxylation for 1,2-*cis*-disubstituted aldol **536**

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.[279-280] It has been synthesised several times previously[281-284] and has also been shown to be a useful synthetic precursor.[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.[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.[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.[281-284]

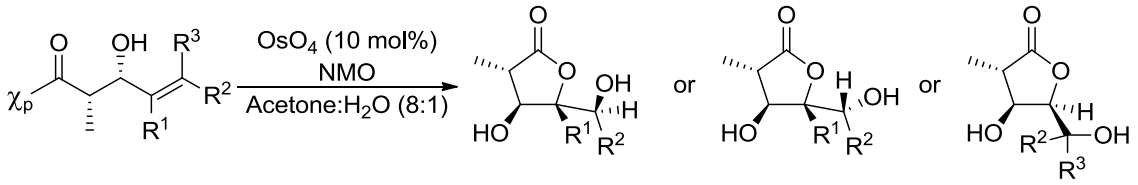


*Reagents and conditions: (i) Bu_2OTf, $N(^iPr)_2Et$, CH_2Cl_2, 0 ˚C, **611**, -78 ˚C to rt; (ii) Zn, NH_4Cl, MeOH, rt; (iii) OsO_4 (10 mol%), NMO, acetone:H_2O (8:1).*

Scheme 134 Asymmetric synthesis of 2-Deoxy-D-ribonolactone **663**

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

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.

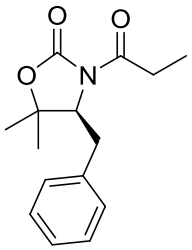
^{1}H and ^{13}C NMR spectra were recorded on a Brüker Advance 250 MHz or a Brüker Advance 300 MHz spectrometer at 303K. The spectra were recorded in $CDCl_3$ solution with chemical shifts reported relative to the residual $CDCl_3$ as an internal standard. Chemical shift is reported in parts per million (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 phosphomolybdic 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^{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

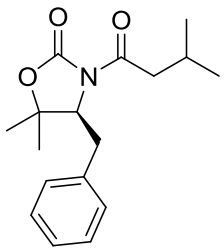
4.1.1 Synthesis of N-Acyl-Oxazolidin-2-ones **95**, **471**-**473**, **515**

(*S*)-4-Benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, 95[242]



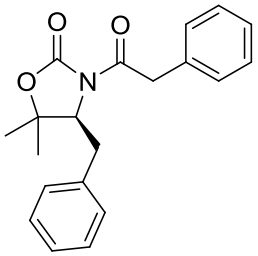
n-BuLi (6.43 mL, 16.0 mmol, 2.5 M solution in hexane) was added to a solution of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **445** (3.00 g, 14.6 mmol) in dry THF (90 mL) at -78 ˚C under nitrogen and was stirred for 30 minutes. Propionyl chloride (1.40 mL, 16.0 mmol) was added in one portion and the 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, $CDCl_3$) δ_H = 7.31-7.17 (5H, m, Ph), 4.48 (1H, dd, *J* = 9.6, 3.9 Hz, C*H*N), 3.12 (1H, dd, *J* = 14.3, 3.9 Hz, CHH_AH$_B$Ph), 2.94-2.81 (3H, m, CH$_A$$H_B$Ph and COC$H_2$), 1.34 (3H, s, C(C$H_3$)(CH$_3$)), 1.33 (3H, s, C(CH$_3$)(C$H_3$)), 1.12 (3H, t, *J* = 7.33 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 1765 (C=O$_{ox}$), 1703 (C=O); HRMS: *m/z* (ES) 262.1446, $C_{15}H_{20}NO_3$ $[M+H]^+$ requires 262.1443; $[\alpha]_D^{25}$ = -42.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-5,5-dimethyl-3-(3-methylbutanoyl)oxazolidin-2-one, 4713[39]



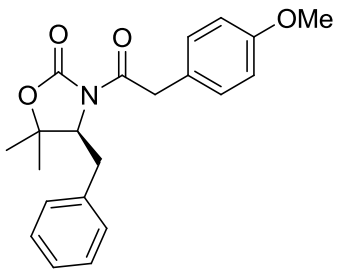
n-BuLi (1.71 mL, 4.29 mmol, 2.5 M solution in hexane) was added to a solution of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **445** (0.80 g, 3.90 mmol) in dry THF (30 mL) at -78 ˚C under nitrogen and was stirred for 30 minutes. Isovaleryl chloride (0.52 mL, 4.29 mmol) was added in one portion and the 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 [CH_2Cl_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}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.17 (5H, m, Ph), 4.49 (1H, dd, *J* = 9.5, 3.9 Hz, C*H*N), 3.11 (1H, dd, *J* = 14.3, 3.9 Hz, CHH_AH$_B$Ph), 2.89-2.77 (3H, m, CHH$_A$$H_B$Ph and COC$H_2$), 2.13 (1H, hep, *J* = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.34 (3H, s, C(CH_3)(CH$_3$)), 1.33 (3H, s, C(CH$_3$)(CH_3)), 0.95 (3H, d, *J* = 1.5 Hz, CH(CH_3)(CH$_3$)), 0.93 (3H, d, *J* = 1.5 Hz, CH(CH$_3$)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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 cm^{-1} ν = 1770 (C=O$_{ox}$), 1694 (C=O); HRMS: *m/z* (ES) 290.1758, $C_{17}H_{24}NO_3$ $[M+H]^+$ requires 290.1756; $[\alpha]_D^{25}$ = -38.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one, 472[291]



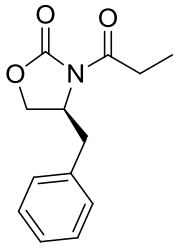
n-BuLi (1.71 mL, 4.29 mmol, 2.5 M solution in hexane) was added to a solution of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **445** (0.80 g, 3.89 mmol) in dry THF (30 mL) at -78 ˚C under nitrogen and was stirred for 30 minutes. Phenylacetyl chloride (0.56 mL, 4.29 mmol) was added in one portion and 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [CH_2Cl_2, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.15 (10H, m, Ph_{ox} and Ph), 4.46 (1H, dd, *J* = 9.6, 3.8 Hz, C*H*N), 4.25 (2H, s, COCH_2Ph), 3.11 (1H, dd, *J* = 14.4, 3.8 Hz, CH_AH$_B$Ph), 2.82 (1H, *J* = 14.4, 9.6 Hz, CH$_A$$H_B$Ph), 1.34 (3H, s, C(C$H_3$)(CH$_3$)), 1.29 (3H, s, C(CH$_3$)(C$H_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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=O_{ox}), 1712 (C=O); HRMS: *m/z* (ES) 324.1605, $C_{20}H_{22}NO_3$ $[M+H]^+$ requires 324.1599; $[\alpha]_D^{25}$ = -36.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



n-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_2Cl_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, $CDCl_3$) δ_H = 7.31-7.19 (7H, m, Ph and $C_6H_2H_2OMe$), 6.87 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2OMe$), 4.50 (1H, dd, *J* = 9.8, 3.7 Hz, C*H*N), 4.22 (2H, s, CH_2Ar), 3.79 (3H, s, OCH_3), 3.13 (1H, dd, *J* = 14.4, 3.7 Hz, CH_AH_BPh), 2.85 (1H, dd, *J* = 14.4, 9.6 Hz, CH$_A$H$_B$Ph), 1.36 (3H, s, C(CH_3)(CH$_3$)), 1.32 (3H, s, C(CH$_3$)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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} ν = 1765 (C=O$_{ox}$), 1711 (C=O); HRMS: *m/z* (ES) 376.1515, $C_{21}H_{23}NNaO_4$ [M+Na]$^+$ requires 376.1524; $[\alpha]_D^{25}$ = -30.0 (*c* = 0.77 g/100 mL in $CHCl_3$).

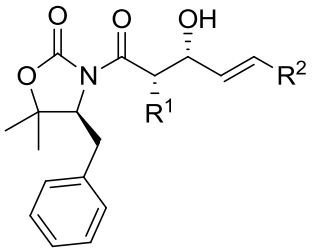
(*S*)-4-Benzyl-3-propionyloxazolidin-2-one, 515[166]



n-BuLi (4.96 mL, 12.42 mmol, 2.5 M solution in hexane) was added to a solution of (*S*)-4-benzyloxazolidin-2-one **444** (2.00 g, 11.29 mmol) in dry THF (60 mL) at -78 ˚C 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 $MgSO_4$ 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}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.15 (5H, m, Ph), 4.66-4.58 (1H, m, C*H*N), 4.17-4.08 (2H, m, CH_2O), 3.24 (1H, dd, *J* = 13.3, 3.2 Hz, CH_AH$_B$Ph), 2.98-2.69 (2H, m, CH_2CH$_3$), 2.73 (1H, dd, *J* = 13.3, 9.5 Hz, CH$_A$$H_B$Ph), 1.15 (3H, t, *J* = 7.3 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 174.0, 153.5, 135.4, 129.4, 128.9, 127.3, 66.2, 55.2, 37.9, 29.2, 8.3; IR cm^{-1} ν = 1785 (C=O$_{ox}$), 1701 (C=O); HRMS: *m/z* (ES) 256.0948, $C_{13}H_{15}NNaO_3$ $[M+Na]^+$ requires 256.0949; $[\alpha]_D^{25}$ = +90.4 (*c* = 0.95 g/100 mL in $CHCl_3$).

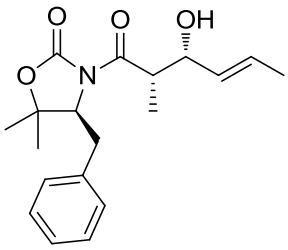
*4.1.2 Synthesis of Syn-Aldol Products **474**-**481**, **517***

Asymmetric *Syn*-Aldol Reaction – General Procedure 1



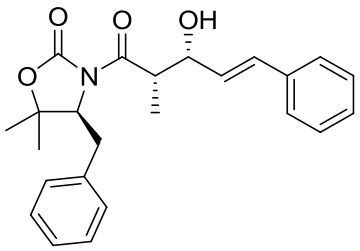
The appropriate acylated auxiliary **95**, **471**-**473**, **515** (1 equiv.) was dissolved in dry dichloromethane at 0 ˚C under nitrogen. Dibutylboron triflate (1.1 equiv., 1.0 M in dichloromethane) was added dropwise. After 30 minutes, *N*,*N*-diisopropylethylamine (1.3 equiv.) was added and the resulting 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 (Na_2PO_4/NaH_2PO_4) (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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford crude product, which was purified as described.

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 474



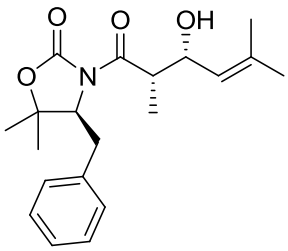
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (1.50 g, 5.74 mmol), dibutylboron triflate (6.31 mL, 6.31 mmol, 1 M in dichloromethane), diisopropylethylamine (1.28 mL, 7.46 mmol) and crotonaldehyde (0.61 mL, 7.46 mmol) in dichloromethane (25 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.54] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*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, dqd, *J* = 15.5, 6.5, 1.0 Hz, CH=C*H*CH_3), 5.48 (1H, ddd, *J* = 15.5, 6.5, 1.5 Hz, C*H*=$CHCH_3$), 4.60 (1H, dd, *J* = 9.0, 4.5 Hz, C*H*N), 4.53 (1H, m, C*H*OH), 3.91 (1H, qd, *J* = 7.0, 4.5 Hz, COC*H*), 3.05 (1H, dd, *J* = 14.5, 4.5 Hz, CH_AH_BPh), 2.90 (1H, dd, *J* = 14.5, 9.0, CH_AH_BPh), 2.60 (1H, d, *J* = 2.5 Hz, O*H*), 1.70 (3H, d, *J* = 6.5 Hz, CH=CHCH_3), 1.39 (3H, s, (CH_3)C(CH_3)), 1.38 (3H, s, (CH_3)C(CH_3)), 1.15 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δc = 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, $C_{19}H_{29}N_2O_4$ $[M+NH_4]^+$ requires 332.1856; $[\alpha]_D^{25}$ = -24.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



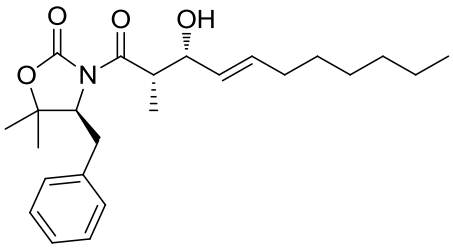
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (1.00 g, 3.83 mmol), dibutylboron triflate (4.21 mL, 4.21 mmol, 1 M in dichloromethane), diisopropylethylamine (0.87 mL, 4.97 mmol) and cinnamaldehyde (0.62 mL, 4.97 mmol) in dichloromethane (12 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.46] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*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, $CDCl_3$) δ_H = 7.40-7.20 (10H, m, Ph_{ox} and Ph), 6.66 (1H, d, *J* = 16.0 Hz, CH=C*H*Ph), 6.19 (1H, dd, *J* = 15.9, 5.9 Hz, C*H*=CHPh), 4.62-4.59 (1H, m, C*H*OH), 4.54 (1H, dd, *J* = 8.8, 4.6 Hz, C*H*N), 4.01 (1H, qd, *J* = 6.8, 4.3 Hz, C*H*CH_3), 3.07 (1H, dd, *J* = 14.4, 4.6 Hz, CH_AH_BPh), 2.91 (1H, dd, *J* = 14.2, 8.7 Hz, CH_AH_BPh), 2.83 (1H, broad s, O*H*), 1.38 (3H, s, C(CH_3)(CH_3)), 1.31 (3H, s, C(CH_3)(CH_3)), 1.20 (3H, d, *J* = 7.4 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 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; $[\alpha]_D^{25}$ = +74.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 476



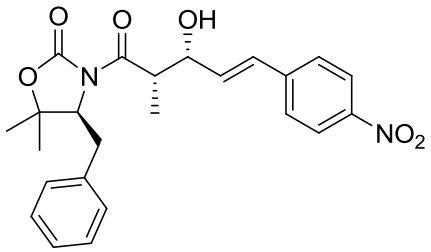
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and 3-methyl-2-butenal (0.38 mL, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.65] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-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, $CDCl_3$) δ_H = 7.33-7.19 (5H, m, Ph), 5.23 (1H, m, C*H*=C$(CH_3)_2$), 4.59 (1H, dd, *J* = 8.7, 5.0 Hz, C*H*OH), 4.51 (1H, dd, *J* = 8.8, 4.6 Hz, C*H*N), 3.97-3.89 (1H, m, C*H*CH_3), 3.05 (1H, dd, *J* = 14.3, 4.5 Hz, CH_AH_BPh), 2.89 (1H, dd, *J* = 14.2, 9.0 Hz, CH_AH_BPh), 2.32 (1H, broad s, O*H*), 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, $CDCl_3$) δ_C = 176.4, 152.7, 136.9, 136.8, 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} ν = 3505 (OH), 1772 (C=O_{ox}), 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-((2*S*,3*R*,*E*)-3-hydroxy-2-methylundec-4-enoyl)-5,5-dimethyloxazolidin-2-one, 477



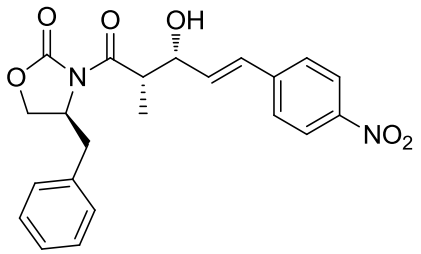
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and *trans*-2-nonenal (0.66 mL, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.68] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*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=C*H*C_6H_{13}), 5.43 (1H, dd, *J* = 15.4, 6.4 Hz, C*H*=CHC_6H_{13}), 4.51 (1H, dd, *J* = 9.0, 4.5 Hz, C*H*N), 4.34 (1H, app. t, *J* = 5.0 Hz, C*H*OH), 3.89 (1H, qd, *J* = 7.0, 4.3 Hz, C*H*CH_3), 3.05 (1H, dd, *J* = 14.3, 4.5 Hz, C$H_A$$H_B$Ph), 2.88 (1H, dd, *J* = 14.3, 9.0 Hz, $CH_A$$H_B$Ph), 2.68 (1H, broad s, O*H*), 2.04-1.97 (2H, m, C=CHCH_2), 1.37-1.24 (14H, m, C_3H_8 and C(CH_3)(CH_3)), 1.13 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.88-0.84 (3H, m, C_5H_{10}CH_3); ^{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_{ox}), 1696 (C=O); HRMS: *m/z* (ES) 424.2451, $C_{24}H_{35}NNaO_4$ $[M+Na]^+$ requires 424.2463; $[\alpha]_D^{25}$ = -18.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)-5,5-dimethyl oxazolidin-2-one, 478



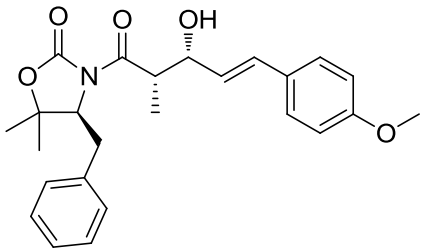
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and *trans*-4-nitrocinnamaldehyde (0.70 g, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [CH_2Cl_2, R_f 0.14] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*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, $CDCl_3$) δ_H = 8.16 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2NO_2$), 7.50 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2NO_2$), 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, CHOH), 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_AH$_B$Ph), 2.92 (1H, dd, *J* = 14.6, 8.8 Hz, CH$_A$$H_B$Ph), 1.41 (3H, s, C(C$H_3$)(CH$_3$)), 1.35 (3H, s, C(CH$_3$)(C$H_3$)), 1.18 (3H, d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 3512 (OH), 1774 (C=O$_{ox}$), 1670 (C=O); HRMS: *m/z* (ES) 461.1657, $C_{24}H_{26}N_2NaO_6$ [M+Na]$^+$ requires 461.1688; $[\alpha]_D^{25}$ = -18.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)oxazolidin-2-one, 517



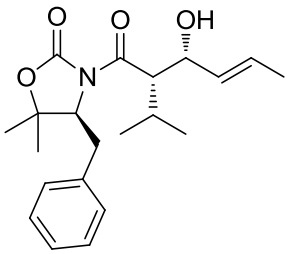
(*S*)-4-Benzyl-3-propionyloxazolidin-2-one **515** (0.80 g, 3.43 mmol) was dissolved in dry dichloromethane (10 mL) at 0 ˚C under nitrogen and was stirred for 30 minutes. 9-Borabicyclo[3.3.1]nonyl triflate (7.54 mL, 3.77 mmol, 0.5 M in hexane) was added dropwise. After 30 minutes, diisopropylethylamine (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-Nitrocinnamaldehyde (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 (Na_2PO_4/NaH_2PO_4) (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 $NaHCO_3$ and 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 [1:4 EtOAc:Petroleum ether, R_f 0.45] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.11 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2NO_2$), 7.46 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2NO_2$), 7.31-7.13 (5H, m, Ph), 6.73 (1H, dd, *J* = 15.9, 1.3 Hz, CH=C*H*$C_6H_4NO_2$), 6.32 (1H, dd, *J* = 15.9, 5.1 Hz, C*H*=$CHC_6H_4NO_2$), 4.72-4.64 (2H, m, C*H*N and C*H*OH), 4.21-4.14 (2H, m, OCH_2), 3.92 (1H, qd, *J* = 7.0, 3.1 Hz, C*H*CH_3), 3.20 (1H, dd, *J* = 13.5, 3.4 Hz, CH_AH_BPh), 2.85 (1H, broad s, O*H*), 2.76 (1H, dd, *J* = 13.4, 9.4 Hz, CH_AH_BPh), 1.23 (3H, d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 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} ν = 3540 (OH), 1773 (C=O_{ox}), 1686 (C=O); HRMS: *m/z* (ES) 433.1358, $C_{22}H_{22}N_2NaO_6$ $[M+Na]^+$ requires 433.1375; $[\alpha]_D^{25}$ = +58.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



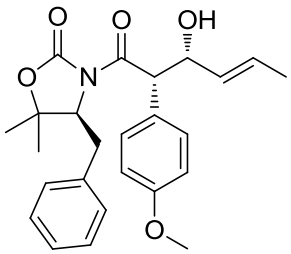
The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.80 g, 3.06 mmol), dibutylboron triflate (3.37 mL, 3.37 mmol, 1 M in dichloromethane), diisopropylethylamine (0.69 mL, 3.98 mmol) and *trans*-4-methoxycinnamaldehyde (0.64 g, 3.98 mmol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:CH_2Cl_2, R_f 0.05] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one **479** (0.72 g, 1.70 mmol) as a yellow solid in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.20 (7H, m, Ph and $C_6H_2H_2OMe$), 6.83 (2H, d, *J* = 8.9 Hz, $C_6H_2H_2OMe$), 6.58 (1H, d, *J* = 15.8 Hz, CH=C*H*C_6H_4OMe), 6.06 (1H, dd, *J* = 15.8, 6.2 Hz, C*H*=CHC_6H_4OMe), 4.59-4.51 (2H, m, C*H*OH and C*H*N), 4.02 (1H, qd, *J* = 7.0, 4.2 Hz, C*H*CH_3), 3.80 (3H, s, OCH_3), 3.06 (1H, dd, *J* = 14.3, 4.6 Hz, CH_AH_BPh), 2.90 (1H, dd, *J* = 14.4, 8.9 Hz, CH_AH_BPh), 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, $CDCl_3$) δ_C = 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} ν = 3509 (OH), 1770 ($C=O_{ox}$), 1692 (C=O), 1511 (OCH_3); HRMS: *m/z* (ES) 446.1926, $C_{25}H_{29}NNaO_5$ $[M+Na]^+$ requires 446.1943; $[\alpha]_D^{25}$ = +8.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-isopropylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 480



The title compound was prepared according to General Procedure 1 from (*S*)-4-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, R_f 0.48] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-isopropylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **480** (0.51 g, 1.42 mmol) as a colourless gum in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.26-7.15 (5H, m, Ph), 5.74-5.58 (2H, m, C*H*=C*H*CH$_3$), 4.54 (1H, dd, *J* = 10.0, 3.7 Hz, C*H*N), 4.36 (1H, app. t, *J* = 6.9 Hz, C*H*OH), 4.09 (1H, dd, *J* = 8.8, 6.7 Hz, C*H*(^{i}Pr)), 3.09 (1H, dd, *J* = 14.3, 3.7 Hz, CH_AH$_B$Ph), 2.83 (1H, dd, *J* = 14.4, 9.8 Hz, CH$_A$*H*$_B$Ph), 2.05-1.92 (1H, m, C*H*(CH$_3$)(CH$_3$)), 1.81 (1H, broad s, O*H*), 1.66 (3H, d, *J* = 5.1 Hz, CH=CHC*H*$_3$), 1.28 (6H, s, C(C*H*$_3$)(C*H*$_3$)), 0.92 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3$)(CH$_3$)), 0.84 (3H, d, *J* = 6.7 Hz, CH(CH$_3$)(C*H*$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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^{-1} ν = 3498 (OH), 1772 (C=O$_{ox}$), 1690 (C=O); HRMS: *m/z* (ES) 382.1984, $C_{21}H_{29}NNaO_4$ [M+Na]$^+$ requires 382.1994; $[\alpha]_D^{25}$ = -14.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

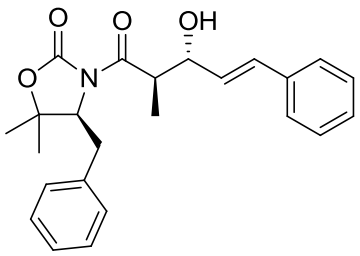
(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 481



The title compound was prepared according to General Procedure 1 from (*S*)-4-benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyloxazolidin-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-((2*S*,3*R*,*E*)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethyloxazolidin-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, $C_6H_2H_2OMe$), 7.19-7.11 (5H, m, Ph), 6.88 (2H, d, *J* = 9.0 Hz, $C_6H_2H_2OMe$), 5.84-5.73 (1H, m, CH=C*H*CH_3), 5.48 (1H, ddd, *J* = 15.3, 7.2, 1.6 Hz, C*H*=$CHCH_3$), 5.13-5.00 (1H, m, C*H*C_6H_4OMe), 4.65 (1H, app. t, *J* = 7.5 Hz, C*H*OH), 4.50 (1H, dd, *J* = 9.2, 4.1 Hz, C*H*N), 3.81 (3H, s, OCH_3), 2.90 (1H, dd, *J* = 14.4, 4.1 Hz, $CH_AH_BCH_3$), 2.70 (1H, dd, *J* = 14.4, 9.2 Hz, $CH_AH_BCH_3$), 2.08 (1H, broad s, O*H*), 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_{ox}), 1693 (C=O), 1511 (OCH_3); HRMS: *m/z* (ES) 446.1945, $C_{25}H_{29}NNaO_5$ $[M+Na]^+$ requires 446.1943; $[\alpha]_D^{25}$ = -74.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

*4.1.3 Synthesis of anti-Aldol Product **483***

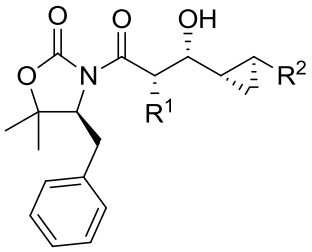
(*S*)-4-Benzyl-3-((2*R*,3*R*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 483



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-((2*R*,3*R*,*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, $CDCl_3$) δ_H = 7.29-7.09 (10H, m Ph and Ph_{ox}), 6.53 (1H, d, *J* = 15.9 Hz, CH=C*H*Ph), 6.15 (1H, dd, *J* = 15.9, 6.7 Hz, C*H*=CHPh), 4.43 (1H, dd, *J* = 9.8, 3.6 Hz, C*H*N), 4.34 (1H, app. t, *J* = 7.1 Hz, C*H*OH), 4.03 (1H, app. quin., *J* = 6.9 Hz, C*H*CH_3), 3.08 (1H, dd, *J* = 14.6, 3.6 Hz, CH_AH_BPh), 3.00 (1H, broad s, O*H*), 2.67 (1H, dd, *J* = 14.6, 9.8 Hz, CH_AH_BPh), 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, $CDCl_3$) δ_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} ν = 3377 (OH), 1774 (C=O_{ox}), 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 $CHCl_3$).

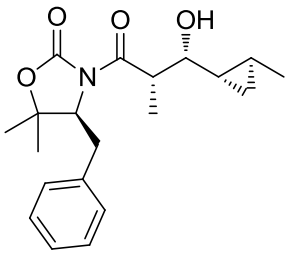
*4.1.4 Synthesis of syn-Cyclopropyl Aldol Products **493**-**501**, **518***

Directed *Syn*-Cyclopropanation – General Procedure 2



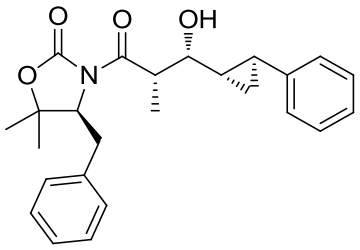
The appropriate *syn*-aldol product **474**-**481**, **483**, **517** (1 equiv.) was dissolved in dichloromethane and stirred at 0 ˚C under nitrogen. Diethylzinc (5 equiv., 1 M in hexane) was added in one portion followed by diiodomethane (5 equiv.). The reaction was stirred for two hours in the absence 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-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 493



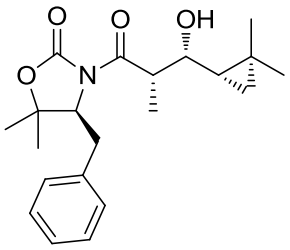
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **474** (0.72 g, 2.17 mmol), diethylzinc (10.86 mL, 10.86 mmol, 1 M in hexane) and diiodomethane (0.87 mL, 10.86 mmol) in dichloromethane (30 mL). The crude product was purified *via* recrystallisation in diethyl ether and hexane to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-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 (Et_2O, hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.18 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.0, 4.3 Hz, C*H*N), 3.98 (1H, qd, *J* = 7.1, 3.8 Hz, (C=O)C*H*), 3.19 (1H, dd, *J* = 8.3, 3.7 Hz, C*H*OH), 3.07 (1H, dd, *J* = 14.3, 4.2 Hz, CH_AH_BPh), 2.88 (1H, dd, *J* = 14.3, 9.2 Hz, CH_AH_BPh), 2.43 (1H, broad s, O*H*), 1.36 (3H, s, $C(CH_3)(CH_3)$), 1.35 (3H, s, $C(CH_3)(CH_3)$), 1.23 (3H, d, *J* = 7.1 Hz, (C=O)CHCH_3), 1.01 (3H, d, *J* = 5.8 Hz, cyclopropyl-CH_3), 0.75-0.60 (2H, m, CHOHC*H*CH_AH_B and cyclopropyl-C*H*CH_3), 0.54-0.48 (1H, m, cyclopropyl-CH_AH_B), 0.33-0.27 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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 ($C=O_{ox}$), 1685 (C=O); HRMS: *m/z* (ES) 368.1827, $C_{20}H_{27}NNaO_4$ $[M+Na]^+$ requires 368.1837; $[\alpha]_D^{25}$ = +4.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



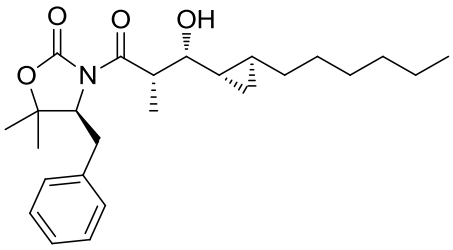
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one **475** (0.70 g, 1.78 mmol), diethylzinc (8.90 mL, 8.90 mmol, 1 M in hexane) and diiodomethane (0.72 mL, 8.90 mmol) in dichloromethane (30 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.28] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **494** (0.69 g, 1.93 mmol) as a white crystalline solid in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.05 (10H, m, Ph_{ox} and Ph), 4.44 (1H, dd, *J* = 9.2, 4.1 Hz, C*H*N), 4.05 (1H, qd, *J* = 7.1, 4.4 Hz, C*H*CH_3), 3.46 (1H, dd, *J* = 8.0, 4.4 Hz, C*H*OH), 3.09 (1H, dd, *J* = 14.3, 4.2 Hz, CH_AH_BPh), 2.87 (1H, dd, *J* = 14.3, 9.3 Hz, CH_AH_BPh), 2.51 (1H, broad s, O*H*), 1.94-1.88 (1H, m, cyclopropyl-Ph), 1.38-1.31 (1H, m, CHOHC*H*CH_AH_B), 1.35 (3H, s, C(CH_3)(CH_3)), 1.26 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.16 (3H, s, C(CH_3)(CH_3)), 1.12-1.06 (1H, m, cyclopropyl-CH_AH_B), 1.02-0.96 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 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 $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one, 495



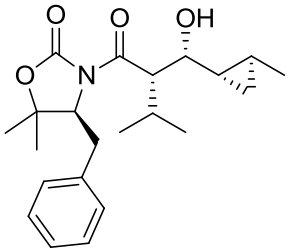
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **476** (0.58 g, 1.68 mmol), diethylzinc (8.39 mL, 8.40 mmol, 1 M in hexane) and diiodomethane (0.67 mL, 8.40 mmol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.47] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **495** (0.59 g, 1.64 mmol) as a colourless oil in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.18 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.2, 4.3 Hz, C*H*N), 3.94 (1H, qd, *J* = 7.1, 3.4 Hz, C*H*CH_3), 3.51 (1H, dd, *J* = 9.3, 3.4 Hz, C*H*OH), 3.08 (1H, dd, *J* = 14.4, 4.2 Hz, CH_AH_BPh), 2.88 (1H, dd, *J* = 14.3, 9.3 Hz, CH_AH_BPh), 2.63 (1H, broad s, O*H*), 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, C*H*-cyclopropyl-(CH_3)(CH_3)), 0.57-0.53 (1H, m, cyclopropyl-CH_AH_B), 0.31-0.28 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 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 $CHCl_3$).

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



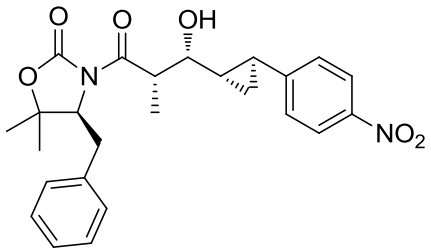
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylundec-4-enoyl)-5,5-dimethyloxazolidin-2-one **477** (0.43 g, 1.04 mmol), diethylzinc (5.17 mL, 5.173 mmol, 1 M in hexane) and diiodomethane (0.42 mL, 5.17 mmol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.40] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-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, $CDCl_3$) δ_H = 7.30-7.17 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.3, 4.0 Hz, C*H*N), 3.97 (1H, qd, *J* = 7.1, 3.3 Hz, C*H*CH_3), 3.21 (1H, dd, *J* = 8.4, 3.3 Hz, C*H*OH), 3.08 (1H, dd, *J* = 14.3, 4.1 Hz, CH_AH_BPh), 2.87 (1H, dd, *J* = 14.3, 9.3 Hz, CH_AH_BPh), 2.53 (1H, broad s, O*H*), 1.36-1.13 (19H, m, C_5H_{10}, CHCH_3, d, *J* = 7.1 Hz, C(CH_3)(CH_3)), 0.88-0.84 (3H, m, $C_5H_{10}CH_3$), 0.78-0.63 (2H, m, CHOHC*H*CH_AH_B and cyclopropyl-C*H*-alkyl), 0.54-0.48 (1H, m, cyclopropyl-CH_AH_B), 0.36-0.30 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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 ($C=O_{ox}$), 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((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one, 497



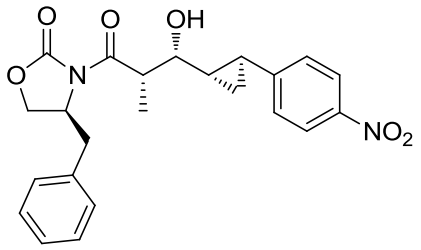
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-isopropylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **480** (0.66 g, 1.84 mmol), diethylzinc (9.18 mL, 9.18 mmol, 1 M in hexane) and diiodomethane (0.73 mL, 9.18 mmol) in dichloromethane (30 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.11] to afford (*S*)-4-benzyl-3-((*S*)-2-((*R*)-hydroxy((1*S*,2*S*)-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, $CDCl_3$) δ_H = 7.28-7.13 (5H, m, Ph), 4.56 (1H, dd, *J* = 10.3, 3.3 Hz, C*H*N), 4.17 (1H, dd, *J* = 8.5, 6.5 Hz, (C=O)C*H*), 3.30 (1H, dd, *J* = 8.9, 6.5 Hz, C*H*OH), 3.16 (1H, dd, *J* = 14.4, 3.3 Hz, CH_AH$_B$Ph), 2.80 (1H, dd, *J* = 14.4, 10.3 Hz, CH$_A$$H_B$Ph), 2.21 (1H, m, C*H*($CH_3$)($CH_3$)), 1.93 (1H, broad s, O*H*), 1.29 (3H, s, C(CH_3)(CH_3)), 1.27 (3H, s, C(CH_3)(CH_3)), 0.99 (3H, d, *J* = 6.0 Hz, cyclopropyl-CH_3), 0.96 (3H, d, *J* = 6.7 Hz, CH(CH_3)(CH_3)), 0.94-0.87 (1H, m, C*H*CH_3), 0.88 (3H, d, *J* = 6.7 Hz, CH(CH_3)(CH_3)), 0.74-0.66 (1H, m, CHOHC*H*CH$_A$H$_B$), 0.43-0.37 (1H, m, cyclopropyl-CH_AH$_B$), 0.24-0.18 (1H, m, cyclopropyl-CH$_A$$H_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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$_{ox}$), 1689 (C=O); HRMS: *m/z* (ES) 396.2161 $C_{22}H_{31}NNaO_4$ $[M+Na]^+$ requires 396.2150; $[\alpha]_D^{25}$ = +18.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-(4-nitrophenyl)cyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 498



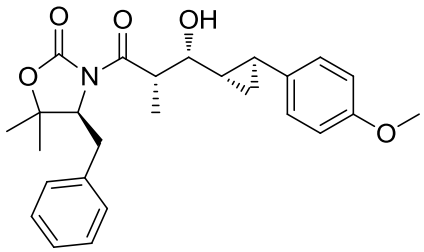
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)-5,5-dimethyloxazolidin-2-one **478** (0.20 g, 0.46 mmol), diethylzinc (2.28 mL, 2.28 mmol, 1 M in hexane) and diiodomethane (0.18 mL, 2.28 mmol) in 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-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-(4-nitrophenyl)cyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **498** (0.19 g, 0.42 mmol) as a yellow oil in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.11 (2H, d, *J* = 8.9 Hz, $C_6H_2H_2NO_2$), 7.33-7.22 (5H, m, Ph), 7.17 (2H, d, *J* = 8.9 Hz, $C_6H_2H_2NO_2$), 4.49 (1H, dd, *J* = 8.9, 4.6 Hz, C*H*N), 4.02 (1H, qd, *J* = 7.0, 3.5 Hz, C*H*CH_3), 3.60 (1H, dd, *J* = 7.1, 3.5 Hz, C*H*OH), 3.05 (1H, dd, *J* = 14.2, 4.6 Hz, $CH_AH_BCH_3$) 2.89 (1H, dd, *J* = 14.2, 9.0 Hz, $CH_AH_BCH_3$), 2.04-1.98 (1H, m, cyclopropyl-$C_6H_4NO_2$), 1.65 (1H, broad s, O*H*), 1.46-1.38 (1H, m, CHOHC*H*CH_AH_B), 1.38 (3H, s, C(CH_3)(CH_3)), 1.32-1.27 (1H, m, cyclopropyl-CH_AH_B), 1.27 (3H, s, C(CH_3)(CH_3)), 1.22 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.14-1.07 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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} ν = 3512 (OH), 1769 ($C=O_{ox}$), 1691 (C=O); HRMS: *m/z* (ES) 475.1835, $C_{25}H_{28}N_2NaO_6$ $[M+Na]^+$ requires 475.1845; $[\alpha]_D^{25}$ = +68.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



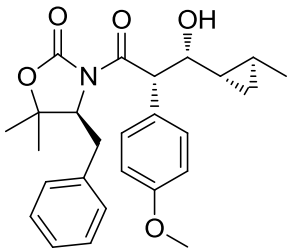
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methyl-5-(4-nitrophenyl)pent-4-enoyl)oxazolidin-2-one **517** (0.20 g, 0.49 mmol), diethylzinc (2.44 mL, 2.44 mmol, 1 M in hexane) and diiodomethane (0.20 mL, 2.44 mmol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, R_f 0.12] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-(4-nitrophenyl)cyclopropyl)propanoyl)oxazolidin-2-one **518** (0.167 g, 0.39 mmol) as an orange oil in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.03 (2H, d, *J* = 8.9 Hz, $C_6H_2H_2NO_2$), 7.29-7.18 (3H, m, Ph), 7.10 (2H, d, *J* = 8.4 Hz, $C_6H_2H_2NO_2$), 7.11-7.08 (2H, m, Ph), 4.58-4.50 (1H, m, C*H*N), 4.07-3.97 (2H, m, CH_AH_BCHN and $CHCH_3$), 3.87 (1H, app. t, *J* = 8.4 Hz, CH_AH_BCHN), 3.50 (1H, dd, *J* = 7.4, 4.1 Hz, C*H*OH), 3.13 (1H, dd, *J* = 13.4, 3.2 Hz, CH_AH_BPh), 2.70 (1H, dd, *J* = 13.4, 9.2 Hz, CH_AH_BPh), 2.51 (1H, broad s, O*H*), 1.94-1.90 (1H, m, cyclopropyl-aryl), 1.46-1.38 (1H, m, $CHOHCHCH_AH_B$), 1.27-1.18 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.25-1.18 (1H, m, cyclopropyl-CH_AH_B), 1.06-1.00 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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 ($C=O_{ox}$), 1695 (C=O); HRMS: *m/z* (ES) 447.1529, $C_{23}H_{24}N_2NaO_6$ $[M+Na]^+$ requires 447.1532; $[\alpha]_D^{25}$ = +176.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropyl)-2-methyl propanoyl)-5,5-dimethyloxazolidin-2-one, 499



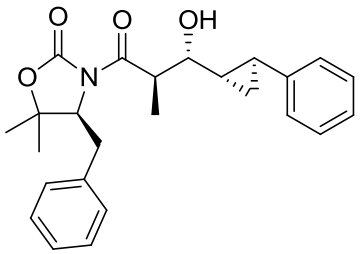
The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one **479** (0.66 g, 1.56 mmol), diethylzinc (7.79 mL, 7.79 mmol, 1 M in hexane) and diiodomethane (0.63 mL, 7.79 mmol) 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-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoyl)-5,5-dimethyloxazolidin-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, $C_6H_2H_2OMe$), 6.79 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2OMe$), 4.45 (1H, dd, *J* = 9.2, 4.2 Hz, C*H*N), 4.06 (1H, qd, *J* = 7.0, 4.2 Hz, C*H*CH_3), 3.76 (3H, s, OCH_3), 3.44 (1H, dd, *J* = 8.0, 4.2 Hz, C*H*OH), 3.09 (1H, dd, *J* = 14.3, 4.2 Hz, C$H_AH_BCH_3$), 2.87 (1H, dd, *J* = 14.3, 9.3 Hz, $CH_AH_BCH_3$), 2.47 (1H, broad s, O*H*), 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, CHOHC*H*CH_AH_B), 1.19 (3H, s, C(CH_3)(CH_3)), 1.06-1.00 (1H, m, cyclopropyl-CH_AH_B), 0.95-0.89 (1H, m, cyclopropyl-CH_AH_B); ^{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_{ox}), 1692 (C=O); HRMS: *m/z* (ES) 460.2107, $C_{26}H_{31}NNaO_5$ $[M+Na]^+$ requires 460.2099; $[\alpha]_D^{25}$ = +62.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-(4-methoxyphenyl)-3-((1*S*,2*S*)-2-methylcyclopropyl) propanoyl)-5,5-dimethyloxazolidin-2-one, 500



The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-(4-methoxyphenyl)hex-4-enoyl)-5,5-dimethyloxazolidin-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, R_f 0.32] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-(4-methoxyphenyl)-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **500** (0.21 g, 0.48 mmol) as a colourless oil in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.35 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2OMe$), 7.28-7.16 (5H, m, Ph), 6.87 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2OMe$), 5.11 (1H, broad d, *J* = 3.5 Hz, (C=O)C*H*), 4.56 (1H, dd, *J* = 9.8, 3.5 Hz, C*H*N), 3.80 (3H, s, OCH_3), 3.55 (1H, dd, *J* = 7.8, 5.8 Hz, C*H*OH), 2.96 (1H, dd, *J* = 14.5, 3.2 Hz, $CH_AH_BCH_3$), 2.68 (1H, dd, *J* = 14.5, 9.5 Hz, $CH_AH_BCH_3$), 2.61 (1H, broad s, O*H*), 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, $CHOHCHCH_AH_B$ and cyclopropyl-CH_AH_B), 0.30-0.23 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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 ($C=O_{ox}$), 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 $CHCl_3$).

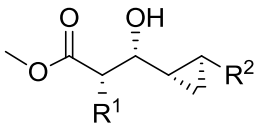
(*S*)-4-Benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 501



The title compound was prepared according to General Procedure 2 from (*S*)-4-benzyl-3-((2*R*,3*R*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)-5,5-dimethyloxazolidin-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, R_f 0.11] to afford (*S*)-4-benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **501** (1.26 g, 3.09 mmol) as a colourless oil in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_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, C*H*N), 4.17 (1H, app. quin., *J* = 7.0 Hz, C*H*CH_3), 3.38 (1H, app. t, *J* = 7.4 Hz, C*H*OH), 3.09 (1H, dd, *J* = 14.7, 3.3 Hz, C$H_A$$H_B$Ph), 2.93 (1H, broad s, O*H*), 2.62 (1H, dd, *J* = 14.5, 9.9 Hz, CH_AH_BPh), 1.94-1.88 (1H, m, cyclopropyl-Ph), 1.30-1.17 (m, 10H, C(CH_3)(CH_3) and CHCH_3 and cyclopropyl-C$H_A$$H_B$), 1.11-0.98 (2H, m, CHOHC*H*CH_AH_B and cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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 $CHCl_3$).

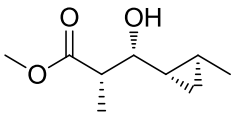
*4.1.5 Synthesis of Methyl Esters **506**-**514***

Synthesis of Methyl Ester – General Procedure 3



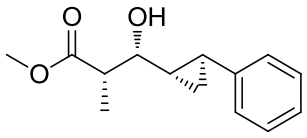
The appropriate *syn*-aldol cyclopropane product ***493***-***501, 518*** (1 equiv.) was dissolved in dichloromethane under nitrogen. A solution of sodium methoxide (1 equiv., 0.5 M in methanol) was added and the reaction was stirred for five minutes. The reaction was quenched with saturated ammonium chloride (5 mL) and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford crude product, which was purified as described.

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



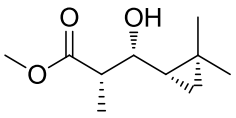
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **493** (0.43 g, 1.25 mmol) and sodium methoxide (2.49 mL, 1.25 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Hexane, R_f 0.14] to afford (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate **506** (0.16 g, 0.93 mmol) as a colourless oil in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.69 (3H, s, OC*H*$_3$), 3.08 (1H, dd, *J* = 8.7, 5.1 Hz, C*H*OH), 2.67 (1H, qd, *J* = 7.0, 5.1 Hz, (C=O)C*H*), 2.26 (1H, broad s, O*H*), 1.24 (3H, d, *J* = 7.0 Hz, (C=O)CHC*H*$_3$), 0.98 (3H, d, *J* = 5.9 Hz, cyclopropyl-C*H*$_3$), 0.69-0.54 (2H, m, CHOHC*H*CH_AH_B and $CHCH_3$), 0.54-0.46 (1H, m, cyclopropyl-C*H*$_A$H$_B$), 0.31-0.26 (1H, m, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 175.9, 76.8, 51.8, 45.6, 23.9, 18.3, 12.4, 11.4, 11.3; IR cm^{-1} ν = 3444 (OH), 1718 (C=O); HRMS: *m/z* (ES) 195.0995 $C_9H_{16}NaO_3$ [M+Na]+ requires 195.0997; $[\alpha]_D^{25}$ = +32.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(2*S*,3*R*)-Methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate, 507



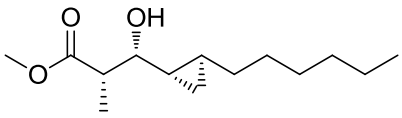
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **494** (0.50 g, 1.23 mmol) and sodium methoxide (2.45 mL, 1.23 mmol, 0.5 M in methanol) in dichloromethane (50 mL). The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, R_f 0.49] to afford (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-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, C*H*OH), 2.76 (1H, qd, *J* = 7.2, 4.7 Hz, C*H*CH_3), 2.51 (1H, broad s, O*H*), 1.87-1.80 (1H, m, cyclopropyl-Ph), 1.38-1.31 (1H, m, CHOHC*H*CH_AH_B), 1.28 (3H, d, *J* = 7.2 Hz, CHCH_3), 1.12-1.05 (1H, m, cyclopropyl-CH_AH_B), 1.01-0.95 (1H, m, cyclopropyl-CH_AH_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; $[\alpha]_D^{25}$ = +74.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(2*S*,3*R*)-Methyl 3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate, 508



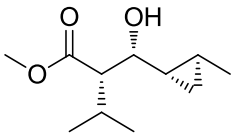
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **495** (0.20 g, 0.56 mmol) and sodium methoxide (1.11 mL, 0.56 mmol, 0.5 M in methanol) in dichloromethane (20 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.47] to afford (2*S*,3*R*)-methyl 3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate **508** (0.09 g, 0.49 mmol) as a colourless liquid in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.71 (3H, s, OCH_3), 3.49 (1H, dd, *J* = 9.6, 4.1 Hz, C*H*OH), 2.64 (1H, qd, *J* = 7.1, 4.4 Hz, (C=O)C*H*), 2.25 (1H, s, O*H*), 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, CHOHC*H*CH_AH_B), 0.59-0.55 (1H, m, cyclopropyl-CH_AH_B), 0.34-0.31 (1H, m, cyclopropyl-CH_AH_B); ^{13}C 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; $[\alpha]_D^{25}$ = +46.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(2*S*,3*R*)-Methyl 3-((1*S*,2*S*)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate, 509



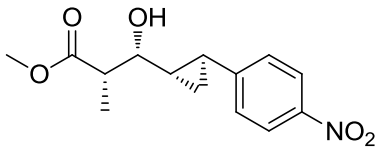
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **496** (0.43 g, 1.05 mmol) and sodium methoxide (2.10 mL, 1.05 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.41] to afford (2*S*,3*R*)-methyl 3-((1*S*,2*S*)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate **509** (0.19 g, 0.78 mmol) as a colourless liquid in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.70 (3H, s, OCH3), 3.16 (1H, dd, *J* = 8.6, 4.3 Hz, C*H*OH), 2.68 (1H, qd, *J* = 7.1, 4.3 Hz, C*H*CH_3), 2.15 (1H, broad s, O*H*), 1.27 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.30-1.11 (10H, m, C_5H_{10}), 0.90-0.85 (3H, m, $C_5H_{10}CH_3$), 0.74-0.47 (3H, m, C*H*CH_3, CHOHC*H*CH_AH_B, cyclopropyl-C*H*$_A$H$_B$), 0.37-0.31 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 176.1, 76.5, 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, $C_{14}H_{26}NaO_3$ [M+Na]$^+$ requires 265.1779; $[\alpha]_D^{25}$ = +38.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-Methyl-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate, 510



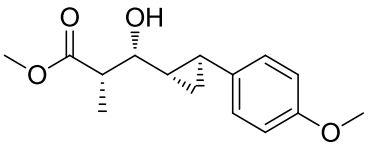
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((*S*)-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoyl)-5,5-dimethyloxazolidin-2-one **497** (0.41 g, 1.10 mmol) and sodium methoxide (2.19 mL, 1.10 mmol, 0.5 M in methanol) in dichloromethane (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, R_f 0.39] to afford (*S*)-methyl-2-((*R*)-hydroxy((1*S*,2*S*)-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, OC*H*$_3$), 3.18 (1H, app. t, *J* = 8.0 Hz, C*H*OH), 2.53 (1H, dd, *J* = 8.0, 6.1 Hz, (C=O)C*H*), 2.21 (1H, app. sex., *J* = 6.8 Hz, CHC*H*(CH_3)(CH_3)), 1.70 (1H, broad s, O*H*), 1.00-0.97 (9H, m, CH(C*H*$_3$)(C*H*$_3$) and cyclopropyl-C*H*$_3$), 0.78-0.64 (2H, m, CHOHC*H*CH_AH_B and C*H*CH_3), 0.50-0.44 (1H, m, cyclopropyl-C*H*$_A$H$_B$), 0.30-0.24 (1H, m, cyclopropyl-CH$_A$*H*$_B$); ^{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; $[\alpha]_D^{25}$ = +12.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



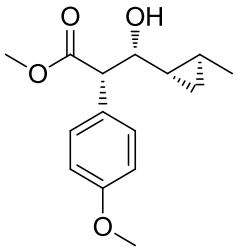
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-(4-nitrophenyl)cyclopropyl)propanoyl)oxazolidin-2-one **498** (0.40 g, 0.94 mmol) and sodium methoxide (1.88 mL, 0.94 mmol, 0.5 M in methanol) in dichloromethane (40 mL). The crude product was purified using flash silica chromatography [2:3 EtOAc:Petroleum ether, R_f 0.20] to afford (2*S*,3*R*)-methyl3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-(4-nitrophenyl)cyclopropyl)propanoate **511** (0.20 g, 0.72 mmol) as an orange crystalline solid in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.10 (2H, d, *J* = 8.9 Hz, $C_6H_2H_2NO_2$), 7.15 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2NO_2$), 3.61 (3H, s, OCH_3), 3.54 (1H, dd, *J* = 7.2, 4.6 Hz, C*H*OH), 2.73 (1H, qd, *J* = 7.1, 4.7 Hz, (C=O)C*H*), 2.47 (1H, broad s, O*H*), 1.99-1.92 (1H, m, C*H*-aryl), 1.44-1.35 (1H, m, CHOHC*H*CH_AH_B), 1.30-1.22 (1H, m, cyclopropyl-C*H*$_A$H$_B$), 1.26 (3H, d, *J* = 7.1 Hz, (C=O)CHC*H*$_3$)), 1.10-1.04 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{14}H_{17}NNaO_5$ $[M+Na]^+$ requires 302.1004; $[\alpha]_D^{25}$ = +114.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



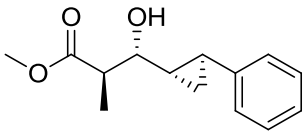
The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-3-((1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **499** (0.08 g, 0.18 mmol) and sodium methoxide (0.37 mL, 0.18 mmol, 0.5 M in methanol) in dichloromethane (10 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.29] to afford (2*S*,3*R*)-methyl-3-hydroxy-3-((1*S*,2*S*)-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, $CDCl_3$) δ_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, OCH_3), 3.39 (1H, dd, *J* = 8.2, 4.7 Hz, C*H*OH), 2.75 (1H, qd, *J* = 7.1, 4.7 Hz, C*H*CH_3), 2.44 (1H, broad s, O*H*), 1.82-1.75 (1H, m, cyclopropyl-aryl), 1.30-1.21 (1H, m, CHOHC*H*CH_AH_B), 1.27 (3H, d, *J* = 7.1 Hz, CHCH_3), 1.04-0.98 (1H, m, cyclopropyl-CH_AH_B), 0.91-0.87 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 3508 (OH), 1721 (C=O); HRMS: *m/z* (ES) 287.1246, $C_{15}H_{20}NaO_4$ $[M+Na]^+$ requires 287.1259; $[\alpha]_D^{25}$ = +90.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-(4-methoxyphenyl)-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-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 (2*S*,3*R*)-methyl-3-hydroxy-2-(4-methoxyphenyl)-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate **513** (0.03 g, 0.11 mmol) as a white crystalline solid in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.32 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2COMe$), 6.88 (2H, d, *J* = 8.7 Hz, $C_6H_2H_2COMe$), 3.80 (3H, s, $C_6H_4COCH_3$), 3.72-3.69 (1H, m, C*H*-aryl), 3.70 (3H, s, OCH_3), 3.47-3.40 (1H, m, C*H*OH), 2.14 (1H, broad s, O*H*), 0.99 (3H, d, *J* = 6.0 Hz, $CHCH_3$), 0.73-0.56 (3H, m, $CHOHCHCH_AH_B$, $CHCH_3$ and cyclopropyl-CH_AH_B), 0.33-0.26 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) 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} ν = 3436 (OH), 1727 (C=O); HRMS: *m/z* (ES) 287.1248, $C_{15}H_{20}NaO_4$ $[M+Na]^+$ requires 287.1259; $[\alpha]_D^{25}$ = -32.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

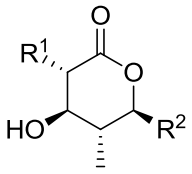
(2*R*,3*R*)-Methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate, 514



The title compound was prepared according to General Procedure 3 from (*S*)-4-benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-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, R_f 0.11] to afford (2*R*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate **514** (0.55 g, 2.35 mmol) as a colourless oil in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.28-7.23 (2H, m, Ph), 7.18-7.13 (1H, m, Ph), 7.06-7.03 (2H, m, Ph), 3.69 (3H, s, OCH_3), 3.39 (1H, app. t, *J* = 7.7, C*H*OH), 3.12 (1H, broad s, O*H*), 2.72 (1H, app. quin., *J* = 7.2 Hz, C*H*CH_3), 1.92-1.85 (1H, m, cyclopropyl-Ph), 1.24 (3H, d, *J* = 7.2 Hz, CHCH_3 and 1H, m, CHOHC*H*CH_AH_B), 1.10-1.04 (1H, m, cyclopropyl-CH_AH_B), 1.00-0.94 (1H, m, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 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 $CHCl_3$).

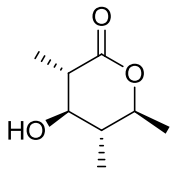
*4.1.6 Synthesis of Highly Substituted δ-Lactones **526**-**532***

Synthesis of δ-Lactones – General Procedure 4



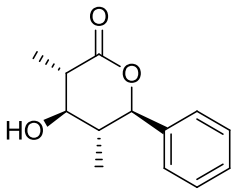
Mercury trifluoroacetate (2.5 equiv.) was added in one portion to a stirred solution of the appropriate methyl ester *syn*-aldol cyclopropane **506**-**514** (1 equiv.) in dichloromethane. The resulting yellow solution was stirred at ambient temperature for 24 hours under nitrogen, before being quenched 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 $MgSO_4$ and concentrated to afford the corresponding organomercurial δ-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 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 corresponding tetrasubstituted δ-lactone. The crude product was purified using flash silica chromatography to remove the mercury residues to afford the clean product.

(3*S*,4*R*,5*R*,6*S*)-4-Hydroxy-3,5,6-trimethyltetrahydro-2H-pyran-2-one, 526



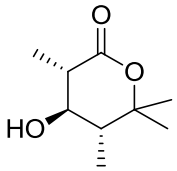
The title compound was prepared according to General Procedure 4 from (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methylcyclopropyl)propanoate **506** (0.10 g, 0.58 mmol) and mercury trifluoroacetate (0.62 g, 1.45 mmol) in dichloromethane (10 mL). The reaction was stirred for 24 hours before 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, R_f 0.20] to afford (3*S*,4*R*,5*R*,6*S*)-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, $CDCl_3$) δ_H = 3.99 (1H, dq, *J* = 10.3, 6.2 Hz, $OCHCH_3$), 3.29 (1H, app. t, *J* = 10.0 Hz, C*H*OH), 2.39 (1H, dq, *J* = 10.0, 7.1 Hz, $COCHCH_3$), 1.95 (1H, broad s, O*H*), 1.64 (1H, ddq, *J* = 10.3, 10.0, 6.5 Hz, $CHOHCHCH_3CHCH_3$), 1.40 (3H, d, *J* = 7.1 Hz, $COCHCH_3$), 1.40 (3H, d, *J* = 6.2 Hz, $OCHCH_3$), 1.09 (3H, d, *J* = 6.5 Hz, $CHOHCHCH_3CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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, $C_8H_{14}NaO_3$ $[M+Na]^+$ requires 181.0840; $[\alpha]_D^{25}$ = -38.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



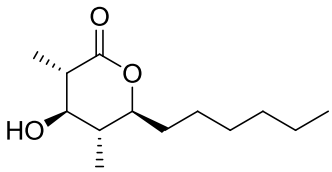
The title compound was prepared according to General Procedure 4 from (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenylcyclopropyl)propanoate **507** (0.27 g, 1.14 mmol) and mercury trifluoroacetate (1.21 g, 2.84 mmol) in dichloromethane (50 mL). The reaction was stirred for 24 hours before 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, R_f 0.08] to afford (3*S*,4*R*,5*R*,6*R*)-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*H*Ph), 3.48 (1H, app. t, *J* = 10.1 Hz, C*H*OH), 2.57 (1H, dq, *J* = 10.0, 7.0 Hz, COC*H*CH_3), 2.16 (1H, broad s, O*H*), 2.04 (1H, ddq, *J* = 10.8, 10.1, 6.5 Hz, CHOHC*H*CH_3), 1.48 (3H, d, *J* = 7.0 Hz, COCHC*H*$_3$), 0.92 (3H, d, *J* = 6.6 Hz, CHOHCHC*H*$_3$); ^{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 243.0997; $[\alpha]_D^{25}$ = +6.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(3*S*,4*R*,5*R*)-4-Hydroxy-3,5,6,6-tetramethyltetrahydro-2H-pyran-2-one, 528



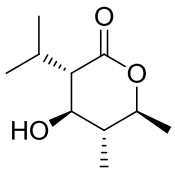
The title compound was prepared according to General Procedure 4 from (2*S*,3*R*)-methyl 3-((*S*)-2,2-dimethylcyclopropyl)-3-hydroxy-2-methylpropanoate **508** (0.17 g, 0.91 mmol) and mercury trifluoroacetate (0.99 g, 2.34 mmol) in dichloromethane (30 mL). The reaction was stirred for 24 hours before 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, R_f 0.09] to afford (3*S*,4*R*,5*R*)-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, C*H*OH), 2.36 (1H, dq, *J* = 9.7, 7.0 Hz, COC*H*CH_3), 2.12 (1H, broad s, O*H*), 1.83 (1H, dq, *J* = 10.8, 6.8 Hz, CHOHC*H*$CH_3C(CH_3)(CH_3)$), 1.43 (3H, s, C(C*H*$_3$)(CH_3)), 1.39 (3H, d, *J* = 7.0 Hz, COCHC*H*$_3$), 1.24 (3H, s, C(CH_3)(C*H*$_3$)), 1.11 (3H, d, *J* = 6.8 Hz, CHOHCHC*H*$_3$ 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, $C_9H_{17}O_3$ $[M+H]^+$ requires 173.1177; $[\alpha]_D^{25}$ = -52.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(3*S*,4*R*,5*R*,6*S*)-6-Hexyl-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-one, 529



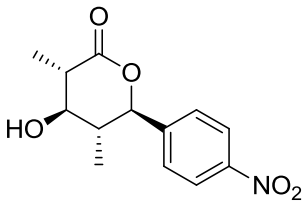
The title compound was prepared according to General Procedure 4 from (2*S*,3*R*)-methyl 3-((1*S*,2*S*)-2-hexylcyclopropyl)-3-hydroxy-2-methylpropanoate **509** (0.14 g, 0.58 mmol) and mercury trifluoroacetate (0.61 g, 1.44 mmol) in dichloromethane (25 mL). The reaction was stirred for 24 hours before 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, R_f 0.17] to afford (3*S*,4*R*,5*R*,6*S*)-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, $CDCl_3$) δ_H = 3.89 (1H, m, OC*H*C_6H_{13}), 3.28 (1H, t, *J* = 10.0 Hz, C*H*OH), 2.37 (1H, dq, *J* = 10.0, 7.0 Hz, COC*H*CH_3), 1.93 (1H, broad s, O*H*), 1.82-1.48 (5H, complex m, CHOHC*H*$CH_3CHC_6H_{13}$ and $C_2H_4C_4H_9$), 1.40 (3H, d, *J* = 7.0 Hz, COCHC*H*$_3$), 1.33-1.28 (6H, m, $C_3H_6CH_3$), 1.08 (3H, d, *J* = 6.5 Hz, CHOHCHC*H*$_3CHC_6H_{13}$), 0.90-0.86 (3H, m, $C_3H_6CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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} ν = 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 $CHCl_3$).

(3*S*,4*R*,5*R*,6*S*)-4-Hydroxy-3-isopropyl-5,6-dimethyltetrahydro-2H-pyran-2-one, 530



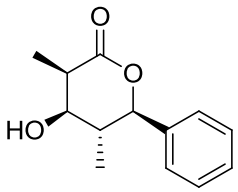
The title compound was prepared according to General Procedure 4 from (*S*)-methyl-2-((*R*)-hydroxy((1*S*,2*S*)-2-methylcyclopropyl)methyl)-3-methylbutanoate **510** (0.11 g, 0.55 mmol) and mercury trifluoroacetate (0.58 g, 1.37 mmol) in dichloromethane (20 mL). The reaction was stirred for 24 hours 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, R_f 0.20] to afford (3*S*,4*R*,5*R*,6*S*)-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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.95 (1H, dq, *J* = 10.3, 6.3 Hz, OC*H*CH_3), 3.48 (1H, dd, *J* = 10.1, 7.5 Hz, C*H*OH), 2.45 (1H, dd, *J* = 7.6, 3.8 Hz, COC*H*), 2.42-2.33 (1H, m, *J* = 6.9, 3.8 Hz, C*H*$(CH_3)_2$), 1.77 (1H, broad s, O*H*), 1.59 (1H, app. tq, *J* = 10.2, 6.6 Hz, CHOHC*H*CH_3), 1.36 (3H, d, *J* = 6.3 Hz, COCHC*H*$_3$), 1.11 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)(CH_3)), 1.08 (3H, d, *J* = 6.6 Hz, CHOHCHC*H*$_3$), 1.06 (3H, d, *J* = 6.8 Hz, CH(CH_3)(C*H*$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{10}H_{18}NaO_3$ $[M+Na]^+$ requires 209.1153; $[\alpha]_D^{25}$ = -32.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(3*S*,4*R*,5*R*,6*R*)-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 (2*S*,3*R*)-methyl-3-hydroxy-2-methyl-3-((1*S*,2*S*)-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, R_f 0.17] to afford (3*S*,4*R*,5*R*,6*R*)-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, $CDCl_3$) δ_H = 8.24 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2CNO_2$), 7.49 (2H, d, *J* = 8.8 Hz, $C_6H_2H_2CNO_2$), 4.90 (1H, d, *J* = 10.8 Hz, C*H*Ar), 3.50 (1H, app. t, *J* = 10.0 Hz, C*H*OH), 2.61 (1H, dq, *J* = 9.9, 7.0 Hz, COC*H*), 1.99 (1H, ddq, *J* = 10.8, 10.2, 6.5 Hz, CHArC*H*CH_3), 1.47 (3H, d, *J* = 7.0 Hz, COCHC*H*$_3$), 0.92 (3H, d, *J* = 6.5 Hz, CHArCHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 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 $CHCl_3$).

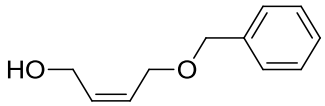
(3*R*,4*R*,5*R*,6*R*)-4-Hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one, 532



The title compound was prepared according to General Procedure 4 from (2*R*,3*R*)-methyl 3-hydroxy-2-methyl-3-((1*S*,2*S*)-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, R_f 0.25] to afford (3*R*,4*R*,5*R*,6*R*)-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, C*H*Ph), 3.87 (1H, app. t, *J* = 3.9 Hz, C*H*OH), 2.82 (1H, qd, *J* = 6.8, 4.3 Hz, COC*H*CH_3), 2.74 (1H, broad s, O*H*), 2.13 (1H, m, C*H*CH_3CHPh), 1.32 (3H, d, *J* = 6.9 Hz, COCHC*H*$_3$), 0.92 (3H, d, *J* = 7.1 Hz, CHOHCHC*H*$_3$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 $CHCl_3$).

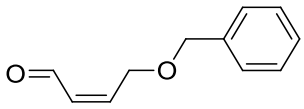
4.1.7 Synthesis of Compounds for Highly Substituted δ-Lactones with a Synthetic Handle

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



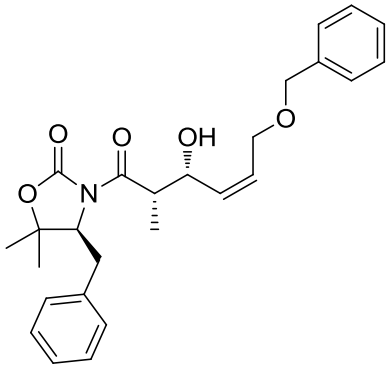
Based on a literature procedure,[187] sodium hydride (0.48 g, 11.35 mmol, 60% dispersion in mineral oil) was added portionwise to *N*,*N*-dimethylformamide (40 mL) at -20 ˚C under nitrogen. The resulting suspension was stirred for five minutes before (*Z*)-but-2-ene-1,4-diol (1.00 mL, 11.35 mmol) was 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 $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.17 (5H, m, Ph), 5.78-5.61 (2H, m, C*H*=C*H*), 4.44 (2H, s, OCH_2Ph), 4.08 (2H, d, *J* = 5.9 Hz, CH_2O), 4.01 (2H, d, *J* = 5.9 Hz, CH_2O), 1.91 (1H, broad s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{11}H_{14}NaO_2$ $[M+Na]^+$ requires 201.0891.

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



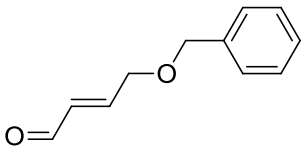
Based on a literature procedure,[187] oxalyl chloride (0.26 mL, 3.09 mmol) was dissolved in dry dichloromethane (10 mL) at -55 ˚C under nitrogen. Dimethylsulfoxide (0.39 mL, 5.61 mmol) was added and the resulting solution was stirred for two minutes. (*Z*)-4-(benzyloxy)but-2-en-1-ol **534** (0.50 g, 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 $NaHCO_3$ before being dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:8 EtOAc:Petroleum ether, R_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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 10.05 (1H, d, *J* = 6.8 Hz, C*H*O), 7.37-7.31 (5H, m, Ph), 6.64 (1H, dt, *J* = 11.6, 5.8 Hz, C*H*=CHCHO), 6.06 (1H, ddt, *J* = 11.6, 6.8, 1.9 Hz, C*H*CHO), 4.59 (2H, s, OCH_2Ph), 4.53 (2H, dd, *J* = 5.5, 1.9 Hz, CH_2OBn); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 191.6, 147.7, 137.4, 129.9, 128.7, 128.2, 127.9, 73.2, 67.1.

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



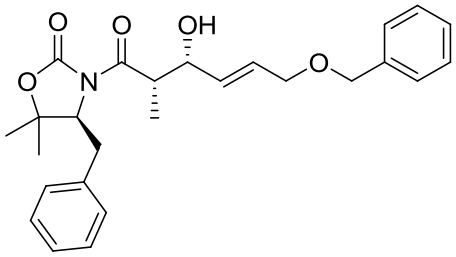
Based on a literature procedure,[187] (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.50 g, 1.91 mmol) was dissolved in dry dichloromethane (20 mL) at -10 ˚C under nitrogen and was stirred for 20 minutes. Dibutylboron triflate (2.29 mL, 2.30 mmol, 1.0 M in dichloromethane) was added 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-(benzyloxy)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_2PO_4/NaH_2PO_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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:2 EtOAc:Petroleum ether, R_f 0.63] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*Z*)-6-(benzyloxy)-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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.29-7.12 (10H, m, Ph), 5.71-5.52 (2H, m, C*H*=C*H*), 4.63-4.49 (1H, m, C*H*OH), 4.44-4.39 (3H, m, CH_2OBn and C*H*N), 4.10 (1H, ddd, *J* = 12.7, 6.5, 1.3 Hz, CH_AH$_B$OBn), 4.00 (1H, ddd, *J* = 12.6, 5.5, 1.3 Hz, CH$_A$$H_B$OBn), 3.87 (1H, m, C*H*CH$_3$), 2.97 (1H, dd, *J* = 14.3, 4.5 Hz, CH_AH$_B$Ph), 2.81 (1H, dd, *J* = 14.3, 9.0 Hz, CH$_A$$H_B$Ph), 2.73 (1H, broad s, O*H*), 1.30 (3H, s, C(CH_3)(CH$_3$)), 1.26 (3H, s, C(CH$_3$)(CH_3)), 1.11 (3H, d, *J* = 7.0 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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^{-1} ν = 3477 (OH), 1771 (C=O$_{ox}$), 1692 (C=O); HRMS: *m/z* (ES) 460.2097, $C_{26}H_{31}NNaO_5$ $[M+Na]^+$ requires 460.2099; $[\alpha]_D^{25}$ = -12.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*E*)-4-(Benzyloxy)but-2-enal, 537



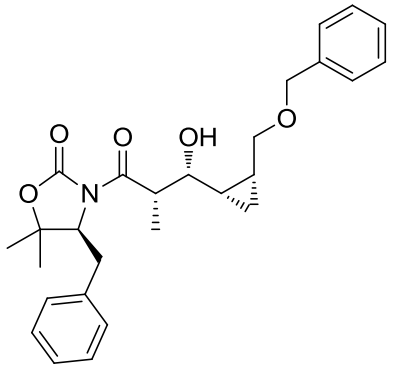
Based on a literature procedure,[187] oxalyl chloride (0.26 mL, 3.09 mmol) was dissolved in dry dichloromethane (10 mL) at -55 ˚C under nitrogen. Dimethylsulphoxide (0.39 mL, 5.61 mmol) was added and the resulting solution was stirred for two minutes. (*Z*)-4-(benzyloxy)but-2-en-1-ol **534** (0.50 g, 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 $NaHCO_3$ before being dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:8 EtOAc:Petroleum ether, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.58 (1H, d, *J* = 7.9 Hz, C*H*O), 7.39-7.28 (5H, m, Ph), 6.85 (1H, dt, *J* = 15.8, 4.1 Hz, C*H*=CHCHO), 6.41 (1H, ddt, *J* = 15.8, 7.9, 1.9 Hz, C*H*CHO), 4.60 (2H, s, OCH_2Ph), 4.29 (2H, dd, *J* = 4.1, 1.9 Hz, CH_2OBn); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{11}H_{12}NaO_2$ $[M+Na]^+$ requires 199.0734.

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyl oxazolidin-2-one, 538



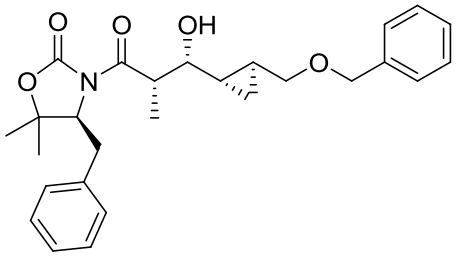
Based on a literature procedure,[187] (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (1.95 g, 7.46 mmol) was dissolved in dry dichloromethane (50 mL) at -10 ˚C under nitrogen and was stirred for 20 minutes. Dibutylboron triflate (8.97 mL, 8.95 mmol, 1.0 M in dichloromethane) was added 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_2PO_4/NaH_2PO_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:Petroleum ether, R_f 0.19] to afford (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-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=C*H*CH_2OBn), 5.68 (1H, dd, *J* = 15.6, 5.4 Hz, C*H*=CHCH_2OBn), 4.48-4.38 (4H, m, CH_2OBn, C*H*N, C*H*OH), 3.96 (2H, d, *J* = 5.4 Hz, CH_2OBn), 3.86 (1H, qd, *J* = 7.0, 4.2 Hz, C*H*CH_3), 2.99 (1H, dd, *J* = 14.2, 4.6 Hz, C$H_A$$H_B$Ph), 2.82 (1H, dd, *J* = 14.4, 9.0 Hz, CH_AH_BPh), 2.76 (1H, broad s, O*H*), 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_{ox}), 1693 (C=O); HRMS: *m/z* (ES) 460.2064, $C_{26}H_{31}NNaO_5$ $[M+Na]^+$ requires 460.2099; $[\alpha]_D^{25}$ = -28.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((1*S*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methyl propanoyl)-5,5-dimethyloxazolidin-2-one, 539



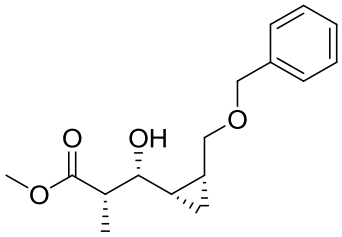
(*S*)-4-Benzyl-3-((2*S*,3*R*,*Z*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **536** (0.50 g, 1.14 mmol) was dissolved in dichloromethane (25 mL) and stirred at -5 ˚C under nitrogen. Diethylzinc (5.71 mL, 5.71 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (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 $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, R_f 0.40] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((1*S*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **539** (0.46 g, 1.02 mmol) as a colourless gum in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.28-7.17 (10H, m, Ph and Ph_{ox}), 4.49-4.41 (3H, m, OC*H*$_2$Ph and C*H*N), 3.94 (1H, qd, *J* = 7.1, 3.0 Hz, C*H*CH_3), 3.67 (1H, dd, *J* = 8.1, 3.0 Hz, C*H*OH), 3.51 (1H, dd, *J* = 10.3, 6.6 Hz, CH_AH_BOBn), 3.41 (1H, dd, *J* = 10.3, 7.5 Hz, CH_AH_BOBn), 3.01 (1H, dd, *J* = 14.3, 4.3 Hz, CH_AH_BPh), 2.83 (1H, dd, *J* = 14.3, 9.1 Hz, CH_AH_BPh), 1.31 (3H, s, C(CH_3)(CH_3)), 1.24 (3H, s, C(CH_3)(CH_3)), 1.23 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.20-1.05 (2H, m, CHOHC*H*CH_AH_B and cyclopropyl-C*H*CH_2OBn), 0.80 (1H, app. dt, *J* = 8.4, 4.8 Hz, cyclopropyl-CH_AH_B), 0.41 (1H, app. dd, *J* = 10.7, 5.7 Hz, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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=O_{ox}), 1689 (C=O); HRMS: *m/z* (ES) 474.2223, $C_{27}H_{33}NNaO_5$ $[M+Na]^+$ requires 474.2256; $[\alpha]_D^{25}$ = -8.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methyl propanoyl)-5,5-dimethyloxazolidin-2-one, 541



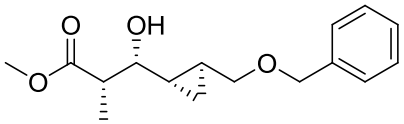
(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **538** (0.50 g, 1.14 mmol) was dissolved in dichloromethane (25 mL) and stirred at -5 ˚C under nitrogen. Diethylzinc (5.71 mL, 5.71 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (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 $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, R_f 0.16] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **541** (0.49 g, 1.09 mmol) as a colourless gum in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.10 (10H, m, Ph and Ph_{ox}), 4.45-4.38 (1H, m, C*H*N), 4.44 (1H, s, OC*H*$_A$H$_B$Ph), 4.43 (1H, s, OCH$_A$*H*$_B$Ph), 3.91 (1H, qd, *J* = 7.1, 3.4 Hz, C*H*CH$_3$), 3.32-3.19 (3H, m, C*H*$_2$OBn and C*H*OH), 3.00 (1H, dd, *J* = 14.3, 4.3 Hz, C*H*$_A$H$_B$Ph), 2.80 (1H, dd, *J* = 14.3, 9.2 Hz, CH$_A$*H*$_B$Ph), 2.49 (1H, broad s, O*H*), 1.29 (3H, s, C(C*H*$_3$)(CH$_3$)), 1.25 (3H, s, C(CH$_3$)(CH$_3$)), 1.18 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.10-0.99 (1H, m, cyclopropyl-CH$_2$OBn), 0.89-0.81 (1H, m, CHOHC*H*CH$_A$H$_B$), 0.63-0.58 (1H, m, cyclopropyl-C*H*$_A$H$_B$), 0.49-0.43 (1H, m, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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$_{ox}$), 1693 (C=O); HRMS: *m/z* (ES) 474.2237, $C_{27}H_{33}NNaO_5$ $[M+Na]^+$ requires 474.2256; $[\alpha]_D^{25}$ = -20.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(2*S*,3*R*)-Methyl 3-((1*S*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methyl-propanoate, 540



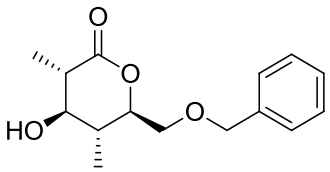
(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((1*S*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **539** (0.20 g, 0.43 mmol) was dissolved in dichloromethane (6 mL) under nitrogen. A solution of sodium methoxide (0.87 mL, 0.43 mmol, 0.5 M in methanol) was added 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 $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:3 EtOAc:Petroleum ether, R_f 0.40] to afford (2*S*,3*R*)-methyl 3-((1*S*,2*R*)-2-((benzyloxy)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, $CDCl_3$) δ_H = 7.27-7.20 (5H, m, Ph), 4.46 (1H, d, *J* = 11.8 Hz, OC*H*$_A$H$_B$Ph), 4.39 (1H, d, *J* = 11.8 Hz, OCH$_A$*H*$_B$Ph), 3.65-3.58 (5H, m, OC*H*$_3$, C*H*$_A$H$_B$OBn and C*H*OH), 3.25 (1H, dd, *J* = 10.0, 8.9 Hz, CH$_A$*H*$_B$OBn), 2.83 (1H, qd, *J* = 7.3, 2.8 Hz, C*H*CH$_3$), 2.52 (1H, broad s, O*H*), 1.26-1.15 (1H, m, CHOHC*H*CH$_A$H$_B$), 1.21 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.10-1.01 (1H, m, cyclopropyl-C*H*CH$_2$OBn), 0.81 (1H, app. td, *J* = 8.4, 4.8 Hz, cyclopropyl-C*H*$_A$H$_B$), 0.36 (1H, dd, *J* = 10.7, 5.6 Hz, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{16}H_{22}NaO_4$ [M+Na]$^+$ requires 301.1416; $[\alpha]_D^{25}$ = +38.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(2*S*,3*R*)-Methyl-3-((1*S*,2*S*)-2-(benzyloxymethyl)cyclopropyl)-3-hydroxy-2-methylpropanoate, 542



(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-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 $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.21] to afford (2*S*,3*R*)-methyl 3-((1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoate **542** (0.21 g, 0.76 mmol) as a colourless oil in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.19 (5H, m, Ph), 4.46 (1H, d, *J* = 12.1 Hz, OC*H*$_A$H$_B$Ph), 4.41 (1H, d, *J* = 12.1 Hz, OCH$_A$*H*$_B$Ph), 3.60 (3H, s, OC*H*$_3$), 3.26-3.19 (3H, m, C*H*OH and C*H*$_2$OBn), 2.63 (2H, qd, *J* = 7.1, 4.8 Hz, C*H*CH$_3$ and OH), 1.21 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.03-0.92 (1H, m, CHOHC*H*CH$_A$H$_B$), 0.84-0.77 (1H, m, cyclopropyl-C*H*CH$_2$OBn), 0.62-0.57 (1H, m, cyclopropyl-C*H*$_A$H$_B$), 0.49-0.43 (1H, m, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{16}H_{22}NaO_4$ $[M+Na]^+$ requires 301.1415; $[\alpha]_D^{25}$ = +30.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

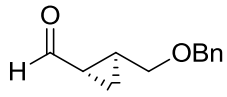
(3*S*,4*R*,5*R*,6*R*)-6-((Benzyloxy)methyl)-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-one, 544



The title compound was prepared according to General Procedure 4 from (2*S*,3*R*)-methyl-3-((1*S*,2*S*)-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, R_f 0.11] to afford (3*S*,4*R*,5*R*,6*R*)-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, $CDCl_3$) δ_H = 7.37-7.26 (5H, m, Ph), 4.63 (1H, d, *J* = 12.0 Hz, O*H*$_A$H$_B$Ph), 4.51 (1H, d, *J* = 12.0 Hz, OH$_A$*H*$_B$Ph), 3.98 (1H, dt, *J* = 10.4, 3.0 Hz, COOC*H*), 3.73 (1H, dd, *J* = 11.2, 2.4 Hz, C*H*$_A$H$_B$OBn), 3.65 (1H, dd, *J* = 11.2, 3.3 Hz, CH$_A$*H*$_B$OBn), 3.30 (1H, app. t, *J* = 10.2 Hz, C*H*OH), 2.40 (1H, dq, *J* = 10.1, 7.1 Hz, COC*H*CH$_3$), 2.11 (1H, broad s, O*H*), 2.10 (1H, ddq, *J* = 10.4, 10.2, 6.5 Hz, CHOHC*H*CH$_3$), 1.39 (3H, d, *J* = 7.0 Hz, COCHC*H*$_3$), 1.07 (3H, d, *J* = 6.5 Hz, CHOHCHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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; IR cm^{-1} ν = 3413 (OH), 1712 (C=O); HRMS: *m/z* (ES) 265.1439, $C_{15}H_{21}O_4$ $[M+H]^+$ requires 265.1439; $[\alpha]_D^{25}$ = -28.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

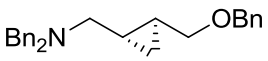
4.1.8 Synthesis of Compounds for N-Protected (S,S)-2-Aminomethyl-1-Cyclopropanecarboxylic Acid

(1*S*,2*S*)-2-((Benzyloxy)methyl)cyclopropanecarbaldehyde, 545



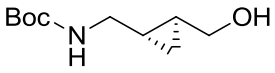
(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-((1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropyl)-3-hydroxy-2-methylpropanoyl)-5,5-dimethyloxazolidin-2-one **541** (2.56 g, 5.67 mmol) was dissolved in toluene (200 mL) at 0 ˚C under nitrogen. LiHMDS (12.48 mL, 12.48 mmol, 1 M in THF) was added dropwise and the resulting 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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.32] to afford (1*S*,2*S*)-2-((benzyloxy)methyl)cyclopropanecarbaldehyde **545** (0.99 g, 5.22 mmol) as a colourless oil in 92% yield. ^{1}H NMR (360 MHz, $CDCl_3$) δ_H = 9.17 (1H, d, *J* = 5.0 Hz, CHO), 7.40-7.21 (5H, m, Ph), 4.53 (2H, s, C*H*$_2$Ph), 3.50 (1H, dd, *J* = 10.5, 5.5 Hz, C*H*$_A$H$_B$OBn), 3.42 (1H, dd, *J* = 10.5, 5.0 Hz, CH$_A$*H*$_B$OBn), 1.89-1.77 (2H, m, C*H*-cyclopropyl), 1.33 (1H, dt, *J* = 8.5, 5.0 Hz, cyclopropyl-C*H*$_A$H$_B$), 1.12-1.04 (1H, m, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (90 MHz, $CDCl_3$) 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, $C_{12}H_{14}NaO_2$ [M+Na]$^+$ requires 213.0886; $[\alpha]_D^{25}$ = +80.0 (*c* = 0.45 g/100 mL in $CHCl_3$).

_N_,_N_-Dibenzyl-1-((1_S_,2_S_)-2-((benzyloxy)methyl)cyclopropyl)methanamine, 546



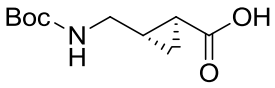
(1*S*,2*S*)-2-((Benzyloxy)methyl)cyclopropanecarbaldehyde **545** (0.99 g, 5.22 mmol) and dibenzylamine (1.00 mL, 5.22 mmol) were dissolved in dichloroethane (35 mL) along with 4Å MS at room temperature under nitrogen. Sodium triacetoxyborohydride (1.77g, 8.35 mmol) was added and the resulting mixture was stirred for four hours. The reaction was quenched with saturated $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with ethyl acetate, the combined organic extracts were combined, dried over $MgSO_4$ and concentrated to afford *N*,*N*-dibenzyl-1-((1*S*,2*S*)-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, $CDCl_3$) δ_H = 7.16-7.40 (15H, m, Ph), 4.47 (2H, s, OCH_2Ph), 3.65 (2H, d, *J* = 13.5 Hz, NCH_2Ph), 3.59 (2H, d, *J* = 13.5 Hz, NCH_2Ph), 3.26-3.32 (2H, m, CH_2NBn$_2$), 2.41 (1H, dd, *J* = 6.0, 13.0 Hz, CH_AH$_B$OBn), 2.27 (1H, dd, *J* = 7.0, 13.0 Hz, CH$_A$$H_B$OBn), 0.80-0.86 (2H, m, C*H*-cyclopropyl), 0.39 (1H, ddd, *J* = 5.0, 5.0, 10.5 Hz, cyclopropyl-CH_AH$_B$), 0.30 (1H, ddd, *J* = 5.0, 5.0, 10.5 Hz, cyclopropyl-CH$_A$$H_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 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, $C_{26}H_{30}NO$ $[M+H]^+$ requires 372.2322; $[\alpha]_D^{15}$ = +18.0 (*c* = 2.1 g/100 mL in $CHCl_3$).

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



N,*N*-Dibenzyl-1-((1*S*,2*S*)-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 NH_4Cl and was diluted with diethyl ether. The layers were separated, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford a 50:50 mixture of *tert*-butyl-benzyl(((1*S*,2*S*)-2-(hydroxymethyl)cyclopropyl)methyl)carbamate **547** and *tert*-butyl-(((1*S*,2*S*)-2-(hydroxymethyl)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 (((1*S*,2*S*)-2-(ydroxymethyl)cyclopropyl)methyl)carbamate **548** (0.65 g, 3.24 mmol) as a colourless oil in quantitative yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H = 3.57 (1H, dd, *J* = 4.5, 8.0 Hz, CH_AH$_B$OH), 3.28 (1H, dd, *J* = 5.0, 8.0 Hz, CH$_A$$H_B$OH), 3.09 (1H, dd, *J* = 4.5, 9.5 Hz, CH_AH$_B$NHBoc), 2.90 (1H, dd, *J* = 5.0, 9.5 Hz, CH$_A$$H_B$NHBoc), 1.42 (9H, s, (C$H_3$)$_3$C), 0.93-1.10 (1H, m, C*H*-cyclopropyl), 0.83-0.91 (1H, m, C*H*-cyclopropyl), 0.42 (2H, dd, *J* = 5.0, 5.0 Hz, CH_2-cyclopropyl); ^{13}C NMR (60 MHz, $CDCl_3$) δ_C = 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, $C_{10}H_{19}NNaO_3$ $[M+Na]^+$ requires 224.1257; $[\alpha]_D^{20}$ = +7.1 (*c* = 0.50 g/100 mL in $CHCl_3$).

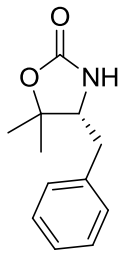
(1*S*,2*S*)-2-(((*tert*-Butoxycarbonyl)amino)methyl)cyclopropanecarboxylic acid, 549



tert-Butyl (((1*S*,2*S*)-2-(ydroxymethyl)cyclopropyl)methyl)carbamate **548** (0.65 g, 3.24 mmol) was dissolved in acetone (60 mL) at 0 ˚C. Jones' reagent (~2% CrO_3 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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford (1*S*,2*S*)-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, $CDCl_3$) δ_H = 5.62 (1H, broad s, COO*H*), 4.72 (1H, broad s, N*H*), 3.16-3.30 (1H, m, CH_AH$_B$NHBoc), 2.95-3.15 (1H, m, CH$_A$$H_B$NHBoc), 1.60-1.74 (1H, m, C*H*-cyclopropyl), 1.57 (1H, ddd, *J* = 13.0, 4.5, 4.5 Hz, C*H*-cyclopropyl), 1.48 (9H, s, (CH_3)$_3$C), 1.23 (1H, ddd, *J* = 13.0, 4.5, 4.5 Hz, C*H*-cyclopropyl), 0.93 (1H, dd, *J* = 7.0, 11.0 Hz, C*H*-cyclopropyl); HRMS: *m/z* (ES) 238.1049, $C_{10}H_{17}NNaO_4$ [M+Na]$^+$ requires 238.1050; $[\alpha]_D^{20}$ = +51 (*c* = 0.30 g/100 mL in $CHCl_3$).

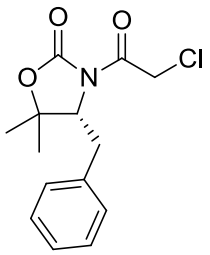
4.1.9 Synthesis of Compounds for (+)-Prelactone B, E and V

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



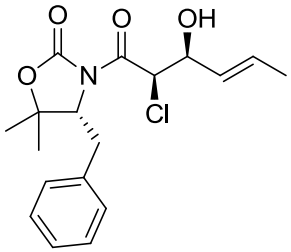
Potassium *tert*-butoxide (3.0 g, 26.8 mmol) was added in one portion to a solution of (*R*)-tert-butyl(3-hydroxy-3-methyl-1-phenylbutan-2-yl)carbamate (5.0 g, 17.9 mmol) in THF (30 mL) at room temperature. The resulting orange solution was stirred for two hours and then THF was removed under reduced pressure. The residue was redissolved in diethyl ether and extracted with saturated ammonium chloride and brine. The combined organic extracts were dried over $MgSO_4$ 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.43-7.22 (5H, m, Ph), 5.27 (1H, broad s, N*H*), 3.76 (1H, ddd, *J* = 10.3, 4.2, 0.7 Hz, C*H*N), 2.90 (1H, dd, *J* = 13.4, 4.2 Hz, CH_AH$_B$Ph), 2.76 (1H, dd, *J* = 13.4, 10.5 Hz, CH$_A$$H_B$Ph), 1.52 (3H, s, C(C$H_3$)(CH$_3$)), 1.51 (3H, s, C(CH$_3$)(C$H_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_{12}H_{15}NNaO_2$ $[M+Na]^+$ requires 228.1000; $[\alpha]_D^{25}$ = +100.0 (*c* = 1.0 g/100 mL in $CHCl_3$).

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



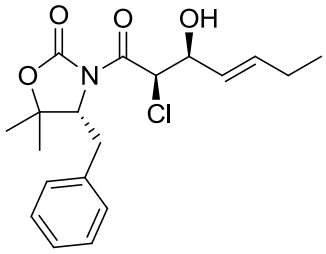
n-BuLi (10.71 mL, 26.8 mmol, 2.5 M solution in hexane) was added to a solution of (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one (5.00 g, 24.3 mmol) in dry THF (150 mL) at -78 ˚C under nitrogen and was stirred for 30 minutes. Chloroacetyl chloride (2.07 mL, 26.8 mmol) was added in one portion and the resulting 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.32-7.20 (5H, m, Ph), 4.76 (1H, d, *J* = 15.8 Hz, COCH_AH$_B$Cl), 4.64 (d, *J* = 15.8 Hz, COCH$_A$$H_B$Cl), 4.49 (1H, dd, *J* = 9.7, 3.9 Hz, C*H*N), 3.20 (1H, dd, *J* = 14.4, 3.8 Hz, CHH_AH$_B$Ph), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, CH$_A$$H_B$Ph), 1.38 (3H, s, C(C$H_3$)(CH$_3$)), 1.36 (3H, s, C(CH$_3$)(C$H_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{14}H_{16}ClNNaO_3$ [M+Na]$^+$ requires 304.0716; $[\alpha]_D^{25}$ = +32.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one, 554



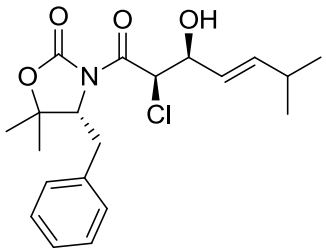
(*R*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **550** (1.65 g, 5.86 mmol) was dissolved in dry dichloromethane (10 mL) at 0 ˚C under nitrogen and was stirred for 30 minutes. Dibutylboron triflate (6.44 mL, 6.44 mmol, 1 M in dichloromethane) was added dropwise. After 30 minutes, *N*,*N*-diisopropylethylamine (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 (Na_2PO_4/NaH_2PO_4) (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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [15:85 EtOAc:Petroleum ether, R_f 0.27] to afford (*R*)-4-benzyl-3-((2*R*,3*S*,*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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.18 (5H, m, Ph), 5.88-5.71 (1H, m, CH=C*H*CH_3), 5.73 (1H, d, *J* = 5.9 Hz, C*H*Cl), 5.52 (1H, ddd, *J* = 15.5, 6.8, 1.0 Hz, C*H*=CHCH_3), 4.53-4.46 (2H, m, C*H*OH and C*H*N), 3.34 (1H, broad s, O*H*), 3.10 (1H, dd, *J* = 14.4, 3.7 Hz, C$H_A$$H_B$Ph), 2.89 (1H, dd, J = 14.4, 9.4 Hz, C$H_A$$H_B$Ph), 1.68 (3H, d, *J* = 6.4 Hz, CH=CHCH_3), 1.36, (3H, s, C(CH_3)(CH_3)), 1.33 (3H, s, C(CH_3)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_{18}H_{23}NO_4Cl$ $[M+H]^+$ requires 352.1315; $[\alpha]_D^{25}$ = +26.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



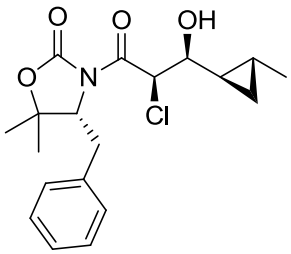
(*R*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **550** (1.37 g, 4.86 mmol) was dissolved in dry dichloromethane (10 mL) at 0 ˚C under nitrogen and was stirred for 30 minutes. Dibutylboron triflate (5.35 mL, 5.35 mmol, 1 M in dichloromethane) was added dropwise. After 30 minutes, *N*,*N*-diisopropylethylamine (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 (Na_2PO_4/NaH_2PO_4) (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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [15:85 EtOAc:Petroleum ether, R_f 0.29] to afford (*R*)-4-benzyl-3-((2*R*,3*S*,*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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.20 (5H, m, Ph), 5.87 (1H, dt, *J* = 15.2, 6.0 Hz, CH=C*H*CH_2CH_3), 5.73 (1H, d, *J* = 5.7 Hz, C*H*Cl), 5.50 (1H, dd, *J* = 15.7, 6.7 Hz, C*H*=CHCH_2CH_3), 4.56-4.47 (2H, m, C*H*OH and C*H*N), 3.45 (1H, broad s, O*H*), 3.11 (1H, dd, *J* = 14.5, 3.7 Hz, CH_AH_BPh), 2.89 (1H, dd, *J* = 14.1, 9.5 Hz, CH_AH_BPh), 2.08-1.99 (2H, m, CH_2CH_3), 1.36 (3H, s, C(CH_3)(CH_3)), 1.32 (3H, s, C(CH_3)(CH_3)), 0.96 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 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_{ox}), 1707 (C=O); HRMS: *m/z* (ES) 388.1368, $C_{19}H_{21}NO_4ClNa$ $[M+Na]^+$ requires 388.1292; $[\alpha]_D^{25}$ = +24.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-2-chloro-3-hydroxy-6-methylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one, 556



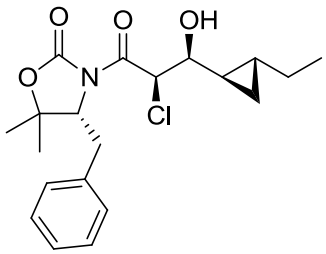
(*R*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **550** (5.00 g, 17.75 mmol) was dissolved in dry dichloromethane (30 mL) at 0 ˚C under nitrogen and was stirred for 30 minutes. 9-Borabicyclo[3.3.1]nonyl triflate (39.01 mL, 19.52 mmol, 0.5 M in hexane) was added dropwise. After 30 minutes, *N*,*N*-diisopropylethylamine (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 (Na_2PO_4/NaH_2PO_4) (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 $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.39] to afford (*R*)-4-benzyl-3-((2*R*,3*S*,*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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.17 (5H, m, Ph), 5.81 (1H, ddd, *J* = 15.4, 6.4, 0.8 Hz, CH=C*H*CH(CH_3)(CH_3)), 5.67 (1H, d, *J* = 5.2 Hz, C*H*Cl), 5.43 (1H, ddd, *J* = 15.6, 6.6, 1.4 Hz, C*H*=CHCH(CH_3)(CH_3)), 4.54 (1H, app. t, *J* = 5.9 Hz, C*H*OH), 4.47 (1H, dd, J = 9.5, 3.9 Hz, C*H*N), 3.13 (2H, dd, *J* = 14.5, 3.8 Hz, C$H_A$$H_B$Ph and broad s, O*H*), 2.88 (1H, dd, *J* = 14.4, 9.5 Hz, CH$_A$$H_B$Ph), 2.27 (1H, app. sex., *J* = 6.8 Hz, CH=CHC*H*(CH_3)(CH_3)), 1.37 (3H, s, (CH_3)C(CH_3)), 1.33 (3H, s, (CH_3)C(CH_3)), 0.97 (6H, dd, *J* = 6.8, 1.8 Hz, CH=CHCH(CH_3)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) 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} ν = 3499 (OH), 1772 (C=O$_{ox}$), 1702 (C=O); HRMS: *m/z* (ES) 402.1462, $C_{20}H_{26}NO_4ClNa$ $[M+Na]^+$ requires 402.1448; $[\alpha]_D^{25}$ = +10.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



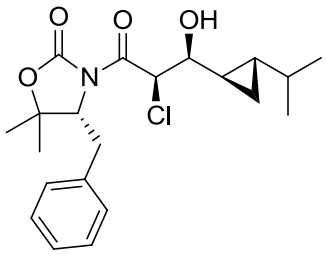
(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-2-chloro-3-hydroxyhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **554** (0.914 g, 2.60 mmol) was dissolved in dichloromethane (30 mL) and stirred at 0 ˚C under nitrogen. Diethylzinc (12.98 mL, 12.98 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.34] to afford (*R*)-4-benzyl-3-((2*R*,3*S*)-2-chloro-3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **557**, (0.80 g, 2.21 mmol) as a colourless oil in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.18 (5H, m, Ph), 5.76 (1H, d, *J* = 4.2 Hz, C*H*Cl), 4.48 (1H, dd, *J* = 9.8, 3.5 Hz, C*H*N), 3.41 (1H, dd, *J* = 7.8, 4.0 Hz, C*H*OH), 3.18 (1H, dd, *J* = 14.4, 3.4 Hz, CH_AH_BPh), 2.87 (1H, dd, *J* = 14.5, 9.8 Hz, CH_AH_BPh), 2.52 (1H, broad s, O*H*), 1.36 (3H, s, C(CH_3)(CH_3)), 1.33 (3H, s, C(CH_3)(CH_3)), 1.00 (3H, d, *J* = 5.8 Hz, CHCH_3), 0.89-0.74 (2H, m, CHOHC*H*-cyclopropyl and cyclopropyl-C*H*), 0.64-0.58 (1H, m, cyclopropyl-C*H*), 0.39-0.33 (1H, m, cyclopropyl-C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 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_{ox}), 1711 (C=O); HRMS: *m/z* (ES) 388.1278, $C_{19}H_{24}ClNNaO_4$ $[M+Na]^+$ requires 388.1291; $[\alpha]_D^{25}$ = +12.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



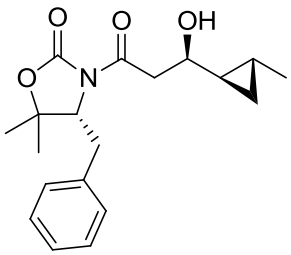
(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-2-chloro-3-hydroxyhept-4-enoyl)-5,5-dimethyloxazolidin-2-one **555** (0.81 g, 2.21 mmol) was dissolved in dichloromethane (25 mL) and stirred at 0 ˚C under nitrogen. Diethylzinc (11.06 mL, 11.07 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.32] to afford (*R*)-4-benzyl-3-((2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-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, $CDCl_3$) δ_H = 7.30-7.18 (5H, m, Ph), 5.79 (1H, d, *J* = 3.7 Hz, C*H*Cl), 4.49 (1H, dd, *J* = 9.8, 3.4 Hz, C*H*N), 3.41 (1H, dd, *J* = 8.2, 3.6 Hz, C*H*OH), 3.19 (1H, dd, *J* = 14.6, 3.4 Hz, CH_AH$_B$Ph), 2.87 (2H, dd and broad s, *J* = 14.4, 9.8 Hz, CH$_A$$H_B$Ph and O*H*), 1.36 (3H, s, C(CH_3)(CH$_3$)), 1.33 (3H, s, C(CH$_3$)(CH_3)), 1.36-1.08 (2H, m, CH_2CH$_3$), 0.94 (3H, t, *J* = 7.3 Hz, CH$_2$CH_3), 0.93-0.73 (2H, m, CHOHC*H*-cyclopropyl and cyclopropyl-C*H*), 0.64-0.58 (1H, m, cyclopropyl-C*H*), 0.43-0.37 (1H, m, cyclopropyl-C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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=O$_{ox}$), 1707 (C=O); HRMS: *m/z* (ES) 402.1469, $C_{20}H_{26}ClNNaO_4$ [M+Na]$^+$ requires 402.1448; $[\alpha]_D^{25}$ = +12.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-chloro-3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one, 559



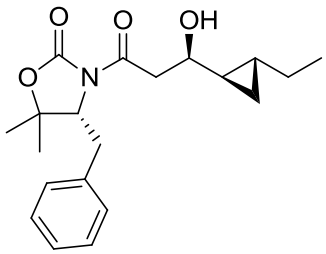
(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-2-chloro-3-hydroxy-6-methylhept-4-enoyl)-5,5-dimethyloxazolidin-2-one **556** (1.85 g, 4.87 mmol) was dissolved in dichloromethane (90 mL) and stirred at 0 ˚C under nitrogen. Diethylzinc (24.35 mL, 24.35 mmol, 1 M in hexane) was added in one portion followed by diiodomethane (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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.13] to afford (*R*)-4-benzyl-3-((2*R*,3*S*)-2-chloro-3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **559** (1.44 g, 3.66 mmol) as a colourless oil in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.20 (5H, m, Ph), 5.78 (1H, d, *J* = 3.0 Hz, C*H*Cl), 4.47 (1H, dd, J = 10.0, 3.3 Hz, C*H*N), 3.35 (1H, dd, *J* = 8.4, 3.0 Hz, C*H*OH), 3.19 (1H, dd, *J* = 14.5, 3.2 Hz, CH_AH$_B$Ph), 2.86 (1H, dd, *J* = 10.0, 14.5 Hz, CH$_A$$H_B$Ph), 2.63 (1H, broad s, O*H*), 1.35 (3H, s, C(CH_3)(CH$_3$)), 1.32 (3H, s, C(CH$_3$)(CH_3)), 0.96-0.93 (9H, m, C*H*(CH_3)(CH_3) and CHOHC*H*-cyclopropyl and cyclopropyl-C*H*CH(CH$_3$)(CH$_3$)), 0.60-0.56 (1H, m, cyclopropyl-CH_AH$_B$), 0.46-0.44 (1H, m, cyclopropyl-CH$_A$$H_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 168.4, 152.0, 136.5, 129.1, 128.8, 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$_{ox}$), 1709 (C=O); HRMS: *m/z* (ES) 416.1599, $C_{21}H_{28}ClNNaO_4$ [M+Na]$^+$ requires 416.1596; $[\alpha]_D^{25}$ = +10.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(*R*)-4-Benzyl-3-((*R*)-3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyl oxazolidin-2-one, 560



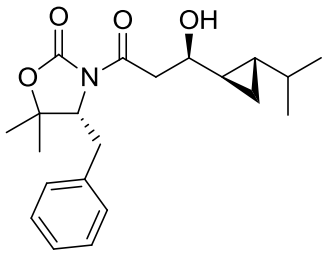
(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-chloro-3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **557**, (0.80 g, 2.21 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.57 g, 8.78 mmol) was added in one portion followed by ammonium chloride (0.47 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-((1*R*,2*R*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **560** (0.50 g, 1.52 mmol) as a yellow gum in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.19 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.0, 4.5 Hz, C*H*N), 3.40 (1H, dd, *J* = 13.6, 6.1 Hz, C*H*OH), 3.20 (2H, d, *J* = 5.9 Hz, COCH_2CHOH), 3.13 (1H, dd, *J* = 14.4, 4.5 Hz, CH_AH$_B$Ph), 2.89 (1H, dd, *J* = 14.3, 9.0 Hz, CH$_A$$H_B$Ph), 2.51 (1H, broad s, O*H*), 1.39 (3H, s, C(CH_3)(CH$_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, CHOHC*H*-cyclopropyl and cyclopropyl-*H*), 0.34-0.29 (1H, m, cyclopropyl-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 3519 (OH), 1773 (C=O$_{ox}$), 1694 (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-((1*R*,2*R*)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyl oxazolidin-2-one, 561



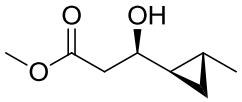
(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one **558** (0.58 g, 1.53 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.39 g, 6.11 mmol) was added in one portion followed by ammonium chloride (0.33 g, 6.11 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 0.24] to afford (*R*)-4-benzyl-3-((*R*)-3-((1*R*,2*R*)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one **561** (0.37 g, 1.07 mmol) as a yellow oil in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.19 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.0, 4.5 Hz, C*H*N), 3.41-3.34 (1H, m, C*H*OH), 3.22-3.20 (2H, m, COCH_2CHOH), 3.13 (1H, dd, *J* = 14.4, 4.5 Hz, CH_AH$_B$Ph), 2.89 (1H, dd, *J* = 14.2, 9.0 Hz, CH$_A$$H_B$Ph), 2.62 (1H, broad s, O*H*), 1.42-1.13 (2H, m, CH_2CH$_3$), 1.38 (3H, s, C(CH_3)(CH$_3$)), 1.37 (3H, s, C(CH$_3$)(CH_3)), 0.94 (3H, app. t, *J* = 7.3 Hz, cyclopropyl-CH$_2$CH_3), 0.77-0.68 (1H, m, cyclopropyl-*H*), 0.60-0.52 (2H, m, CHOHC*H*-cyclopropyl and cyclopropyl-*H*), 0.39-0.33 (1H, m, cyclopropyl-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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$_{ox}$), 1694 (C=O); HRMS: *m/z* (ES) 368.1946, $C_{20}H_{27}NNaO_4$ [M+Na]$^+$ requires 368.1838; $[\alpha]_D^{25}$ = +44.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



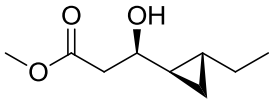
(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-chloro-3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **559** (1.40 g, 3.55 mmol) was dissolved in methanol at room temperature under nitrogen. Zinc dust (0.93 g, 14.22 mmol) was added in one portion followed by ammonium chloride (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, R_f 0.13] to afford (*R*)-4-benzyl-3-((*R*)-3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **562** (0.72 g, 2.00 mmol) as a colourless oil in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30-7.17 (5H, m, Ph), 4.51 (1H, dd, *J* = 9.2, 4.5 Hz, C*H*N), 3.35 (1H, td, *J* = 4.0, 8.0 Hz, C*H*OH), 3.22-3.19 (2H, m, COCH_2CHOH), 3.12 (1H, dd, *J* = 14.2, 4.2 Hz, CH_AH$_B$Ph), 2.87 (2H, dd, *J* = 14.2, 9.0 Hz, CH$_A$$H_B$Ph and broad s, O*H*), 1.35 (3H, s, C(CH_3)(CH$_3$)), 1.34 (3H, s, C(CH$_3$)(CH_3)), 0.94 (7H, m, C*H*(CH_3)(CH_3)), 0.80-0.71 (1H, m, CHOHC*H*-cyclopropyl), 0.56-0.50 (2H, m, cyclopropyl-C*H*CH(CH$_3$)(CH$_3$)), and cyclopropyl-CH_AH$_B$), 0.47-0.35 (1H, m, cyclopropyl-CH$_A$$H_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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=O$_{ox}$), 1696 (C=O); HRMS: *m/z* (ES) 382.2026, $C_{21}H_{29}NNaO_4$ [M+Na]$^+$ requires 382.1989; $[\alpha]_D^{25}$ = +50.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



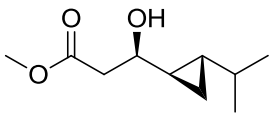
(*R*)-4-Benzyl-3-((*R*)-3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **560** (0.50 g, 1.51 mmol) was dissolved in dichloromethane (15 mL) at room temperature under nitrogen. A solution of sodium methoxide (3.02 mL, 1.51 mmol, 0.5 M in methanol) was added and the 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.22] to afford (*R*)-methyl 3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoate **563** (0.15 g, 0.94 mmol) as a colourless oil in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.60 (3H, s, OC*H*$_3$), 3.30-3.23 (1H, m, C*H*OH), 2.90 (1H, broad s, O*H*), 2.51 (2H, d, *J* = 6.4 Hz, COC*H*$_2$CHOH), 0.91 (3H, d, *J* = 5.4 Hz, cyclopropyl-C*H*$_3$), 0.59-0.51 (2H, m, CHOHC*H*-cyclopropyl and cyclopropyl-*H*), 0.49-0.41 (1H, m, cyclopropyl-*H*), 0.22-0.17 (1H, m, cyclopropyl-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_8H_{14}NaO_3$ $[M+Na]^+$ requires 181.0840; $[\alpha]_D^{25}$ = -16.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



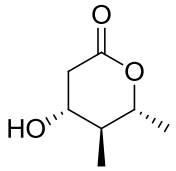
(*R*)-4-benzyl-3-((*R*)-3-((1*R*,2*R*)-2-ethylcyclopropyl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one **561** (0.37 g, 1.07 mmol) was dissolved in dichloromethane (12 mL) at room temperature under nitrogen. A solution of sodium methoxide (2.14 mL, 1.07 mmol, 0.5 M in methanol) was added and the 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.21] to afford (*R*)-methyl 3-((1*R*,2*R*)-2-ethylcyclopropyl)-3-hydroxypropanoate **564** (0.14 g, 0.78 mmol) as a colourless oil in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.62 (3H, s, OCH_3), 3.26 (1H, ddd, *J* = 15.5, 8.3, 5.3 Hz, C*H*OH), 2.83 (1H, broad s, O*H*), 2.53 (2H, d, *J* = 2.3 Hz, CH_2CHOH), 1.31-1.16 (1H, m, CH_AH$_B$CH$_3$), 1.13-0.99 (1H, m, CH$_A$$H_BCH_3$), 0.85 (3H, t, *J* = 7.3 Hz, cyclopropyl-CH$_2$CH_3), 0.63-0.42 (3H, m, CHOHC*H*-cyclopropyl and cyclopropyl-*H*), 0.28-0.23 (1H, m, cyclopropyl-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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) 195.1052, $C_9H_{16}NaO_3$ [M+Na]$^+$ requires 195.0997; $[\alpha]_D^{25}$ = -6.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

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



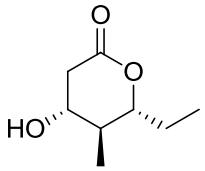
(*R*)-4-Benzyl-3-((*R*)-3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoyl)-5,5-dimethyloxazolidin-2-one **562** (0.71 g, 1.99 mmol) was dissolved in dichloromethane (20 mL) at room temperature under nitrogen. A solution of sodium methoxide (3.97 mL, 1.99 mmol, 0.5 M in methanol) was added and 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.27] to afford (*R*)-methyl 3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoate **565** (0.23 g, 1.25 mmol) as a colourless oil in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.62 (3H, s, OC*H*$_3$), 3.23 (1H, m, C*H*OH), 2.89 (1H, broad s, O*H*), 2.53 (2H, m, C*H*$_2$CHOH), 0.91-0.86 (7H, m, C*H*(C*H*$_3$)(C*H*$_3$)), 0.68-0.59 (1H, m, CHOHC*H*-cyclopropyl), 0.47-0.42 (1H, m, cyclopropyl-C*H*CH(CH_3)(CH_3)), 0.38-0.27 (2H, m, cyclopropyl-C*H*$_A$H$_B$ and cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{10}H_{18}NaO_3$ $[M+Na]^+$ requires 209.1148; $[\alpha]_D^{25}$ = +16.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(+)-Prelactone V - (4*R*,5*S*,6*R*)-4-Hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-one, 566



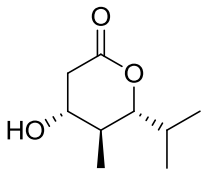
Mercury trifluoroacetate (0.99 g, 2.32 mmol) was added in one portion to a stirred solution of (*R*)-methyl 3-hydroxy-3-((1*R*,2*R*)-2-methylcyclopropyl)propanoate **563** (0.147 g, 0.93 mmol) in dichloromethane (10 mL). The resulting yellow solution was stirred at ambient temperature for 24 hours under 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 (4*R*,5*S*,6*R*)-4-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-one **566** (0.087 g, 0.60 mmol) as a gummy solid in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.98 (1H, dq, *J* = 10.4, 6.4 Hz, COOC*H*CH_3), 3.76 (1H, td, *J* = 8.0, 5.9 Hz, C*H*OH), 2.91 (1H, dd, *J* = 17.3, 5.9 Hz, COCH_AH_BCHOH), 2.50 (1H, dd, *J* = 17.3, 8.1 Hz, COCH_AH_BCHOH), 2.21 (1H, broad s, O*H*), 1.66-1.53 (1H, m, CHOHC*H*CH_3CHCH_3O), 1.40 (3H, d, *J* = 6.4 Hz, COOCHCH_3), 1.08 (3H, d, *J* = 6.7 Hz, CHOHCHCH_3CHCH_3O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.9, 79.2, 69.7, 43.4, 39.2, 19.7, 13.9; IR cm^{-1} ν = 3413 (OH), 1718 (C=O); HRMS: *m/z* (ES) 145.0866, $C_7H_{13}O_3$ $[M+H]^+$ requires 145.0864; $[\alpha]_D^{25}$ = +8.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(+)-Prelactone E - (4*R*,5*S*,6*R*)-6-Ethyl-4-hydroxy-5-methyltetrahydro-2H-pyran-2-one, 567



Mercury trifluoroacetate (0.84 g, 1.96 mmol) was added in one portion to a stirred solution of (*R*)-methyl 3-((1*R*,2*R*)-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 $MgSO_4$ 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 (0.089 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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [1:1 EtOAc:Petroleum ether, R_f 0.21] to afford (4*R*,5*S*,6*R*)-6-ethyl-4-hydroxy-5-methyltetrahydro-2H-pyran-2-one **567** (0.064 g, 0.41 mmol) as a gummy solid in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 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, C*H*OH and C*H*CH_2CH_3), 2.89 (1H, dd, *J* = 17.1, 5.9 Hz, COCH_AH_B), 2.48 (1H, dd, *J* = 17.1, 7.8 Hz, $COCH_AH_B$), 2.51 (1H, broad s, O*H*), 1.82 and 1.74-1.48 (1H, app. sex. of doublets, *J* = 7.5, 3.0 Hz and 2H, m, C*H*CH_3 and CH_2CH_3), 1.06 (3H, d, *J* = 6.7 Hz, CHCH_3), 1.00 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_8H_{15}O_3$ $[M+H]^+$ requires 159.1021; $[\alpha]_D^{25}$ = +36.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

(+)-Prelactone B - (4*R*,5*S*,6*R*)-4-hydroxy-6-isopropyl-5-methyltetrahydro-2H-pyran-2-one, 568

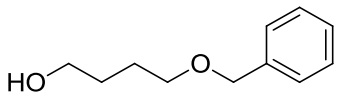


Mercury trifluoroacetate (0.68 g, 1.60 mmol) was added in one portion to a stirred solution of (*R*)-methyl 3-hydroxy-3-((1*R*,2*S*)-2-isopropylcyclopropyl)propanoate **565** (0.12 g, 0.64 mmol) in dichloromethane (10 mL). The resulting yellow solution was stirred at ambient temperature for 24 hours 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 $MgSO_4$ 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 $MgSO_4$ and concentrated to afford the crude product. The crude product was purified using flash silica chromatography [3:7 EtOAc:Petroleum ether, R_f 0.10] to afford (4*R*,5*S*,6*R*)-4-hydroxy-6-isopropyl-5-methyltetrahydro-2H-pyran-2-one **568** (0.10 g, 0.60 mmol) as a gummy solid in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.73 (2H, m, COOC*H*CH(CH_3)(CH_3) and C*H*OH), 3.41 (1H, broad s, O*H*), 2.85 (1H, dd, *J* = 17.1, 5.9 Hz, COC$H_A$$H_B$CHOH), 2.43 (1H, dd, *J* = 17.1, 7.7 Hz, COC$H_A$$H_B$CHOH), 1.94 (1H, dhep, *J* = 6.9, 2.1 Hz, COOCHC*H*(CH_3)(CH_3)), 1.70 (1H, m, C*H*CH_3), 1.03 (6H, m, COOCHCH(CH_3)(CH_3) and CHCH_3), 0.87 (3H, d, *J* = 6.8 Hz, COOCHCH(CH_3)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_9H_{16}NaO_3$ $[M+Na]^+$ requires 195.0997; $[\alpha]_D^{25}$ = +28.0 (*c* = 0.5 g/100 mL in $CHCl_3$).

4.2 Compounds from Chapter 3

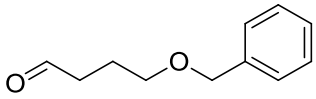
4.2.1 Synthesis of Non-Commercially Available Aldehydes

4-(Benzyloxy)butan-1-ol



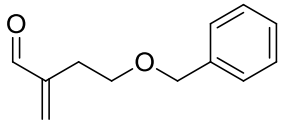
NaH (0.98 g, 24.41 mmol, 60% dispersion in mineral oil) was added portionwise to THF (20 mL) at 0 ˚C. Butane-1,4-diol (2.0 g, 22.19 mmol) was added dropwise followed by benzyl bromide (3.17 mL, 26.63 mmol). The resulting suspension was stirred at room temperature for five hours before being quenched 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:4 EtOAc: Petroleum ether, R_f 0.21] to afford 4-(benzyloxy)butan-1-ol (1.57 g, 8.65 mmol) as a colourless oil in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.18 (5H, m, Ph), 4.43 (2H, s, OC*H*$_2$Ph), 3.50 (2H, t, *J* = 6.1 Hz, HOC*H*$_2$), 5.82 (2H, t, *J* = 5.8 Hz, C*H*$_2$OBn), 3.10 (1H, broad s, O*H*), 1.67-1.50 (4H, m, C*H*$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{11}H_{17}O_2$ $[M+H]^+$ requires 181.1228.

4-(Benzyloxy)butanal, 603



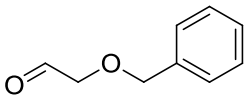
Oxalyl chloride (1.03 mL, 12.20 mmol) was dissolved in dry dichloromethane (50 mL) at -55 ˚C under nitrogen. Dimethylsulphoxide (1.58 mL, 22.20 mmol) was added and the resulting solution was stirred for two minutes. 4-(Benzyloxy)butan-1-ol (2.00 g, 11.10 mmol) in dichloromethane (5 mL) was added dropwise 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 $NaHCO_3$ before being dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.63] to afford 4-(benzyloxy)butanal **603** (1.48 g, 8.30 mmol) as a colourless liquid in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.68 (1H, s, C*H*O), 7.30-7.18 (5H, m, Ph), 4.41 (2H, s, OCH_2Ph), 3.43 (2H, t, *J* = 6.1 Hz, CH_2OBn), 2.45 (2H, t, *J* = 7.1 Hz, CHOCH_2), 1.87 (2H, app. quintet, *J* = 6.6 Hz, $CH_2CH_2CH_2$OBn); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_{11}H_{14}NaO_2$, $[M+Na]^+$ requires 201.0891.

4-(Benzyloxy)-2-methylenebutanal, 604



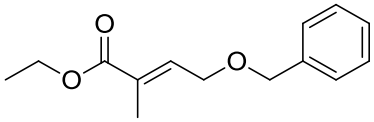
4-(Benzyloxy)butanal **603** (0.50 g, 2.80 mmol) was dissolved in 37% aqueous formaldehyde solution (0.27 mL, 3.70 mmol). Dimethylamine hydrochloride (0.30 g, 3.70 mmol) was added and the mixture was heated at 70 ˚C for 24 hours. The reaction was cooled to room temperature, quenched with saturated $NaHCO_3$, extracted into hexane and the combined organic fractions were washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.31] to afford 4-(benzyloxy)-2-methylenebutanal **604** (0.41 g, 2.20 mmol) as a colourless liquid in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.46 (1H, s, C*H*O), 7.30-7.19 (5H, m, Ph), 6.31 (1H, s, C=CH_AH$_B$), 6.00 (1H, s, C=CH$_A$$H_B$), 4.43 (2H, s, OC$H_2$Ph), 3.53 (2H, t, *J* = 6.4 Hz, CH_2OBn), 2.51 (2H, t, *J* = 6.4 Hz, CH$_2$=CCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 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, $C_{12}H_{14}NaO_2$, $[M+Na]^+$ requires 213.0886.

2-(Benzyloxy)acetaldehyde, 606



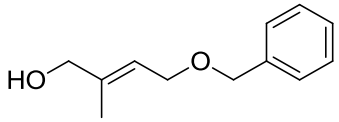
Oxalyl chloride (0.18 mL, 2.17 mmol) was dissolved in dry dichloromethane (7 mL) at -55 ˚C under nitrogen. Dimethylsulfoxide (0.28 mL, 3.94 mmol) was added and the resulting solution was stirred for two minutes. 2-(Benzyloxy)ethanol (0.30 g, 1.97 mmol) was added dropwise to the solution to form a light 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 $NaHCO_3$ before being dried over $MgSO_4$ 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.57 (1H, s, C*H*O), 7.27-7.19 (5H, m, Ph), 4.50 (2H, s, OCH_2Ph), 3.97 (2H, d, *J* = 0.7 Hz, CHOCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_9H_{10}NaO_2$ $[M+Na]^+$ requires 173.0578.

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



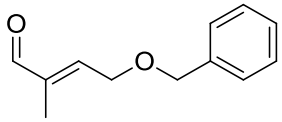
(Carbethoxyethylidene)triphenylphosphorane (0.65 g, 1.80 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0 ˚C. 2-(Benzyloxy)acetaldehyde **606** (0.24 g, 1.60 mmol) in dichloromethane (1 mL) was added dropwise and the resulting solution was stirred for 30 minutes. The dichloromethane was removed under reduced pressure and the crude product was purified using flash silica chromatography [1:99 EtOAc:Petroleum ether, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.18 (5H, m, Ph), 6.80 (1H, td, *J* = 5.8, 1.1 Hz, CH_3C=C*H*), 4.45 (2H, s, OCH_2Ph), 4.11 (4H, app. quartet, *J* = 7.1 Hz, C=CHCH_2 and CH_3CH_2OC=O), 1.74 (3H, s, CH_3C=CH), 1.20 (3H, t, *J* = 7.0 Hz, CH_3CH_2OC=O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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, $C_{14}H_{18}NaO_3$ $[M+Na]^+$ requires 257.1153.

(*E*)-4-(Benzyloxy)-2-methylbut-2-en-1-ol, 609



(*E*)-Ethyl 4-(benzyloxy)-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 $NaHCO_3$ before being dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.19] to afford (*E*)-4-(benzyloxy)-2-methylbut-2-en-1-ol **609** (0.08 g, 0.43 mmol) as a colourless liquid in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.18 (5H, m, Ph), 5.57 (1H, tq, *J* = 6.6, 1.3 Hz, CH_3C=C*H*), 4.43 (2H, s, CH_2OPh), 3.99 (2H, d, *J* = 6.6 Hz, CH_2OBn), 3.90 (2H, s, CH_2OH), 2.27 (1H, broad s, O*H*), 1.57 (3H, s, CH_3C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) 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, $C_{12}H_{16}NaO_2$ $[M+Na]^+$ requires 215.1048.

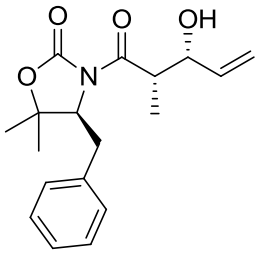
(*E*)-4-(Benzyloxy)-2-methylbut-2-enal, 610



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 $NaHCO_3$ before being dried over $MgSO_4$ and concentrated. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.33 (1H, s, C*H*O), 7.30-7.16 (5H, m, Ph), 6.50 (1H, tq, *J* = 5.6, 1.3 Hz, (CH_3C=C*H*)), 4.48 (2H, s, OCH_2Ph), 4.25 (2H, dd, *J* = 5.6, 1.1 Hz, CH_2OBn), 1.63 (3H, app. quartet, *J* = 1.1 Hz, CH_3C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{12}H_{14}NaO_2$ $[M+Na]^+$ requires 213.0891.

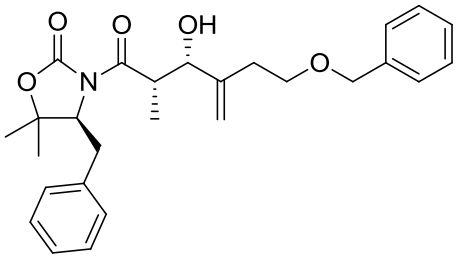
*4.2.2 Synthesis of syn-Aldol Products **613**, **614**, **615***

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



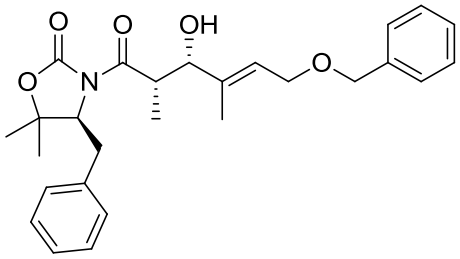
The title compound was prepared according to General Procedure 1 from 9-BBN-OTf (3.78 mL, 1.90 mmol), (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.40 g, 1.70 mmol), *N*,*N*-diisopropylethylamine (0.43 ml, 2.50 mmol) and acrolein (0.16 mL, 2.50 mmol) in dichloromethane (90 mL). The crude product was purified using flash silica chromatography to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-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, $CDCl_3$) δ_H = 7.26-7.12 (5H, m, Ph), 5.83-5.70 (1H, ddd, *J* = 10.5, 5.5, 5.3 Hz, C*H*=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}$$H_{trans}$=C), 4.49 (1H, dd, *J* = 9.0, 4.5 Hz, C*H*N), 4.38 (1H, m, C*H*OH), 3.85 (1H, dq, *J* = 7.0, 4.0 Hz, C*H*CH_3), 3.0 (1H, dd, *J* = 14.5, 4.5 Hz, CH_AH$_B$Ph), 2.85 (1H, dd, *J* = 14.5, 9.0 Hz, CH$_A$$H_B$Ph), 2.65 (1H, broad s, OH), 1.33 (3H, s, (CH_3)C(CH_3)), 1.31 (3H, s, (CH_3)C(CH_3)), 1.10 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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$_{ox}$); 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-((2*S*,3*S*)-6-(benzyloxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-di methyloxazolidin-2-one, 614



The title compound was prepared according to General Procedure 1 from dibutylboron 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, R_f 0.27] to afford (*S*)-4-benzyl-3-((2*S*,3*S*)-6-(benzyloxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxa zolidin-2-one **614** (0.57 g, 1.30 mmol) as a colourless oil in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27-7.16 (10H, m, Ph and Ph_{ox}), 5.11 (1H, s, C=CH_AH_B), 4.95 (1H, s, C=CH_AH_B), 4.45-4.40 (3H, m, OCH_2Ph, C*H*N), 4.32 (1H, broad d, *J* = 5.8 Hz, C*H*OH), 4.00 (1H, app. quintet, *J* = 6.6 Hz, C*H*CH_3), 3.62-3.48 (2H, m, CH_2OBn), 3.18 (1H, broad s, O*H*), 2.99 (1H, dd, *J* = 14.4, 4.3 Hz, CH_AH_BPh), 2.83 (1H, dd, *J* = 14.1, 8.7 Hz, CH_AH_BPh), 2.44-2.35 (1H, m, CH_AH_BOBn), 2.29-2.21 (1H, m, CH_AH_BOBn), 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, $CDCl_3$) δ_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} ν = 3467 (OH), 1770 (C=O_{ox}), 1694 (C=O); HRMS: *m/z* (ES) 452.2458, $C_{27}H_{34}NO_5$ $[M+H]^+$ requires 452.2436; $[\alpha]_D^{17}$ = -30.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

(*S*)-4-Benzyl-3-((2*S*,3*S*,*E*)-6-(benzyloxy)-3-hydroxy-2,4-dimethylhex-4-enoyl)-5,5-dimeth yloxazolidin-2-one, 615



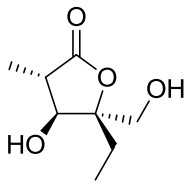
The title compound was prepared according to General Procedure 1 from dibutylboron triflate (1.50 mL, 1.50 mmol), (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **95** (0.36 g, 1.40 mmol), *N*,*N*-diisopropylethylamine (0.31 mL, 1.80 mmol) and (*E*)-4-(benzyloxy)-2-methylbut-2-enal[246] **610** (0.34 g, 1.80 mmol) in dichloromethane (3 mL). The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.24] to afford (*S*)-4-benzyl-3-((2*S*,3*S*,*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, $CDCl_3$) δ_H = 7.27-7.15 (10H, m, Ph and Ph_{ox}), 5.71 (1H, broad t, *J* = 6.3 Hz, C=C*H*), 4.46-4.43 (3H, m, OCH_2Ph and C*H*N), 4.28 (1H, d, *J* = 3.7 Hz, C*H*OH), 4.02 (2H, d, *J* = 6.6 Hz, CH_2OBn), 3.96-3.91 (1H, m, C*H*CH_3), 3.01 (1H, dd, *J* = 14.3, 4.0 Hz, C$H_A$$H_B$Ph), 2.82 (2H, dd, broad s, *J* = 14.3, 9.1 Hz, $CH_A$$H_B$Ph and O*H*), 1.57 (3H, s, CH_3C=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, $CDCl_3$) δ_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} ν = 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 $CHCl_3$).

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

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

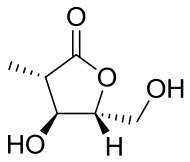
Osmium tetroxide (OsO_4) (0.1 equiv.) was added in one portion to a stirring solution of the appropriate β-alkenyl-β-hydroxy-*N*-acyloxazolidin-2-one **613-616**, **536**, **538** (1.0 equiv.) in acetone/water (8:1 ratio) under nitrogen. After five minutes, NMO (*N*-methylmorpholine *N*-oxide, 60% by 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.

(3*S*,4*S*,5*R*)-5-Ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one, 599



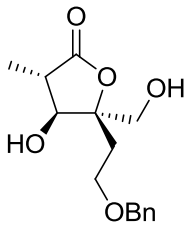
OsO_4 (0.022 g, 0.09 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one **592** (0.31 g, 0.88 mmol) in acetone/water (8:1, 3 mL) followed by addition of NMO (60% by weight in water, 0.16 mL, 0.97 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3*S*,4*S*,5*R*)-5-ethyl-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one **599** (0.12 g, 0.61 mmol) as a colourless oil in 69 % yield and 49:1 dr. ^{1}H NMR (500 MHz, MeOD) δ_H = 4.24 (1H, d, *J* = 9.4 Hz, C*H*OH), 3.74 (1H, d, *J* = 12.1 Hz, CH_AH$_B$OH), 3.52 (1H, d, *J* = 12.2 Hz, CH$_A$$H_B$OH), 2.68 (1H, qd, *J* = 9.4, 7.1 Hz, C*H*CO), 1.81 (1H, dq, *J* = 15.0, 7.5 Hz, CH_AH$_B$CH$_3$), 1.71 (1H, dq, *J* = 15.0 , 7.5 Hz, CH$_A$$H_BCH_3$), 1.28 (3H, d, *J* = 7.5 Hz, CH_3), 1.01 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, MeOD) δ_C = 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, $C_8H_{15}O_4$ [M+H]$^+$ requires 175.0970; $[\alpha]_D^{24}$ = - 3.4 (*c* = 0.88 g/100 mL in $CHCl_3$).

(3*S*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one, 632



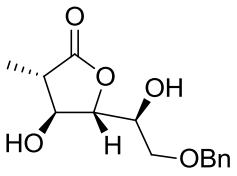
OsO_4 (0.015 g, 0.06 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl)-5,5-dimethyloxazolidin-2-one **613** (0.15 g, 0.52 mmol) in acetone/water (8:1, 5 mL) followed by addition of NMO (60% by weight in water, 0.09 mL, 0.52 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-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. **(3*S*,4*S*,5*R*)-major:** ^{1}H NMR (500 MHz, MeOD) δ_H = 4.19-4.17 (1H, m, C*H*CH_2OH), 4.02 – 3.99 (1H, m, C*H*OH), 3.94 (1H, dd, *J* = 12.8, 2.5 Hz, C$H_A$$CH_B$OH), 3.72 (1H, dd, *J* = 12.8, 4.8 Hz, CH_ACH_BOH), 2.66 (1H, dq, *J* = 8.9, 7.1 Hz, C*H*CH_3), 1.30 (3H, d, *J* = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, MeOD) δ_C = 180.0, 86.8, 75.6, 62.0, 45.7, 13.6; **(3*S*,4*S*,5*S*)-minor:** ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 4.57 (1H, dt, *J* = 5.8, 3.7 Hz, C*H*CH_2OH), 4.27 (1H, t, *J* = 6.0 Hz, C*H*OH), 3.90 (2H, d, *J* = 3.7 Hz, CH_ACH_BOH), 2.71 (1H, dt, *J* = 13.6, 7.6 Hz, C*H*CH_3), 1.29 (3H, d, *J* = 7.5 Hz, CH_3); ^{13}C 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, $C_6H_{11}O_4$ $[M+H]^+$ requires 147.0657; $[\alpha]_D^{24}$ = +4.0 (*c* = 0.50 g/100 mL in MeOH).

(3*S*,4*S*,5*R*)-5-(2-(Benzyloxy)ethyl)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one, 633



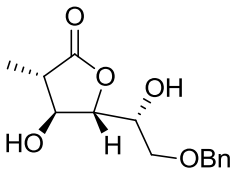
OsO_4 (0.008 g, 0.03 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*S*)-6-(benzyloxy)-3-hydroxy-2-methyl-4-methylenehexanoyl)-5,5-dimethyloxazolidin-2-one **614** (0.14 g, 0.31 mmol) in acetone/water (8:1, 1.5 mL) followed by addition of NMO (60% by weight in water, 0.07 mL, 0.34 mmol) according 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 (3*S*,4*S*,5*R*)-5-(2-(benzyloxy)ethyl)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one **633** (0.08 g, 0.28 mmol) as a colourless oil in 93% yield and 10:1 dr. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.18 (5H, m, Ph), 4.43 (2H, s, OCH_2Ph), 4.12 (1H, broad s, O*H*), 3.96 (1H, d, *J* = 8.4 Hz, C*H*OH), 3.59-3.49 (4H, m, CH_2OBn, CH_2OH), 2.80 (1H, broad s, OH), 2.49 (1H, app. quintet, *J* = 7.4 Hz, C*H*CH_3), 2.07-1.91 (2H, m, CH_2CH_2OBn), 1.20 (3H, d, *J* = 7.4 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{15}H_{20}NaO_5$, $[M+Na]^+$ requires 303.1208; $[\alpha]_D^{24}$ = +18.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

(3*S*,4*S*,5*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-2(3H)-one, 634



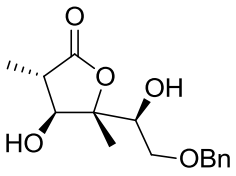
OsO_4 (0.006 g, 0.02 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*R*,*E*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **538** (0.10 g, 0.22 mmol) in acetone/water (8:1, 1.2 mL) followed by addition of NMO (60% by weight in water, 0.04 mL, 0.25 mmol) according 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 (3*S*,4*S*,5*S*)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-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, OC*H*$_2$Ph), 4.04-3.90 (3H, m, CH_3CHC*H*OH, COOC*H*, OCH_2C*H*OH), 3.63-3.52 (3H, m, C*H*$_2$OBn, O*H*), 2.95 (1H, d, *J* = 4.3 Hz, O*H*), 2.61-2.51 (1H, m, C*H*CH_3), 1.22 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$); ^{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; $[\alpha]_D^{24}$ = +4.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

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



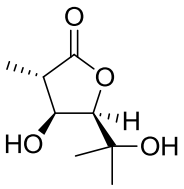
OsO_4 (0.006 g, 0.02 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*R*,*Z*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl)-5,5-dimethyloxazolidin-2-one **536** (0.10 g, 0.22 mmol) in acetone/water (8:1, 1.2 mL) followed by addition of NMO (60% by weight in water, 0.04 mL, 0.25 mmol) according to General Procedure 5 to afford the crude product as black oil. The crude product was purified using flash silica chromatography [EtOAc:Petroleum ether] to afford (3*S*,4*S*,5*S*)-5-((*R*)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-2(3H)-one **635** as a colourless oil as a separarable diastereomeric mixture in overall 74% yield and 2:1 dr. The diastereomers were separated using flash coloum 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). **(3*S*,4*S*,5*R*)-5-(*S*)-major:** ^{1}H NMR (300 MHz, 50:50 $CDCl_3$:C_6H_6) δ_H = 7.32-21 (5H, m, Ph), 4.43 (1H, d, *J* = 11.6 Hz, OC*H*$_A$H$_B$Ph), 4.36 (1H, d, *J* = 11.6 Hz, OCH$_A$*H*$_B$Ph), 4.03 (1H, dd, *J* = 9.9, 7.3 Hz, CH_3CHC*H*OH), 3.85 (1H, dd, *J* = 7.3, 5.1 Hz, COOC*H*), 3.79-3.75 (1H, m, OCH_2C*H*OH), 3.51 (1H, dd, *J* = 10.3, 3.3 Hz, C*H*$_A$H$_B$OBn), 3.46 (1H, dd, 10.3, 4.2 Hz, CH$_A$*H*$_B$OBn), 3.21 (1H, broad s, O*H*), 2.59 (1H, broad s, O*H*), 2.50 (1H, dq, *J* = 9.9, 7.1 Hz, C*H*CH_3), 1.25 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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, $C_{14}H_{18}NaO_5$, $[M+Na]^+$ requires 289.1051; $[\alpha]_D^{24}$ = -2.0 (*c* = 0.50 g/100 mL in $CHCl_3$). **(3*S*,4*S*,5*S*)-5-(*R*)-minor:** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.40-7.30 (5H, m, Ph), 4.59 (2H, s, OC*H*$_2$Ph), 4.43 (1H, dd, *J* = 8.0, 4.7 Hz, COOC*H*), 4.32 (1H, dd, *J* = 4.7, 2.6 Hz, CH_3CHC*H*OH), 4.18-4.13 (1H, m, OCH_2C*H*OH), 3.79 (1H, dd, *J* = 9.9, 3.3 Hz, C*H*$_A$H$_B$OBn), 3.69 (1H, dd, *J* = 9.9, 5.0 Hz, CH$_A$*H*$_B$OBn), 3.11 (1H, broad s, O*H*), 2.87 (1H, broad s, O*H*), 2.68 (1H, qd, *J* = 7.8, 2.5 Hz, C*H*CH_3), 1.30 (3H, d, *J* = 7.8 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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, $C_{14}H_{18}NaO_5$, $[M+Na]^+$ requires 289.1051; $[\alpha]_D^{24}$ = -6.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

(3*S*,4*S*,5*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-4-hydroxy-3,5-dimethyldihydrofuran-2(3H)-one, 636



OsO_4 (0.004 g, 0.02 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*S*,*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 (3*S*,4*S*,5*S*)-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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.31-7.17 (5H, m, Ph), 4.49 (1H, d, *J* = 11.6 Hz, OCH_AH_BPh), 4.43 (1H, d, *J* = 11.6 Hz, OCH_AH_BPh), 3.86 (1H, d, *J* = 10.5 Hz, $CHCH_3CH$OH), 3.77 (1H, dd, *J* = 7.6, 6.2 Hz, C*H*OHCH_2OBn), 3.54 (1H, dd, *J* = 10.0, 6.2 Hz, CH_AH_BOBn), 3.47 (1H, dd, *J* = 9.8, 7.8 Hz, CH_A-H_BOBn), 3.42 (1H, broad s, O*H*), 2.90 (1H, broad s, O*H*), 2.65-2.53 (1H, m, C*H*CH_3), 1.20-1.16 (6H, m, CHCH_3, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{15}H_{21}O_5$, $[M+H]^+$ requires 281.1388; $[\alpha]_D^{23}$ = -12.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

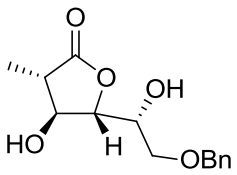
(3*S*,4*S*,5*R*)-4-Hydroxy-5-(2-hydroxypropan-2-yl)-3-methyldihydrofuran-2(3*H*)-one, 637



OsO_4 (0.014 g, 0.05 mmol) was added to a solution of (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethylhex-4-enoyl)-5,5-dimethyloxazolidin-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 (3*S*,4*S*,5*R*)-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methyldihydrofuran-2(3*H*)-one **637** (0.038 g, 0.22 mmol) as a colourless oil in 41% yield and 5:1 dr. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.94 (1H, d, *J* = 4.1 Hz, OH), 4.26 (1H, app. dt, *J* = 3.9, 1.5 Hz, C*H*OH), 4.09 (1H, d, *J* = 4.1 Hz, C*H*OCO), 2.96 (1H, broad s, OH), 2.68 (1H, qd, *J* = 7.8, 1.5 Hz, C*H*C$(CH_3)_2$OH), 1.38 (3H, s, (C*H*$_3$)C(CH_3)), 1.36 (3H, s, (CH_3)C(C*H*$_3$)), 1.19 (3H, d, *J* = 7.8 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_8H_{15}O_4$ $[M+H]^+$ requires 175.0970; $[\alpha]_D^{23}$ = -55.6 (*c* = 0.99 g/100 mL in $CHCl_3$).

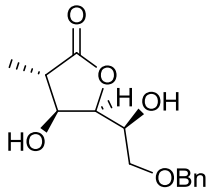
Sharpless Asymmetric Dihydroxylations

(3*S*,4*S*,5*S*)-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 ^{t}BuOH and water (1.8 mL, 10 mL/mmol of allylic alcohol). $MeSO_2NH_2$ (0.017 g, 0.18 mmol) was added and the biphasic suspension was cooled to 0 ˚C. (*S*)-4-Benzyl-3-((2*S*,3*R*,*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 OsO_4 (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 $MgSO_4$ and concentrated. The crude product was purified using flash column chromatography [1:1 EtOAc:Petroleum ether, R_f 0.15] to afford (3*S*,4*S*,5*S*)-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.

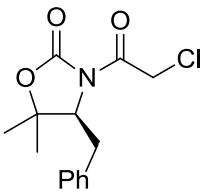
(3*S*,4*S*,5*R*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-2(3H)-one, 658



AD-mix-α (0.25 g, 1.4 g/mmol of allylic alcohol) was dissolved in a 1:1 mixture of ^{t}BuOH and water (1.8 mL, 10 mL/mmol of allylic alcohol). $MeSO_2NH_2$ (0.017 g, 0.18 mmol) was added and the biphasic suspension was cooled to 0 ˚C. (*S*)-4-Benzyl-3-((2*S*,3*R*,*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 OsO_4 (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 $MgSO_4$ and concentrated. The crude product was purified using flash column chromatography [1:1 EtOAc:Petroleum ether, R_f 0.15] to afford (3*S*,4*S*,5*R*)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxy-3-methyldihydrofuran-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.

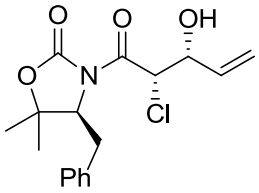
4.2.4 Synthesis of Compounds for 2-Deoxy-D-Ribonolactone

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



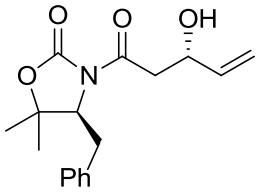
n-BuLi (10.71 mL, 26.8 mmol, 2.5 M solution in hexane) was added to a solution of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one (5.00 g, 24.3 mmol) in dry THF (150 mL) at -78 ˚C under nitrogen and was stirred for 30 minutes. Chloroacetyl chloride (2.07 mL, 26.8 mmol) was added in one portion and the resulting 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 $MgSO_4$ and concentrated to afford crude product. The crude product was purified using flash silica chromatography [1:9 EtOAc:Petroleum ether, R_f 0.50] to afford (*R*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **660** (5.69 g, 20.1 mmol) as a colourless oil in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.32-7.20 (5H, m, Ph), 4.76 (1H, d, *J* = 15.8 Hz, COCH_AH$_B$Cl), 4.64 (d, *J* = 15.8 Hz, COCH$_A$$H_B$Cl), 4.49 (1H, dd, *J* = 9.7, 3.9 Hz, C*H*N), 3.20 (1H, dd, *J* = 14.4, 3.8 Hz, CHH_AH$_B$Ph), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, CH$_A$$H_B$Ph), 1.38 (3H, s, C(C$H_3$)(CH$_3$)), 1.36 (3H, s, C(CH$_3$)(C$H_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 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, $C_{14}H_{16}ClNNaO_3$ $[M+Na]^+$ requires 304.0716; $[\alpha]_D^{25}$ = -32.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

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



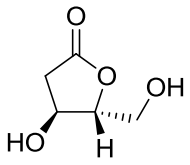
The title compound was prepared according to General Procedure 1 from dibutylboron triflate (7.70 mL, 7.70 mmol), (*S*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **660** (1.97 g, 7.00 mmol), *N*,*N*-diisopropylethylamine (1.58 mL, 9.10 mmol) and acrolein (0.61 mL, 9.10 mmol) in dichloromethane (15 mL). The crude product was purified using flash silica chromatography [1:4 EtOAc:Petroleum ether, R_f 0.27] to afford (*S*)-4-benzyl-3-((2*S*,3*R*)-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, $CDCl_3$) δ_H = 7.31-7.17 (5H, m, Ph), 5.88 (1H, ddd, *J* = 17.3, 10.5, 5.8 Hz, C*H*=CH_2), 5.72 (1H, d, *J* = 5.1 Hz, C*H*Cl), 5.40 (1H, dt, *J* = 17.3, 1.3 Hz, CH=CH_AH_B), 5.28 (1H, dt, *J* = 10.5, 1.2 Hz, CH=CH_AH_B), 4.59 (1H, app. t, *J* = 5.5 Hz, C*H*OH), 4.48 (1H, dd, *J* = 9.5, 3.8 Hz, C*H*N), 3.14 (1H, dd, *J* = 14.4, 3.8 Hz CH_AH_BPh), 3.00 (1H, broad s, O*H*), 2.88 (1H, dd, *J* = 14.4, 9.5 Hz, CH_AH_BPh), 1.36 (3H, s, C(CH_3)(CH_3)), 1.33 (3H, s, C(CH_3)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 167.9, 152.0, 136.4, 135.0, 129.1, 128.8, 127.0, 118.9, 83.3, 72.9, 64.0, 59.1, 34.9, 28.5, 22.2; IR cm^{-1} ν = 3496 (OH), 1771 (C=O_{ox}), 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 $CHCl_3$).

(*S*)-4-Benzyl-3-((*S*)-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 662



(*S*)-4-Benzyl-3-((2*S*,3*R*)-2-chloro-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-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, R_f 0.18] to afford (*S*)-4-benzyl-3-((*S*)-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-2-one **662** (0.79 g, 2.60 mmol) as a colourless oil in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.33-7.24 (5H, m, Ph), 5.89 (1H, ddd, *J* = 17.3, 10.5, 5.4 Hz, C*H*=CH_2), 5.32 (1H, d, *J* = 17.3 Hz, CH=C$H_A$$H_B$), 5.15 (1H, d, *J* = 10.5 Hz, CH=C$H_A$$H_B$), 4.58-4.50 (2H, m, C*H*OH, C*H*N), 3.16-3.09 (3H, m, C$H_A$$CH_BPh, CH_2$CHOH), 2.93-2.85 (2H, m, CH_ACH_BPh, CHOH), 1.39 (3H, s, C(CH_3)(CH_3)), 1.37 (3H, s, C(CH_3)(CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_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} ν = 3483 (OH), 1771 (C=O), 1694 (C=O_{ox}); HRMS: *m/z* (ES) 304.1511, $C_{17}H_{22}NO_4$, $[M+H]^+$ requires 304.1548; $[\alpha]_D^{20}$ = -52.0 (*c* = 0.50 g/100 mL in $CHCl_3$).

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



OsO_4 (0.016 g, 0.06 mmol) was added to a solution of (*S*)-4-benzyl-3-((*S*)-3-hydroxypent-4-enoyl)-5,5-dimethyloxazolidin-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 (4*S*,5*R*)-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. **(4*S*,5*R*)-major:** ^{1}H NMR (500 MHz, MeOD) δ_H = 4.46 (1H, dt, *J* = 6.7, 2.3 Hz, C*H*OH), 4.40–4.39 (1H, m, C*H*CH_2OH), 3.79 (1H, dd, *J* = 12.4, 3.3 Hz, C$H_A$$H_B$OH), 3.72 (1H, dd, *J* = 12.4, 3.7 Hz, CH_AH_BOH), 2.94 (1H, dt, *J* = 17.9, 6.8 Hz, C$H_A$$H_B$C=O), 2.40 (1H, dd, *J* = 17.9, 2.5 Hz, CH_AH_BC=O); ^{13}C NMR (75 MHz, MeOD) δ_C = 179.5, 91.0, 70.6, 63.4, 40.0; **(4*S*,5*S*)-minor:** ^{1}H NMR (500 MHz, MeOD) δ_H = 4.63-4.50 (2H, m, C*H*OH & C*H*CH_2OH), 3.90 (2H, dd, *J* = 5.4, 1.6 Hz, CH_2OH), 2.93 (1H, dd, *J* = 17.6, 5.9 Hz, C$H_A$$H_B$C=O), 2.45 (1H, dd, *J* = 17.7, 1.6 Hz, CH_ACH_BC=O); ^{13}C 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, $C_5H_8NaO_4$, $[M+Na]^+$ requires 155.0320; $[\alpha]_D^{25}$ = +4.0 (*c* = 0.50 g/100 mL in MeOH) [lit: $[\alpha]_D^{25}$ = +2.17 (*c* = 0.6 g/100 mL in MeOH)].

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6 Appendix

X-Ray Crystal Structure Data for δ-Lactone **527**

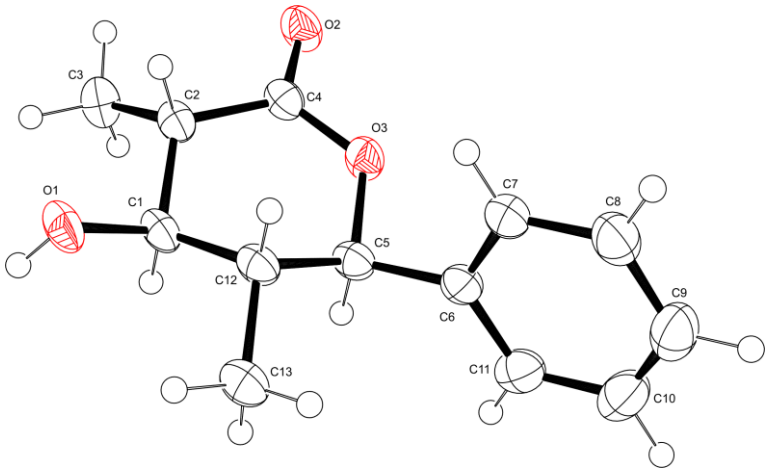

Figure i X-Ray crystal structure for (3*S*,4*R*,5*R*,6*R*)-4-hydroxy-3,5-dimethyl-6-phenyltetrahydro-2H-pyran-2-one

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

Empirical formula	$C_{13}H_{16}O_3$
Formula weight	220.26
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 7.8508(3) Å α = 90° b = 6.9320(3) Å β = 90.905(3)° c = 10.6342(4) Å γ = 90°
Volume	578.66(4) $Å^3$
Z	2
Calculated density	1.264 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	236
Crystal size	0.50 × 0.25 × 0.15 mm
Theta range for data collection	4.35 to 27.48 °
Limiting indices	-10 ≤ h ≤ 10, -8 ≤ k ≤ 8, -13 ≤ l ≤ 13
Reflections collected/unique	12446 / 2642 [R(int) = 0.0781
Completeness to theta= 27.48	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. Transmission	0.9868 and 0.9569
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2642/1/151
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0392, wR2 = 0.0911
R indices (all data)	R1 = 0.0516, wR2 = 0.0975
Extinction coefficient	-0.3(9)
Largest diff. peak and hole	0.155 and -0.218 e. $Å^{-3}$

Table ii

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

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

Table iii

Selected bond lengths (Å) for δ-lactone **527**

Bond	Length (Å)
O(1)-C(1)	1.4286(19)
O(1)-H(1A)	0.81(2)
O(2)-C(4)	1.2150(18)
O(3)-C(4)	1.3384(17)
O(3)-C(5)	1.4714(17)
C(1)-C(12)	1.525(2)
C(1)-C(2)	1.526(2)
C(1)-H(1)	1.0000
C(2)-C(4)	1.514(2)
C(2)-C(3)	1.527(2)
C(2)-H(2)	1.0000
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(5)-C(6)	1.506(2)
C(5)-C(12)	1.525(2)
C(5)-H(5)	1.0000
C(6)-C(11)	1.390(2)
C(6)-C(7)	1.393(2)
C(7)-C(8)	1.389(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.388(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.373(3)
C(9)-H(9)	0.9500

C(10)-C(11)	1.392(3)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-C(13)	1.527(2)
C(12)-H(12)	1.0000
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800

Table **iv**

Selected bond angles (°) for δ-lactone **527**

Bond	Angle (°)
C(1)-O(1)-H(1A)	108.9(15)
C(4)-O(3)-C(5)	122.58(11)
O(1)-C(1)-C(12)	109.85(12)
O(1)-C(1)-C(2)	106.95(11)
C(12)-C(1)-C(2)	111.07(13)
O(1)-C(1)-H(1)	109.6
C(12)-C(1)-H(1)	109.6
C(2)-C(1)-H(1)	109.6
C(4)-C(2)-C(1)	115.08(12)
C(4)-C(2)-C(3)	110.53(12)
C(1)-C(2)-C(3)	111.84(13)
C(4)-C(2)-H(2)	106.2
C(1)-C(2)-H(2)	106.2
C(3)-C(2)-H(2)	106.2
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(2)-C(4)-O(3)	117.07(13)
O(2)-C(4)-C(2)	122.19(13)
O(3)-C(4)-C(2)	120.68(12)
O(3)-C(5)-C(6)	105.78(12)
O(3)-C(5)-C(12)	112.21(11)

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

C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5

Table v

Anisotropic displacement parameters ($Å^2 \times 10^3$) for δ-lactone **527**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$.

	U11	U22	U33	U23	U13	U12
O(1)	33(1)	20(1)	53(1)	-5(1)	0(1)	3(1)
O(2)	49(1)	23(1)	37(1)	3(1)	-4(1)	2(1)
O(3)	41(1)	22(1)	31(1)	1(1)	0(1)	5(1)
C(1)	26(1)	19(1)	42(1)	-2(1)	0(1)	0(1)
C(2)	26(1)	23(1)	34(1)	-2(1)	-1(1)	0(1)
C(3)	41(1)	31(1)	39(1)	-6(1)	-6(1)	3(1)
C(4)	26(1)	25(1)	34(1)	0(1)	-2(1)	-1(1)
C(5)	29(1)	23(1)	34(1)	4(1)	2(1)	1(1)
C(6)	38(1)	21(1))	31(1)	4(1)	4(1)	3(1)
C(7)	43(1)	27(1)	33(1)	2(1)	2(1)	-2(1)
C(8)	57(1)	32(1)	37(1)	1(1)	-7(1)	-5(1)
C(9)	76(1)	37(1)	32(1)	-1(1)	-2(1)	8(1)
C(10)	64(1)	42(1)	35(1)	4(1)	12(1)	15(1)
C(11)	41(1)	32(1)	40(1)	7(1)	8(1)	9(1)
C(12)	28(1)	21(1)	37(1)	3(1)	1(1)	1(1)
C(13)	51(1)	25(1)	43(1)	5(1)	2(1)	1(1)

Table vi

Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for δ-lactone **527**.

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

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

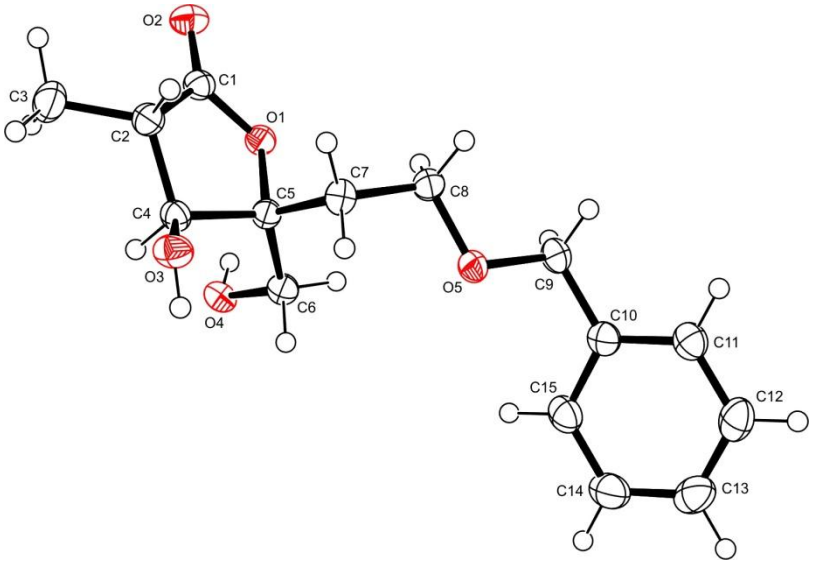

Figure ii X-Ray crystal structure for (3*S*,4*S*,5*R*)-5-(2-(benzyloxy)ethyl)-4-hydroxy-5-(hydroxymethyl)-3-methyldihydrofuran-2(3H)-one

Table i Crystal data and structure refinement for γ-lactone **633**

Empirical formula	$C_{15}H_{20}O_5$
Formula weight	280.31
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*P* 2_1 2_1 2_1
Unit cell dimensions	a = 5.8808(2) Å α = 90° b = 11.1665(2) Å β = 90° c = 21.9865(6) Å γ = 90°
Volume	1443.81(7) $Å^3$
Z	4
Calculated density	1.290 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	600
Crystal size	0.60 x 0.25 x 0.05 mm
Theta range for data collection	3.71 to 27.49 °
Limiting indices	$-7 \le h \le 7$, $-14 \le k \le 14$, $-28 \le l \le 28$
Reflections collected/unique	19206 / 3314 [R(int) = 0.0834]
Completeness to theta= 27.48	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. Transmission	0.9952 and 0.9445
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3314/0/190
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.0915
R indices (all data)	R1 = 0.0555, wR2 = 0.0981
Extinction coefficient	0.2(8)
Largest diff. peak and hole	0.246 and -0.334 e. $Å^{-3}$

Table ii

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for γ-lactone **633**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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

Table iii

Selected bond lengths (Å) for γ-lactone **633**

Bond	Length (Å)
O(1)-C(1)	1.3557(18)
O(1)-C(5)	1.4734(17)
O(2)-C(1)	1.2055(19)
O(3)-C(4)	1.4091(18)
O(3)-H(3)	0.83(2)
O(4)-C(6)	1.4271(19)
O(4)-H(4A)	0.82(2)
O(5)-C(8)	1.4368(19)
O(5)-C(9)	1.4368(18)
C(1)-C(2)	1.510(2)
C(2)-C(4)	1.518(2)
C(2)-C(3)	1.522(2)
C(2)-H(2)	1.0000
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-C(5)	1.5501(19)
C(4)-H(4)	1.0000
C(5)-C(6)	1.518(2)
C(5)-C(7)	1.524(2)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.517(2)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900

C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.500(2)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(15)	1.394(2)
C(10)-C(11)	1.395(2)
C(11)-C(12)	1.383(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.385(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.385(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.385(2)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500

Selected bond angles (°) for γ-lactone **633**

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

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

H(9A)-C(9)-H(9B)	108.3
C(15)-C(10)-C(11)	118.73(15)
C(15)-C(10)-C(9)	121.01(15)
C(11)-C(10)-C(9)	120.25(15)
C(12)-C(11)-C(10)	120.91(16)
C(12)-C(11)-H(11)	119.5
C(10)-C(11)-H(11)	119.5
C(11)-C(12)-C(13)	119.69(18)
C(11)-C(12)-H(12)	120.2
C(13)-C(12)-H(12)	120.2
C(14)-C(13)-C(12)	120.17(18)
C(14)-C(13)-H(13)	119.9
C(12)-C(13)-H(13)	119.9
C(13)-C(14)-C(15)	120.10(17)
C(13)-C(14)-H(14)	119.9
C(15)-C(14)-H(14)	119.9
C(14)-C(15)-C(10)	120.39
C(14)-C(15)-H(15)	119.8
C(10)-C(15)-H(15)	119.8

Table iv

1Anisotropic displacement parameters ($Å^2 \times 10^3$) for γ-lactone **633**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$.

	U11	U22	U33	U23	U13	U12
O(1)	25(1)	26(1)	21(1)	0(1)	-2(1)	1(1)
O(2)	34(1)	30(1)	35(1)	7(1)	-5(1)	3(1)
O(3)	39(1)	28(1)	24(1)	0(1)	-9(1)	0(1)
O(4)	29(1)	29(1)	22(1)	2(1)	-1(1)	-5(1)
O(5)	27(1)	28(1)	20(1)	-1(1)	1(1)	2(1)
C(1)	23(1)	24(1)	28(1)	3(1)	2(1)	-2(1)
C(2)	28(1)	24(1)	25(1)	-1(1)	0(1)	-1(1)
C(3)	41(1)	35(1)	36(1)	-8(1)	3(1)	8(1)
C(4)	27(1)	24(1)	19(1)	-1(1)	-1(1)	-1(1)
C(5)	22(1)	26(1)	19(1)	-1(1)	-3(1)	3(1)
C(6)	26(1)	27(1)	24(1)	0(1)	-2(1)	-1(1)
C(7)	25(1)	28(1)	28(1)	-4(1)	1(1)	0(1)
C(8)	26(1)	31(1)	25(1)	2(1)	0(1)	5(1)
C(9)	36(1)	34(1)	20(1)	-3(1)	3(1)	4(1)
C(10)	34(1)	27(1)	22(1)	-5(1)	-2(1)	-1(1)
C(11)	35(1)	32(1)	27(1)	-4(1)	1(1)	-2(1)
C(12)	38(1)	43(1)	34(1)	-11(1)	0(1)	7(1)
C(13)	57(1)	39(1)	33(1)	-7(1)	-6(1)	17(1)
C(14)	65(1)	31(1)	31(1)	1(1)	3(1)	5(1)
C(15)	41(1)	34(1)	26(1)	-3(1)	4(1)	-2(1)

Table v

Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for γ-lactone **633**.

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