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Synthetic Studies Towards The Cephalosporolide Family

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

By

Orla Finch

School of Chemical Science
University of Auckland
October 2013
Some parts of this work have been published


Abstract

The cephalosporolides are a family of natural products containing a small but interesting β,γ-fused-5,5-spiroacetal-γ-lactone moiety 23. There are seven members of this family which differ in the stereochemistry about the spirocentre at C-6 and the side-chain attached to C-9.

![Diagram of cephalosporolide structure]

The simplest members of this family are cephalosporolides E 24 and F 25, which only differ in the stereochemistry at C-6. The first section of this thesis describes the synthesis of cephalosporolides E 24 and F 25. The key step of the synthesis is the chelation-controlled Mukaiyama aldol reaction between silyl enol ether 234 and aldehyde 162 using MgBr₂·OEt₂ in CH₂Cl₂ to form the cyclisation precursor β-hydroxyketone 160 with the required syn selectivity at C-3 and C-4. Double deprotection of the benzyl groups followed by acid-catalysed lactonisation afforded cephalosporolides E and F as a 3:2 separable mixture.

![Chemical reaction diagram]

Chapter three of this thesis reports synthetic studies towards several other members of the cephalosporolide family, namely cephalosporolides H 28 and I 29, and penisporolides A 26 and B 27. These natural products differ from cephalosporolides E and F by the presence of a gem-dimethyl group α to the γ-lactone and the long alkyl substituent attached to C-9. The synthesis of four possible stereoisomers of the spiroacetal core of the natural products penisporolides A and B and cephalosporolides H and I is described. Despite the various attempts to synthesise the key β-hydroxyketone 247 via an aldol reaction, a cycloaddition reaction, a dithiane coupling or an alkylation reaction, the results were disappointing.
The final reaction sequence involved the cross metathesis coupling of alkene $347$ and alkene $354$ to afford alkene $360$. The desired stereochemistry of the $\gamma$-lactone was installed by employing a Sharpless asymmetric dihydroxylation of alkene $360$. The (DHQD)$_2$PHAL ligand was used to install the $(3R,4R)$ stereochemistry of cephalosporolides H and I and the (DHQ)$_2$PHAL ligand afforded the $(3S,4S)$ stereochemistry at C-3 and C-4 of penisporolides A and B. Oxidative radical cyclisation of the newly formed lactones $345a$, $345b$, $380$ and $381$ afforded the spiroacetal core of the natural products.
The final section of this thesis is the biological evaluation of analogues of (2’S)-spirolaxine methyl ether 455 against *Helicobacter pylori*. *Helicobacter pylori* is the bacterium responsible for stomach ulcers and gastritis and was classified as a class 1 carcinogen in 1994. (2’S)-Spirolaxine methyl ether 455 was synthesised by Brimble *et al.* in 2007 and exhibits potent activity against *H. pylori*. In addition to spirolaxine, a series of analogues 462-469 were also prepared by Brimble *et al.* and these were all evaluated for their anti-*Helicobacter pylori* activity.
ACKNOWLEDGEMENTS

First, I would like to thank my supervisor, DProf. Margaret Brimble for allowing me to participate in this great research group. I am grateful for all your advice and immense knowledge of organic chemistry, incredible speed at proofreading everything and the hours spent on this thesis.

To the postdocs over the years, Dr. Amanda Heapy for helping me get started on this project and for all the hours spent proof reading this thesis. Dr. Daniel Furkert thanks for all the advice and discussions about chemistry.

A thank you must go to Dr. Michael Schmitz for maintaining the NMR facilities. Raisa Imatdieva and Dr. Nicolas Llyod thanks for the mass spectra. Anoma Ratnayake, Tim Layt and Janice Choi thank you for keeping the lab running. Thank you also to Dr. Tanya Groutso for crystal structure analysis.

To all friends on the 7th floor past and present (sorry can’t put all your names) for making these last years so special. Thank you to my fumehood buddy Briar for always listening to me complain and cheering me up. Thank to all the members of the east lab past and present for the laughs and the serious discussions on life. I will really miss you all.

To Paul, Anaïs and Steffî thank you for the lunch time conversations that never failed in making me laugh and putting me in a good mood © you have made this journey so much easier. Thank to Freda for the conversations that never failed in cheering me up and saving my sanity, I hope all goes well for you in finishing your studies.

A special thank you must go to all those you have helped me write this thesis for all the hours spent proof reading and correcting all my silly mistakes, Dr. Amanda Heapy, Dr. Tsz Ying Yuen, Dr. Anaïs Noisier, and Dr. Joanna Dowle and Dr. Manuel Johannes.

Finally and most importantly I would like to thank my family. To my sister Claire and brother Peter thank you both for listening to me, for your caring, understanding and always being there! My parents Conor and Anne, thank you for always helping me, having the right words and always supporting me both financially and emotionally, without you this thesis would not have been possible! This thesis is dedicated to you all!

Táim an bhuíoch díot as an tacaíocht agus an comhoiriú a thug tú dom. Chuir tú spreagadh ionaim nuair a cheap mé go raibh mé ag fiach i ndiaidh na gealaí. Tiomnáim an tráchtas seo duit.

Orla Finch

2013
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<td>angstrom</td>
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<td>m</td>
<td>multiplet or milli</td>
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<td>Me</td>
<td>methyl</td>
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<td>MHz</td>
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<td>m.p.</td>
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<td>Ms</td>
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<td>PPI</td>
<td>proton pump inhibitor</td>
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<td>PPTS</td>
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<tr>
<td>/Pr</td>
<td>iso-propyl</td>
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<td>PT</td>
<td>phenyl tetrazole</td>
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<td>Definition</td>
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<tr>
<td>PTSA</td>
<td><em>para</em>-toluenesulfonic acid</td>
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<tr>
<td>pyr.</td>
<td>pyridine</td>
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<td>q</td>
<td>quartet</td>
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<td>rt</td>
<td>room temperature</td>
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<td>t</td>
<td>triplet</td>
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<td>TBAF</td>
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<td>TBDPS</td>
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<td>TBS</td>
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<tr>
<td>TBT</td>
<td><em>tert</em>-butyltetrazole</td>
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<td>TCIA</td>
<td>trichloroisocyanuric acid</td>
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<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxy</td>
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CHAPTER ONE: INTRODUCTION
1.1 Natural products as pharmaceutical leads

Natural products, isolated from sources such as plants, microbes and insects are a great source of diversity of chemical compounds. Metabolites produced by these natural sources often exhibit interesting biological activity such as antifungal or antiviral properties. These natural products contain privileged scaffolds which have developed over millions of years to interact with specific biological targets. This specificity of interaction makes natural products promising leads for drug development. This is indicated by the fact that in 2010 approximately 50% of new drugs approved for the market were from natural sources or derivatives thereof. However, nature only provides these products in small quantities. Therefore, usually only through the use of total synthesis can sufficient quantities be made available for biological testing and pharmaceutical development. The scarcity, novel architecture and interesting biological activity of these natural metabolites makes them interesting synthetic targets for the organic chemist.

1.2 Spiroacetals

Among the complex frameworks found in many biologically active natural products is the spiroacetal moiety. The spiroacetal scaffold comprises a bicyclic acetal in which two rings are joined by a single atom with two oxygen atoms flanking this spiro-fused carbon, each belonging to one of the rings. It is thought that the conformationally restricted framework of the spiroacetal offers precise orientation of attached functional groups for interaction with biological systems. Most naturally occurring spiroacetals fall within one of the three structural classes shown below (Figure 1): 1,7-dioxaspiro[5.5]undecane 1, 1,6-dioxaspiro[4.5]decane 2 and 1,6-dioxaspiro[4.4]nonane 3. These three compounds are more often referred to as 6,6-spiroacetal, 6,5-spiroacetal and 5,5-spiroacetal, respectively. Also known but less common are spirofused seven-membered and four-membered rings.

![Figure 1: Structural classes of naturally occurring spiroacetals.](image)

The properties of the different classes of spiroacetals differ significantly, and the most common 6,6, 6,5 and 5,5-spiroacetals will be discussed separately in the next section.

1.2.1 6,6-Spiroacetals

Due to their abundance in natural products, notably the spirastrellolide family, the conformation of the 6,6-spiroacetal ring system has been studied extensively. Six-membered rings can form either chair or boat conformations, with the chair conformation being the most favoured and the form found in the spiroacetal framework. In a chair conformation, substituents occupy defined axial and equatorial positions, the orientation of...
which in the spiroacetal are determined by the following three factors: 1) the anomeric effect, 2) steric effects and 3) intramolecular H-bonding.\(^7\)

### 1.2.1.1 The anomeric effect

The anomeric effect is the stabilising effect obtained when an electronegative substituent at the anomeric centre of a pyranose ring occupies the axial position instead of the predicted less sterically demanding equatorial position.\(^{12-14}\) This effect was first observed in 1955 by J. T. Edwards who demonstrated that alkoxy groups at C-1 of pyranose rings are more stable in the axial position than in the equatorial configuration.\(^{15}\) He proposed that this increase in stability is due to the repulsive interaction between the ring dipole, generated by the unpaired electrons of the oxygen and the nearly parallel polar bonds in the equatorial conformation (Figure 2).

![Figure 2: The Edward-Lemieux theory focused on the unfavourable dipole interaction of the β-anomer.](image)

This theory, however, fails to account quantitatively for the observed axial preference. This led to the 1968 “rabbit-ear effect”\(^{16}\) which proposed that the conformation in which unpaired electrons on non-adjacent atoms are in parallel is disfavoured (Figure 3).

![Figure 3: Electrostatic repulsion in the β-anomer 4 due to the “rabbit-ear effect”.](image)

It is now widely accepted that the anomeric stabilisation in spiroacetals is due to the interaction between one lone pair of electrons on one oxygen atom and the antibonding (\(\sigma^*\)) orbital of the adjacent carbon-oxygen bond (Figure 4).\(^{12}\) In order to overlap, the nonbonding (n) orbital must adopt an antiperiplanar arrangement with respect to the carbon-oxygen bond. There are two ways this can be achieved; the endo anomeric effect and the exo anomeric effect (Figure 4).

![Figure 4: Stabilisation in spiroacetals.](image)
Deslongchamps et al.\textsuperscript{17} showed that of the four possible all-chair conformations that potentially exist for 6,6-spiroacetals (Figure 5), conformation 6 which displays two anomeric effects is the most stable.

\textbf{Figure 5:} Four possible conformations of unsymmetrically substituted 6,6-spiroacetals.\textsuperscript{17}

The 6,6-spiroacetal ring system is a relatively rigid structure and there is a clearly defined energy barrier between the anomeric and non-anomeric conformations.\textsuperscript{18} Thus the anomeric effect provides a reliable method for predicting the configuration of such unsubstituted ring systems when formed under thermodynamic conditions. Although during synthesis, the stereochemistry of the 6,6-spiroacetal centre can be predicted by the anomeric effect, steric effects and hydrogen bonding capabilities of the substituents contribute to the ultimate stereochemical outcome.

1.2.1.2 Steric effects

Large or sterically demanding substituents appended to 6,6-spiroacetals can have a profound influence on the conformation of the spiroacetal. Such substituents may favour formation of a non-anomERICally stabilised conformer to minimise severe 1,3-diaxial interactions and prevent ring flipping to an anomERICally stabilised conformation.

The effect of steric interaction is demonstrated in the synthesis of spirofungin A (Scheme 1) by Rizzacasa et al.\textsuperscript{19} Ketone 10 was deprotected to give a mixture of spiroacetals 11 and 12 in 2:1 ratio in favour of the mono anomERICally stabilised spiroacetal 12. It was also observed that each isolated pure spiroacetal led to the same 2:1 equilibrium mixture under acidic conditions. The instability of the doubly anomERIC structure spiroacetal 11 is due to unfavourable steric interactions between axial benzyloxymethyl side chain and the axial hydrogen (Scheme 1). This interaction is not possible in the mono anomERICally stabilised spiroacetal 12 where the benzyloxymethyl substituent occupies the equatorial position.
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Reagents and conditions: a) PPTS, CH₂Cl₂, MeOH, rt, 3 h, 80%, 1:2 11:12; b) PPTS, CH₂Cl₂, rt, 24 h, 1:2 11:12.

Scheme 1: Synthesis of spiroacetals 11 and 12.¹⁹

1.2.1.3 Intramolecular H-bonding

The conformation which the spiroacetal ring adopts may be further influenced by intramolecular hydrogen bonding. In each case, the thermodynamically more stable conformer will predominate under equilibrating conditions. An example of intramolecular H-bonding is observed in the X-ray crystal structure of a 6,6-spiroacetal 13 bearing an axial 1,3-hydroxyl substituent. In this case the hydrogen bonding reinforces the anomeric effect (Figure 6).²⁰

![Figure 6: Hydrogen bonding of 6,6-spiroacetal with 1,3-axial hydroxyl substituent.]

Rizzacasa et al.¹⁹ also employed the influence of H-bonding to control the conformation of spiroacetals 14 and 15 in the synthesis of spirofungin A (Scheme 2). Spiroacetals 16 and 17 were treated with camphorsulfonic acid (CSA) to give a separable 9:1 ratio in favour of the anomerically stabilised anomer 14. The H-bonding in spiroacetal 14 increases the stability of this isomer over spiroacetal 15. A slight increase in the electron density of the oxygen atom due to the alkyne could account for the formation of the strong intermolecular H-bond in isomer 14. This increase was indicated in x-ray analysis and calculations conducted by the presence of an increase in “lone pair” density on the oxygen atom as well as a decrease in the valence shell charge on the alkyne carbon atom.

Reagents and conditions: a) CSA, CH₂Cl₂/Methanol, rt, 18 h, 85% 9:1 14:15; b) CSA, CH₂Cl₂, rt, 18 h, 13:1 14:15.

Scheme 2: Equilibration of spiroacetal isomers 14 and 15.¹⁹
1.2.2 6,5-Spiroacetals

6,5-Spiroacetals comprise an important structural component of the rubromycin\textsuperscript{21-22} and pectenotoxin\textsuperscript{23-25} families of natural products. While not as prevalent in nature as 6,6-spiroacetals, their conformation is influenced by the same effects as the 6,6-spiroacetals; steric effects, intramolecular H-bonding and to a lesser extent the anomeric effect (Figure 7).\textsuperscript{8,26} The lessened influence of the anomeric effect will be better explained in reference to the 5,5-spiroacetal ring system.

![Figure 7: Two conformers of 6,5 spiroacetals.](image)

1.2.3 5,5-Spiroacetals

The analysis of spiroacetal ring systems which contain five-membered rings is much more complex than that of their six-membered ring counterparts as they are unable to adopt the defined chair structure of the six-membered ring system. Five-membered rings are known to exhibit rapid pseudorotation and deformation in which the ring and its substituents may assume a continuous set of conformations, four of which are shown in Figure 8.\textsuperscript{27} The more complex array of conformers adopted by five-membered rings has implications on the degree of influence that the anomeric effect can have over the configuration about the spirocentre. The 180º antiperiplanar arrangement required between a lone pair non-bonding oxygen orbital and the C-O bond for optimal anomeric stabilisation is not attainable in the 5,5-spiroacetal. Instead, this dihedral angle for a bis “pseudo-axial” conformation is only approximately 165º. Consequently, it is not easy to predict the conformation that a ring system will adopt upon spirocyclisation based on the anomeric effect, if one or two five-membered rings are involved.\textsuperscript{7} In essence, the anomeric effect exerts very little effect on the stereocontrol of the reaction in the formation of 5,5-spiroacetals and it is rare to isolate products that adopt a single conformation.

![Figure 8: Different conformation of five-membered rings.](image)

1.3 Natural products containing a 5,5-spiroacetal moiety

Although not as prevalent as 6,6-spiroacetals, several natural products have been isolated and shown to contain the 5,5-spiroacetal moiety. A recent example is the pleurospiroketals A-E (18-22) (Figure 9), which were isolated from the edible mushroom \textit{Pleurotus cornucopiae} in 2013.\textsuperscript{28} All five compounds contain the same cyclohexane fused 5,5-spiroacetal but differ in the stereochemistry at the spirocentre and the substituents about
the tetrahydrofuran ring. Pleurospirokets A-C (18-20) exhibit anti-inflammatory activity by inhibiting the production of nitric oxide. They also exhibit cytotoxicity against the HeLa cell line (cervix carcinoma).

![Figure 9: Pleurospirokets A-E (18-22).](image)

Other examples of bioactive natural products containing the 5,5-spiroacetal moiety include the cephalostatins, ritterazines, pyrenolide D, symbiospirols A-C and halichondrins. Interestingly, while targeting the marine sponge natural product halichondrin C for total synthesis, Kishi et al. produced a structurally simplified intermediate. This intermediate was found to retain the bioactivity of the more structurally complex molecule and has since been approved as a drug for the treatment of metastatic breast cancer.

### 1.3.1 Cephalosporolides

Among the 5,5-spiroacetal natural products with interesting biological activity are a group of natural products containing the β,γ-fused-[4,4]-spiroacetal-γ-lactone (Figure 10). Seven compounds namely cephalosporolides E and F, penisporolides A and B, cephalosporolide H and I as well as ascospiroketal B all containing this moiety have been isolated.

![Figure 10: β,γ-Fused-[4,4]-spiroacetal-γ-lactone.](image)

#### 1.3.1.1 Cephalosporolides E and F

The simplest members of this group are cephalosporolides E and F. These two natural products both contain a methyl group appended at C-9 of the spiroacetal and differ only in the stereochemistry at the C-6 spirocentre (Figure 11).

† Nomenclature confusion has arisen in this family as some members have been named based on their natural product source and some based on their similarity to the cephalosporolides E and F.
Cephalosporolides E 24 and F 25 were first isolated from the fermentation broth of the fungus *Cephalosporium aphidicola* under sulphur limiting conditions by Ackland *et al.* in 1985.\(^{35}\) The relative stereochemistry of cephalosporolides E 24 and F 25 was elucidated using NMR, IR and X-ray crystallography. Also isolated from this same fungus were the ten-membered macrolactones cephalosporolides B 31 and C 32, the eight-membered macrolactone cephalosporolide D 33 and the dimeric sulfide thiobiscephalosporolide 34 (Figure 12).

Cephalosporolides E 24 and F 25 were proposed by Ackland *et al.*\(^{35}\) to be formed from cephalosporolide C 32 via one of the two possible pathways shown below (Scheme 3). The first pathway (pathway A) involves the hydrolysis of cephalosporolide C 32 to give the acyclic form, followed by cyclisation to give the desired cephalosporolides E 24 and F 25. The second possible pathway (pathway B) is the transesterification of cephalosporolide C 32 to give (+)-bassianolone 35 followed by spiroacetalsation to give the desired products. However, attempts to synthetically reproduce the conversion of cephalosporolide C 32 to cephalosporolides E 24 and F 25 have been unsuccessful.\(^{35}\)
Although cephalosporolides E 24 and F 25 (Figure 11) were initially thought to be artefacts of the isolation process,\textsuperscript{35} their re-isolation in 2004 from the fungus \textit{Cordyceps militaris}\textsuperscript{36} and the discovery of other related natural products cephalosporolides H and I,\textsuperscript{37} penisporolides A and B,\textsuperscript{38} and ascospiroketal B\textsuperscript{39} led to the conclusion that these are actual natural products.

In 2005, cephalosporolides E 24 and F 25 were again isolated from a different fungal source, \textit{Beauveria bassiana}.\textsuperscript{40} Also isolated from \textit{Beauveria bassiana} fungus in low nitrogen media was (+)-bassianolone 35, the precursor to spirocycles cephalosporolides E 24 and F 25. Antimicrobial testing was carried out on these three compounds against a wide range of bacteria. Cephalosporolides E and F proved to be inactive against Gram positive \textit{Staphylococcus aureus} and \textit{Bacillus megaterium} as well as Gram negative \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa} and the fungus \textit{Candida albicans}. Recently, in 2012 cephalosporolide E 24 has again been isolated from the ethyl acetate extracts of the fungus \textit{Armillaria tabescens} (strain JNB-OZ344).\textsuperscript{41} (+)-Bassianolone 35, however, completely inhibited the visible growth of a large number of microorganisms including \textit{Staphylococcus aureus} and \textit{Candida albicans}. To date no total synthesis of (+)-bassianolone 35 has been reported.
1.3.1.2 Cephalosporolides H and I

![Cephalosporolide H 28 and Cephalosporolide I 29](image)

Figure 13: Cephalosporolide H 28 and cephalosporolide I 29.37

Other members of the cephalosporolide family which exhibit the same β,γ-fused-[4,4]-spiroacetal-γ-lactone scaffold as cephalosporolides E 24 and F 25 have been isolated. Cephalosporolides H 28 and I 29 (Figure 13) were extracted from a marine fungus Penicillium sp. in 2007 by Li et al.37 The structures were elucidated on the basis of $^1$H, $^{13}$C and 2D NMR as well as MS analysis. Both cephalosporolides H 28 and I 29 contain bis-methyl substitution of the lactone ring and differ only in the substitution at C-9. Cephalosporolide H 28 has a saturated heptyl side chain whereas cephalosporolide I 29 has a four carbon chain bearing a terminal carboxylic acid. Only one stereoisomer of both cephalosporolides H 28 and I 29 was isolated.

The biological activity of cephalosporolides H 28 and I 29 was evaluated against xanthine oxidase and 3α-hydroxysteroid dehydrogenase and were found to exhibit potent inhibition of both enzymes at concentrations under 290 µM. Xanthine oxidase is present in the kidneys and liver of humans and catalyses the transformation of oxygen to superoxide radicals and hydrogen peroxide. These reactive oxygen species are responsible for oxidative injury in ischaemic diseases of the heart, bowel, liver, kidney and brain.18,42,43 Therefore inhibitors of xanthine oxidase may be beneficial if administered after an ischaemic event such as stroke or myocardial infarction. Additionally due to their ability to inhibit 3α-hydroxysteroid dehydrogenase,44 the main function of which is the regulation of steroid production in the body, cephalosporolides H and I have strong potential to be developed as anti-inflammatory agents.
1.3.1.3 Penisporolides A and B

Penisporolides A 26 and B 27 (Figure 14) isolated from a fungus *Penicillium sp.*, possess similar structural features to that of cephalosporolides H 28 and I 29. While the side chain at C-9 of the 5,5-spiroacetal is 5-hydroxyheptyl in the case of penisporolides A 26, penisporolide B 27 bears a 3-oxohexyl substituent. Both penisporolides 26 and 27 have no reported biological activity.

1.3.1.4 Ascospiroketal B

Ascospiroketals B 30, containing the same tricyclic core as cephalosporolides E 24 and F 25 was isolated in 2007 from the marine fungus *Ascochyta salicorniae*. This spiroacetal differs for cephalosporolides E 24 and F 25 in the elaborate side chain at C-9 as well as the geminal substitution alpha to the lactone. Biological testing has yet to be undertaken.

Although the spiroacetal remains to be constructed and the elaborate tail synthesised and appended, some progress toward a synthesis of ascospiroketal B 30 has been reported by Lee *et al.* A chiral auxiliary approach was employed to introduce the bis-geminal stereochemistry on the lactone ring.
1.5 Methods for formation of the 5,5-spiroacetal moiety

The following section will briefly outline the most commonly used methods that have been reported in literature for the formation of the 5,5-spiro scaffold. There are a variety of methods available for the construction of the spiroacetal framework, however the choice of the appropriate methodology is often dictated by the synthetic compatibility of the incorporated functional groups. It is notable that unlike 6,6-spiroacetals nearly all synthesise of 5,5-spiroacetals report the isolation of mixtures of diastereomers about the spiroacetal centre. The following five general methods will be discussed.

1. Cyclisation of a dihydroxyketone
2. Metal mediated spirocyclisation
3. Cyclic enol ether reactions
4. Oxidative methods
5. Carbonyl cascade reactions
1.5.1 Acid-catalysed spiroacetalisation of dihydroxyketone

Acid catalysed cyclisation of dihydroxyketones is the most frequently employed route for the synthesis of spiroacetals. The ketone or diol functionality is often masked during the course of the synthesis until the cyclisation step, in which acid-catalysed deprotection promotes spiroacetal formation.

1.5.1.1. Exposure of the diol moiety promoting cyclisation

The synthesis of the 5,5-spiroacetal fragment of ritterazine 39 (Scheme 4) was reported by Taber et al. Deprotection of the hydroxy silyl protecting groups of ketone 40 revealed the corresponding diol which underwent in situ cyclisation. The lack of stereocontrol afforded to spiroacetals containing the five-membered rings is evident by the fact that a mixture of four diastereomers (41-44) were obtained upon spirocyclisation. Each isomer could be separated and the stereochemistry of each confirmed by NMR studies.

Regents and conditions: a) 1 M HCl, THF, rt, 3 h, 87%; b) PPTS, CH₂Cl₂, 80 °C, 5 h, 74%.

Scheme 4: Synthesis of the 5,5-spiroacetal of ritterazines.
The spiroacetal mixture could be equilibrated with pyridinium p-toluenesulfonate (PPTS) in CH$_2$Cl$_2$ to give 41 in 74% yield. The conformation of spiroacetal 41, the most thermodynamically stable in which the spiroacetal forms a half chair structure with the oxygen substituent in the pseudo-axial position, was verified by synthesising crystalline bis-dinitrobenzoate 45 under careful non-acidic conditions (Scheme 5) to deliver a crystal suitable for X-ray analysis.

Reagents and conditions: a) O$_3$, MeOH/CH$_2$Cl$_2$, -78 °C, NaBH$_4$, 0 °C, 1h; b) TBAF, THF, rt, 3 h; c) 3,5-dinitrobenzoyl chloride, DMAP, NEt$_3$, CH$_2$Cl$_2$, rt, o/n, 69%.

Scheme 5: Synthesis of crystalline bis-dinitrobenzoate 45. 47

1.5.1.2. Exposure of the ketone moiety promoting cyclisation

The Nef reaction 48 enables a nitroalkene to be converted to a carbonyl function and has been utilised in the synthesis of enantiopure 2,7-diaryl-1,6-dioxaspiro[4.4]nonane 46 and 47 (Scheme 6). 49 Conversion of nitroalkene 48 to the corresponding ketone 49 under acid conditions directly underwent spiroacetalisation to form 46 and 47 in 2.5:1 diastereomeric mixture, favouring the thermodynamically stabilised isomer 46.

Reagents and conditions: a) NaOH, EtOH, rt, 10 min; H$_2$SO$_4$, hexanes, H$_2$O, 0 °C, 1 h, rt, 12 h, 70%.

Scheme 6: Synthesis of 5,5-spiroacetals 46 and 47 by Nef reaction. 49

The conversion of nitroalkenes to spiroacetals has been reviewed by Ballini et al. 50 giving several biologically significant examples.
1.5.2 Metal-mediated spirocyclisation

The synthesis of spiroacetals catalysed by transition metals has recently been reviewed by Aponick et al. The following are selected examples that contain the 5,5-spiroacetal moiety.

1.5.2.1. Metal-mediated double intramolecular hydroalkoxylation of internal alkynes

The intramolecular addition of a hydroxy group to an internal alkyne can proceed regioselectively, under mild conditions to afford oxygen containing heterocycles, such as spiroacetals. This palladium catalysed cyclisation was used by Utimoto et al. to synthesise a range of simple substituted 5,5-(3) and 5,6-(50) spiroacetals in high yield (Scheme 7).  

![Diagram of schemes 7 and 8](image)

Reagents and conditions: a) PdCl$_2$(PhCN)$_2$, Et$_2$O, rt, 5 h, 90%; b) PdCl$_2$, MeCN, reflux, 1 h, 60-90%:

Scheme 7: Selected spiroacetal examples prepared by Ultimoto.

Other metals have been employed in this spirocyclisation reaction and have been incorporated into the synthesis of several natural products including spiroacetal 51 (Scheme 8), isolated from hop extracts from pilsner beer and Japanese hop oil. Alkynediol 52 was prepared by coupling terminal alkyne 53 with aldehyde 54 and silyl deprotecting of the resultant alkyne. Gold catalysed spirocyclisation of alkynediol 52 led to spiroacetal 51.

![Diagram of schemes 7 and 8](image)

Reagents and conditions: a) nBuLi, THF, -78 °C to rt, 2.5 h, 81%; b) TBAF, THF, 45 °C, 18 h, 90%; c) Au[P(tBu)$_2$(o-biphenyl)]Cl, AgOTf, THF, 45 °C, 1 h, 74%.

Scheme 8: Synthesis of natural hop extract 51.

The use of an alkyne as a dihydroxyketone surrogate avoids chemosensitivity issues that might arise in the use of highly functionalised ketones.
1.5.2.2. Ring closing metathesis

Ruthenium catalysts, namely Grubbs’ catalysts have been employed previously in the ring closing metathesis (RCM) reaction to prepare unsaturated oxygen containing spirocyclic compounds. Ring closing metathesis was used in 1999 by Bassindale et al. to complete the synthesis of 5,5-spiroacetal 55 from alkene 56 (Scheme 9).\textsuperscript{56}

![Diagram of ring closing metathesis](image)

*Reagents and conditions:* a) 5 mol\% Grubbs’ II, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 6 h, 90%.

**Scheme 9:** Synthesis of 5,5-spiroacetal 55 using ring closing metathesis.\textsuperscript{56}

The resulting endocyclic double bond of the spiroacetal is amenable to a wide variety of functional group transformations. Kaliappan et al.\textsuperscript{57} employed the double bond of spiroacetal 57 in a Diels-Alder reaction to prepare complex anthraquinone moiety 58. This functional group is an important component of many biologically active compounds (Scheme 10).

![Diagram of Diels-Alder reaction](image)

*Reagents and conditions:* a) toluene, 80 °C, 12 h; b) NEt\textsubscript{3}, CHCl\textsubscript{3}, rt, 61%.

**Scheme 10:** Diels-Alder reaction of anthraquinone 58.\textsuperscript{57}
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1.5.2.3 Cyclic enol ethers

Dihydroxyalkene 59 can be converted into spiroacetal 60 via a sequence involving an initial iodocyclisation step to form 61 (Scheme 11). Elimination of the iodide to the corresponding enol ether 62 followed by silver mediated spirocyclisation lead to an inseparable mixture of diastereoisomers.

Reagents and conditions: a) IDCP (iodonium dicollidine perchlorate), CH$_2$Cl$_2$; rt, 15 min, 85%; b) AgOTf, collidine, CH$_2$Cl$_2$, rt, 15 min, 70% (1:1 diastereoisomers).

Scheme 11: Iodoetherification-dehydroiodination strategy.

The advantage of the cyclic enol ether strategy is its compatibility with a variety of functional groups and the precursor hydroxyalkenes are often readily accessible from an olefin metathesis reaction.

1.5.3 Oxidative methods

1.5.3.1. Intramolecular hydrogen abstraction

Intramolecular hydrogen abstraction has been recently reviewed by Brimble et al. illustrating the use of this reaction in the synthesis of naturally occurring spiroacetals. The proposed mechanism (Scheme 12) involves the generation of an alkoxy radical by thermodynamic or photochemical cleavage of the I-O bond of 63, which is formed by reacting alcohol 64 with iodosobenzene diacetate (PhI(OAc)$_2$). The mechanism involves the 6-membered transition state 65 which may explain why 5-membered ring formation has a higher yield than that of the 6-membered spiroacetal which proceeds via a seven-membered transition state. The oxidative radical cyclisation is useful for spiroacetalisation when delicate or acid labile substituents are involved.

Scheme 12: Mechanism of intramolecular hydrogen abstraction modified from Brimble et al.
The utility of oxidative radical cyclisation was recently demonstrated by the Brimble group in the total synthesis of danshenspiroketallactone 66 and its epimer 67 (Scheme 13). Alcohol 68 was cyclised thus forming spiroacetals 66 and 67 in a 1:1.5 mixture of spiroacetals presumably via oxonium ion 69.

Reagents and conditions: a) I₂, PhI(OAc)₂, hv, cyclohexane, 10 °C, 3.5 h, 47% (1.5:1 mixture of diastereoisomers).


This reaction will be further discussed in chapter three (vide infra) as the main disconnection in the current synthesis of cephalosporolide H 28.

1.5.3.2. Oxidative cyclisation

Furan oxidative cyclisation was used to synthesise (+)-pyrenolide D 70 and (-)-4-epi-pyrenolide D 71. Oxidative cyclisation occurred on furan 72 in the presence of *meta*-chloroperoxybenzoic acid (*m*-CPBA) to form the unstable 5,5-spiroacetal 73 which was oxidised directly with pyridinium dichromate (PDC) to give lactone 74. Finally, benzyl deprotection led to the 3:2 mixture of pyrenolide D 70 and its C-4 epimer 71.

Reagents and conditions: a) *m*-CPBA, CH₂Cl₂, 0 °C, 4h; b) PDC, DMF, 0 °C, 4h, 77% over two steps; c) TiCl₄, CH₂Cl₂, 0 °C to rt, 2 h, 87%.

Scheme 14: Synthesis of pyrenolide D 70 and epi-pyrenolide D 71.

1.5.3.3. Oxidative ring expansion

The key step in Werz et al’s synthesis of spiroacetal 75 (Scheme 15) is the ring expansion of the substituted cyclopropane derivative into the five-membered enol ether system. The exocyclic enol ether 76 is converted by cyclopropanation using ethyl diazoacetate to ester 77. Reduction of ester 77 using LiAlH₄ to afford the
corresponding alcohol 78 and subsequent oxidation by hypervalent iodine reagents led directly to the desired spiroacetal 75.

\[
\begin{align*}
\text{76} & \xrightarrow{a} \text{77} & \xrightarrow{b} \text{78} & \xrightarrow{c} \text{75}
\end{align*}
\]

Reagents and conditions: a) N\textsubscript{2}CHCO\textsubscript{2}Et, Cu powder, toluene, 80 °C, 30 min, 83%; b) LiAlH\textsubscript{4}, THF, rt, 2 h, 81%; c) IBX, Yb(OTf)\textsubscript{3}, DMSO, rt, 8 h, 55%.

Scheme 15: Ring expansion methodology in the synthesis of a 5,5-spiroacetal 75.\textsuperscript{63}

1.5.3.4. Oxidation of furan by singlet oxygen

The bis-spiroacetal 79 was obtained in one step using singlet oxygen, which is prepared in situ from molecular triplet oxygen in the presence of the photosensitiser methylene blue and a visible spectrum light source (Scheme 16). Furan 80 underwent a [4+2] cycloaddition reaction with molecular oxygen followed by intramolecular attack by a hydroxyl group. The resulting hydroperoxide was reduced to the hemiacetal which in turn is cyclised in the presence of trace amounts of acid to give a 1:1 mixture of diastereoisomers 79.

\[
\begin{align*}
\text{80} & \xrightarrow{a} \text{79}
\end{align*}
\]

Reagents and conditions: a) O\textsubscript{2}, hv, methylene blue, CH\textsubscript{2}Cl\textsubscript{2}, Me\textsubscript{2}S, 0 °C to rt, 12 h, 80%.

Scheme 16: Synthesis of bis-spiroacetal 79.\textsuperscript{64}
1.5.4 Carbonyl cascade reactions

A carbonyl cascade reaction involves the attack on a carbonyl compound by nucleophilic oxygen to form the spiro carbon centre. The oxygen of the carbonyl compound can then act as a nucleophile, contributing the second oxygen to the spiroacetel upon cyclisation with an electrophilic acceptor.

Ley et al.\textsuperscript{20} demonstrated this strategy in the synthesis of compound 81 (Scheme 17), a pheromone isolated from \textit{Pityogenes chalcographus}.	extsuperscript{65} Treatment of the mixture of hydroxyketone 82 and hemiacetal 83 with \textit{N}-phenylselenophthalimide gives a mixture of spiroacetals 84. Reductive removal of the phenylseleno-substituent gave the desired spiroacetals 81.

\begin{center}
\begin{tikzpicture}

\node (A) at (0,0) {82};
\node (B) at (1.5,0) {83};
\node (C) at (3,0) {84};
\node (D) at (4.5,0) {81};
\draw[->] (A) -- (B) node[pos=0.5, above] {a};
\draw[->] (B) -- (C) node[pos=0.5, below] {b};
\end{tikzpicture}
\end{center}

Reagents and conditions: a) NPSP (\textit{N}-phenylselenophthalimide), CH\textsubscript{2}Cl\textsubscript{2}, ZnBr\textsubscript{2}, rt, 1-2 h, 45%; b) Raney-Ni, Et\textsubscript{2}O, H\textsubscript{2}, rt, 3-5 h, 90%.

\textbf{Scheme 17:} Organoselenium mediated cyclisation.\textsuperscript{20}
1.6 **Previous syntheses of the cephalosporolides**

The following section summaries the current syntheses of cephalosporolides E 24, F 25 and H 28 with keen interest in the cyclisation method employed.

1.6.1 **Total synthesis of ent-cephalosporolides E and F by Ramana et al.**

A total synthesis of the enantiomers of cephalosporolides E 85 and F 86 was published in 2009 by Ramana *et al.* confirming the absolute stereochemistry of cephalosporolides E 24 and F 25.66 The key step of this synthesis used a Pd-mediated alkynediol cycloisomerisation (Scheme 18). Retrosynthesis of *ent*-cephalosporolides E 85 and F 86 involves the late stage installation of the sensitive lactone from lactol 87. The spiroacetal 87 itself is obtained by double intramolecular hydroalkylation of alkynediol 88. The latter can be obtained from coupling of iodide 89 with alkyne 90, which can in turn be obtained from chiral pool starting materials L-malic acid 91 and D-glucose 92 respectively.

**Scheme 18:** Retrosynthesis of *ent*-cephalosporolide E 85 and *ent*-cephalosporolide F 86 by Ramana *et al.*66
The alkyne coupling partner 90 was synthesised from D-glucose. The first step involved a one-pot chlorination and terminal acetonide migration of glucose diacetonide 93 to afford chloride 94. Alkyne 90 was prepared by base induce elimination of chloride 94 followed by 1,3-acetonide deprotection and the resulting alcohol protected as a TBS ether (Scheme 19).

![Chemical Structure](image)

**Reagents and conditions:** a) (Chloromethylene)dimethyliminium chloride, 1,1,2,2-tetrachloroethane, rt, 3 h, then reflux, 3h; b) LiNH$_2$/Liq NH$_3$ (or) LDA, THF, -78 °C; c) TBSCI, imidazole, CH$_2$Cl$_2$, rt, 6 h, 92%.

**Scheme 19:** Synthesis of alkyne 90 by Ramana et al.

(3S)-Butane-1,3-diol 95 was obtained from L-malic acid 91 in three steps according to procedure by Yadav et al. Monotosylation of diol 95 followed by TBS protection gave alkane 96. Iodide displacement of the primary tosylate lead to coupling partner 89 (Scheme 20).

![Chemical Structure](image)

**Reagents and conditions:** a) p-TsCl, Et$_3$N, CH$_2$Cl$_2$, -20 °C, 3 h, rt, 36 h, 72%; b) TBSCI, imidazole, CH$_2$Cl$_2$, rt, 8 h, 91%; c) NaI, acetone, reflux, 3 h, 87%.

**Scheme 20:** Synthesis of alkyl iodide 89 by Ramana et al.
With the two fragments in hand, coupling of alkyne 90 to iodide 89 using nBuLi in HMPA-THF gave TBS protected alkynediol 97. Double silyl deprotection followed by Pd-mediated double intramolecular hydroalkylation using 10 mol% Pd(CH3CN)2Cl2 in acetonitrile gave a (1:1) mixture of tricyclic ketal 87. Acetonide deprotection followed by selective oxidation of lactols 98 using Fètizon reagent gave lactones 99 and 100 which were able to be separated at this point. The α-hydroxy function underwent Barton-McCombie deoxygenation to give ent-cephalosporolide E 85 and ent-cephalosporolide F 86, the enantiomers of the natural products (Scheme 21).

**Reagents and conditions:**
- a) nBuLi, HMPA, THF, -40 °C, 1 h, 68%;
- b) TBAF, THF, rt, 2 h, 89%;
- c) Pd(CH3CN)2Cl2, MeCN, rt, 4 h, 62%;
- d) 40% AcOH in H2O, 80 °C, 4 h, 65%;
- e) Ag2CO3/celite, toluene, reflux, 3 h, 77% (2:1 diastereoisomers);
- f) PhOC(S)Cl, DMAP, CH3CN, rt, 1 h;
- g) Bu3SnH, AIBN, toluene, reflux, 3 h.

**Scheme 21:** Synthesis of ent-cephalosporolide E 85 and ent-cephalosporolide F 86 by Ramana et al.66
1.6.2 Synthesis of cephalosporolides E and F by Fernandes et al.

The first total synthesis of the natural products cephalosporolides E 24 and F 25 was achieved by Fernandes et al.\textsuperscript{70} in 2010. The retrosynthesis of cephalosporolides E 24 and F 25 identified the key step as the Sharpless asymmetric dihydroxylation of 101 to install the lactone moiety of 102 prior to spirocyclisation (Scheme 22). The α,β-unsaturated ester 102 was obtained from a cross metathesis of olefin fragments 103 and 104. Olefin 103 was accessed from commercially available (R)-methyl lactate 105.

![Scheme 22: Retrosynthesis of cephalosporolide E 24 and cephalosporolide F 25 adopted by Fernandes et al.\textsuperscript{70}](image)

The synthesis began with the preparation of key intermediate 103 from (R)-methyl lactate 105. Protection of the secondary alcohol as a TBS ether followed by DIBAL-H reduction to the corresponding aldehyde and finally Wittig olefination afforded ester 106. Catalytic hydrogenation of the double bond yielded ester 107 which underwent reduction and subsequent Grignard addition of allylmagnesium chloride to the resultant aldehyde to give alcohol 103 (Scheme 23).

![Scheme 23: Synthesis of alkene precursor 103 by Fernandes et al.\textsuperscript{70}](image)

Reagents and conditions: a) imidazole, TBSCI, CH₃Cl₂, rt, 12 h; b) DIBAL-H, CH₃Cl₂, -78 °C, 1.5 h; c) Ph₃P=CHCO₂Et, THF, rt, 12 h, 82%; d) Pd/C, EtOH, H₂, rt, 12 h, 98%; e) DIBAL-H, CH₃Cl₂, -78 °C, 1.5 h; f) allylmagnesium chloride, THF, 0 °C for 1 h, rt for 1 h, 92%.
With allyl alcohol 103 in hand, the next step was the cross metathesis reaction of alcohol 103 and olefin 104 using Grubbs’ II catalyst to afford olefin 108 with E/Z selectivity of 5:1 in 82% yield. IBX oxidation of alcohol 108 gave ketone 109. Acetalisation of 109 with ethylene glycol provided 101, which subsequently underwent Sharpless asymmetric dihydroxylation and \textit{in situ} cyclisation to give the corresponding lactone 102. Removal of the TBS ether followed by conversion of the acetal to the corresponding ketone enables facile spirocyclisation thus affording cephalosporolides E 24 and F 25 as a separable mixture in 59% and 33% yield, respectively (Scheme 24).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme24.png}
\caption{Synthesis of cephalosporolide E 24 and cephalosporolide F 25 by Fernandes et al.\textsuperscript{70}}
\end{figure}

\textit{Reagents and conditions:} a) Grubbs’ II, CH\textsubscript{2}Cl\textsubscript{2}, reflux, 12 h, 82%; b) IBX, EtOAc, reflux, 6 h, 89%; c) (CH\textsubscript{2}OH)\textsubscript{2}, PTSA, benzene, reflux, 14 h, 77%; d) K\textsubscript{3}Fe(CN)\textsubscript{6}, K\textsubscript{2}CO\textsubscript{3}, MeSO\textsubscript{3}NH\textsubscript{2}, (DHQ)\textsubscript{2}PHAL, K\textsubscript{2}OsO\textsubscript{4}·2H\textsubscript{2}O, tBuOH:H\textsubscript{2}O (1:1), 0 °C, 24 h, 70%; e) Bu\textsubscript{4}NF, THF, rt, 2 h, 70%; f) CAN, MeCN:H\textsubscript{2}O (1:1), 70 °C, 5 min, 59, 33% respectively.
1.6.3 Synthesis of cephalosporolides E and F by Britton et al.

Most recently in 2013 the synthesis of cephalosporolides E 24 and F 25 was achieved via a silver promoted carbonyl cascade reaction of keto-chlorodiol 110 by Britton and co-workers.\textsuperscript{71} Keto-chlorodiol 110 was prepared by an aldol condensation between ketone 111 and α-chloroaldehyde 112, which were obtained from \((R)\)-propylene oxide 113 and 4-pentenal 114, respectively.

\textbf{Scheme 25:} Retrosynthesis of cephalosporolides E and F by Britton \textit{et al.}\textsuperscript{71}
The synthesis of cephalosporolides E 24 and F 25 started with the synthesis of alkene 115 from organocuprate addition of 2-methylallylmagnesium chloride 116 to (R)-propylene oxide 113 followed by direct protection of the resultant alcohol (Scheme 26). Ozonolysis of alkene 115 afforded ketone 111 and subsequent aldol condensation with α-chloroaldehyde 112 (available from 4-pentanol 114) afforded β-hydroxyketone 110. Removal of the TMS protecting group followed by a silver promoted carbonyl cascade provided the desired spiroacetal core. Oxidative cleavage of the mixture of alkenes 117 and 118 enabled lactone formation, thus revealing cephalosporolides E 24 and F 25 as a separable (1:1.6) mixture of diastereoisomers. The overall yields of cephalosporolides E 24 and F 25 were 6.3 and 3.5% respectively.

Reagents and conditions: a) CuI, THF, (R)-propylene oxide 113, 0 °C, 3 h; b) TMSCl, NEt₃, THF, 0 °C to rt, 16 h, 86%; c) O₃, CH₂Cl₂, PPh₃, -78 °C to rt, 24 h, 78%; d) ketone 111, LDA, THF, -78°C, 30 min, aldehyde 108, 30 min, 52%; e) 20 mol % 119, Cu(TFA)₂, LiCl, Na₂S₂O₅, H₂O, MeCN, 0 °C, 10 min; aldehyde 114, rt, 20 h, 71%; f) TBAF, THF, 0 °C, 8 min, 91%; g) AgOTf, Ag₂O, acetone, sonication 0 °C to 40 °C, 17 h, 75%; h) K₂OsO₄·2H₂O, DMF, rt, 30 min, i) oxone, rt, 19 h, 69%.

Scheme 26: Synthesis of cephalosporolides E 24 and F 25 by Britton et al.⁷¹
1.6.4 Synthesis of cephalosporolide E by Dudley et al.

Synthesis of cephalosporolide E 24 to date, has been as a mixture of cephalosporolide E 24 and F 25. Dudley et al.\textsuperscript{72} succeeded in synthesising cephalosporolide E 24 in a stereoselective manner employing the retrosynthesis below (Scheme 27). Cephalosporolide E can be obtained from the 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) oxidation of diol 120, which can be obtained from gold-mediated spirocyclisation of alkyne diol 121. Alkyne 121 can be prepared by the coupling of (R)-propylene oxide 113 and terminal alkyne 122.

\begin{center}
\includegraphics[width=\textwidth]{scheme27.png}
\end{center}

Scheme 27: Retrosynthesis of cephalosporolide E by Dudley et al.\textsuperscript{72}

The synthesis of cephalosporolide E 24 started with the synthesis of terminal alkyne 122 from known alcohol 123 (Scheme 28). PMB protection and asymmetric dihydroxylation of alcohol 123 afforded diol 124. Subsequent oxidation with DDQ and TBS protection, deprotection strategy produced alcohol 125. Alcohol 125 was converted into alkyne 122 over two steps, oxidation to the corresponding aldehyde followed by Ohira-Bestmann ethynylation.

\begin{center}
\includegraphics[width=\textwidth]{scheme28.png}
\end{center}

Scheme 28: Synthesis of terminal alkyne 122.\textsuperscript{72}

Reagents and conditions: a) PMBCl, NaH, DMF, TBAI, reflux, 12 h, 82%; b) AD-mix α, CH\textsubscript{3}SO\textsubscript{2}NH\textsubscript{2}, tBuOH/H\textsubscript{2}O, 0 °C, 3.5 d, 73%; c) DDQ, M.S., CH\textsubscript{2}Cl\textsubscript{2}, 0°C to rt, 3 h, 63%; d) TBSCI, imidazole, DMF, rt, 24 h, 82%; e HF/pyridine, CH\textsubscript{2}Cl\textsubscript{2}, 0°C to rt, 12 h, 99%; f) DMP, NaHCO\textsubscript{3}, 0 °C to rt, 1 h, 98%; g) Ohira-Bestmann reagent, MeOH, K\textsubscript{2}CO\textsubscript{3}, rt, 12 h, 80%.
With terminal alkyne 122 in hand, attention next turned to the coupling with (R)-propylene oxide 113 to afford the internal alkyne 121. Gold-mediated spirocyclisation produced a mixture of spiroacetals which were deprotected to give diol 120 as a 45:55 ratio of diastereomers. The mixture of diols converged to 120a upon treatment with zinc chloride. TEMPO oxidation of diol 120a led to the formation of cephalosporolide E 24.

Reagents and conditions: a) nBuLi, THF, BF₃·OEt₂, -78 °C to 0 °C, 2.5 h, 96%; b) AuCl, MeOH, rt, 5 h; c) TBAF, THF, rt, 2 h, 71% over two steps; d) ZnCl₂, MgO, CH₂Cl₂, rt, 12 h; e) TEMPO, Phl(OAc)₂, CH₂Cl₂, rt, 12 h, 43 % over two steps.

Scheme 29: Synthesis of cephalasporolide 24.⁷²
1.6.5 Synthetic studies towards cephalosporolides E and F by Brimble et al.

An initial attempt to effect the synthesis of cephalosporolides E 24 and F 25 (Scheme 30) has been carried out in the Brimble group\textsuperscript{73} using a strategy that hinged on use of a Fukuyama reaction to prepare key intermediate ketone 126. Unfortunately the traditional Fukuyama reaction employed to couple thioester 127 to zinc iodide 128 proved unsuccessful. A modified version of the reaction was attempted, which involved the coupling of alkyne 129 and thioester 127 to afford ketone 126. It was envisaged that acid-catalysed silyl deprotection would be followed by \textit{in situ} spiroacetal formation to reveal cephalosporolides E 24 and F 25.

![Scheme 30: Brimble retrosynthesis of cephalosporolides E 24 and F 25.]()

The common thioester intermediate 127 was synthesised in nine steps starting from butane-1,4-diol 130. Diol 130 was converted to known $\beta,\gamma$-unsaturated methyl ester 131 over four steps.\textsuperscript{74} Sharpless asymmetric dihydroxylation of ester 131 with \textit{in situ} lactonisation afforded lactone 132 in $>95\%$ ee (Scheme 31). Silyl protection of the secondary alcohol followed by benzyl deprotection afforded primary alcohol 133. Oxidation to the corresponding carboxylic acid 134 followed coupling to ethanthiol provided the key thioester 127.
Reagents and conditions: a) (DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeSO$_2$NH$_2$, OsO$_4$, tBuOH/H$_2$O, 0 °C, 86%, >95% ee; b) TBSCl, NEt$_3$, DMAP, CH$_2$Cl$_2$, rt, 24 h, 72%; c) H$_2$, Pd/C, EtOH, rt, 2.5 h, 95%; d) TEMPO, NaClO$_2$, NaOCl, MeCN, phosphate buffer (pH 6.7), 35 °C, 4 h, 95%; e) DIC, HOBt, CH$_2$Cl$_2$, 0 °C to rt, 12 h, 52%.

Scheme 31: Synthesis of thioester 127.

With thioester 127 in hand, attention turned to the modified Fukuyama coupling of alkyne 129 and thioester 127. Alkyne 129 was prepared from TBS protection of commercially available (R)-but-3-yn-2-ol. Modified Fukuyama coupling with thioester 127 provided the desired alkyne 135 albeit in low yield. The alkyne 135 was then reduced completely to the corresponding alkane 126 using high pressure hydrogenation. Unfortunately none of the attempts made to remove the TBS protection groups were successful and only yielded the formation of complex mixtures.

Reagents and conditions: a) CuI, PdCl$_2$(dppf), P(2-furyl)$_3$, DMF, NEt$_3$, 50 °C, 3 h, 34%; b) Pd/C, H$_2$ (60 psi), EtOAc, 2 h, 75%.

Scheme 32: Attempted synthesis of cephalosporolides E 24 and F 25 by Brimble et al.
1.6.6 Summary of previous syntheses of cephalosporolides E and F

As described above there have been three total synthesis of cephalosporolides E 24 and F 25 and one attempted synthesis by Brimble et al.\textsuperscript{73} (Scheme 33). During the synthesis of the enantiomers ent-cephalosporolides E 85 and F 86 by Ramana et al.\textsuperscript{56} the absolute stereochemistry of the natural products was assigned and later confirmed by Fernandes et al.\textsuperscript{70} in the total synthesis of the natural products themselves.

All approaches made use of coupling reaction between two key fragments:

1) Fernandes et al.\textsuperscript{70} employed a cross metathesis reaction between alkenes 103 and 104 as well as a Sharpless asymmetric dihydroxylation as their key steps.

2) an aldol condensation reaction between methyl ketone 111 and chloraldehyde 112 followed by a silver promoted carbonyl cascade was employed by Britton et al.\textsuperscript{71}

3) Dudley et al.\textsuperscript{66} coupled alkyne 122 to (R)-propylene oxide 113 and employed a metal mediated double intramolecular hydroalkylation of the internal alkyne to form the spiroacetals.

4) attempts by the Brimble group\textsuperscript{73} involved a Fukuyama coupling reaction of thioester 127 with alkyne 129 with the aim that acid-catalysed deprotection and spirocyclisation would form the desired cephalosporolides E 24 and F 25.

\begin{center}
\textbf{Scheme 33: Summary of the synthetic strategies to cephalosporolides E 24 and F 25 to date.}\textsuperscript{70-73}
\end{center}
1.6.7 Synthesis of cephalosporolide H by Dudley et al.

The first total synthesis of cephalosporolide H 28 to date was published in 2010 by Dudley et al.\textsuperscript{9,75} The retrosynthesis of cephalosporolide H 28, illustrated in Scheme 34 shows the installation of the 5,5-spiroacetal core 136 from the intermediate alkyne 137 via a gold catalysed double intramolecular hydroalkylation. Alkyne 137 in turn could be obtained from the opening of epoxide 138 with the anion derived from terminal alkyne 139.

\begin{center}
\textbf{Scheme 34: Retrosynthesis of cephalosporolide H by Dudley et al.}^9
\end{center}

The synthesis of cephalosporolide H 28 started from the readily available alcohol 140\textsuperscript{76} (Scheme 35). Swern oxidation followed by addition of propynylmagnesium bromide gave alkynol 141 as a 1:3 mixture of diastereomers. Oxidation of the newly formed secondary alcohol 141 followed by diastereoselective CBS reduction gave alcohol 142 as the sole diastereomer. Migration of the internal alkyne followed by TBS protection of the secondary alcohol afforded terminal alkyne 139. Coupling of this terminal alkyne with epoxide 138 gave the internal alkyne 143.
Reagents and conditions: a) DMSO, (COCl)$_2$, Et$_3$N, -78 °C, 1 h; b) CH$_3$CCMgBr, THF, 0 °C to rt, 1.5 h, 83% (2 steps); c) DMSO, (COCl)$_2$, Et$_3$N, -78 °C, 1 h; d) (S)-CBS, BH$_3$·SMe$_2$, -40 °C, 6 h, 76% (2 steps); e) NH$_2$(CH$_2$)$_3$NH$_2$, KH, 0 °C, 11 h, 92%; f) TBSCI, imidazole, DMF, rt, 24 h, 93%; g) nBuLi, BF$_3$·Et$_2$O, -78 °C -0 °C, 7 h, 91%; h) AuCl, MeOH, rt, 4 h, 80%; i) ZnCl$_2$, MgO, CH$_2$Cl$_2$, rt, 8 h, 86%; j) TEMPO, Phl(OAc)$_2$, CH$_2$Cl$_2$, rt, 15 h, 81%; k) Pd(CH$_3$CN)$_2$Cl$_2$, CH$_3$CN, rt, 1.5 h, 42%; l) TBAF, THF, rt, 3 h, 73%; m) TEMPO, Phl(OAc)$_2$, CH$_2$Cl$_2$, rt, 6 h, 68%.

Scheme 35: Two pathways employed by Dudley et al. to synthesise cephalosporolide H 28 and its epimer 144.

Dudley et al. carried out a model study on simplified intermediate 145 to determine the best conditions for the spirocyclisation step (Scheme 36). Different catalysts and solvent systems were evaluated to form spiroacetal 146. The best conditions were found to be AuCl, MeOH, rt, 12 h (two additions of 25 mol% catalyst needed for full conversion) which gave spiroacetal 146 with the highest yield of 68%. The use of methanol as a solvent appears to suppress the formation of the undesired furan 147 side product.

Reagents and condition: a) 50 mol% AuCl, MeOH, rt, 12 h, 68%.

Scheme 36: Spirocyclisation model study by Dudley et al.

Thus during the first attempt at the synthesis of cephalosporolide H 28 (Scheme 35), alkyne 139 was treated with 40 mol% AuCl in methanol to give 80% of the spiroacetal core as a (1:1) mixture of epimers. This mixture was then directly chelated with zinc chloride (ZnCl$_2$) to give spiroacetal 136 as a single kinetically favoured anomer. Oxidation of the resulting alcohol directly afforded the desired lactone moiety and thus the reported structure of cephalosporolide H 28.

The spectroscopic data however did not match the isolated compound reported by Li et al. Therefore a second sequence was undertaken whereby Pd(CH$_3$CN)$_2$Cl$_2$ was used as the catalyst to promote spirocyclisation and thus afford the thermodynamically stabilised spiroketal 148 (Scheme 35). Desilylation using
tetra-n-butylammonium fluoride (TBAF) followed by TEMPO oxidation led to the structural epimer of the proposed structure of cephalosporolide H 144. The spectral data matched that of the isolation paper but an authentic sample could not be obtained for comparison.

### 1.6.8 Synthesis of cephalosporolide H by Fernandes et al.

Recently Fernandes et al. synthesized both diastereomers of the reported structure of cephalosporolide H (Scheme 37). The retrosynthesis shows the acid-catalysed deprotection and cyclisation of lactone 149 should afford spiroacetals 28 and 144 as the final step of the synthesis. The lactone 149 could be obtained via Sharpless asymmetric dihydroxylation of olefin 150 and subsequent dimethylation of the resultant lactone. Olefin 150 could in turn be formed by the cross metathesis of olefin 151 and commercially available olefin 152.

The synthesis (Scheme 38) started with the allylation of octanal 153 catalysed by (S)-BINOL to provide homoallylic alcohol 154 in 83% yield and 95% ee. Protection of the newly formed secondary alcohol 154 was followed by hydroboration-oxidation to give the primary alcohol 155. Swern oxidation of the alcohol to the corresponding aldehyde and allyl Grignard addition afforded olefin 151. The cross metathesis reaction was carried out between the newly formed olefin 151 and olefin 152 to form β,γ-unsaturated ester 156 in 75% yield with a 7:1 E/Z ratio. Next, IBX oxidation of the secondary alcohol of 156 to the corresponding ketone and subsequent ketalisation gave olefin 150. The Sharpless asymmetric dihydroxylation of this olefin 150 employing (DHQD)$_2$PHAL afforded lactone 157 as a single diastereomer. At this point the gem-dimethylation was preformed with 7 eq LDA and 10 eq of methyl iodide giving monomethylated lactone 158 in 72% yield and 14% of the dimethylated lactone 149. A repeat of the reaction on the monomethylated lactone 158 afforded the desired dimethylated lactone 149 in 75% yield. Finally an acid-catalysed spirocyclisation afforded a 3:2 mixture of the reported structure of cephalosporolide H 28 and it diastereomer 144.
Reagents and conditions: a) (S)-BINOL-Ti(PrO)₄, 4Å molecular sieves, toluene, allyltributyltin, -15 °C, 36 h, 83%, 95% ee; b) TBSCI, imidazole, CH₂Cl₂, 0 °C to rt, 12 h, 92%; c) BH₃SMe₂, THF, 0 °C to rt, 3 h, EtOH, 4N aq. NaOH, H₂O₂, 0 °C to rt, 2 h, 72%; d) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, 45 min, then NEt₃, rt, 1 h; e) allylMgBr, THF, 0 °C, 1 h; rt 1 h, 82% over 2 steps; f) 0.2 mol% Grubbs’ II, CH₂Cl₂, reflux, 48 h, 75%; g) IBX, EtOAc, reflux, 6 h, 95%; h) (CH₂OH)₂, p-TsOH, benzene, reflux, 48 h, 78%; i) (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, K₂OsO₄·2H₂O, tBuOH/H₂O, 0 °C, 12 h, rt, 6 h, 75%; j) LDA, THF, -78 °C, 1 h, MeI, HMPA, -78 °C, 2 h, 72% x, 14% x; k) LDA, THF, -78 °C, 1 h, Mel, HMPA, -40 °C, 8 h, 75%; l) 4N aq. HCl, MeOH, 0 °C to rt, 2 h, 54% 28, 34% 144.

Scheme 38: Synthesis of cephalosporolide H 28 and its diastereomer 144 by Fernandes et al.⁷⁷

The optical rotation value of the reported isolation structure of cephalosporolide H 28 (αD +57.6, c 0.7, MeOH)⁷⁷ does not match that of the synthetic structure (αD -4.6, c 0.5, MeOH). However the data for the diastereomer 144 (αD +59.8, c 0.5, MeOH) is in good agreement with the isolation⁷ and the previously synthesised compound as described by Dudley et al. (αD +65, c 0.5, MeOH).⁹
1.7 Aims of the current research

The aim of the current research is to investigate a synthetic route that would allow easy access to all members of the cephalosporolide family. The following route (Scheme 39) was devised to enable installation of the correct stereochemistry for the natural products cephalosporolides E 24 and F 25 that could also be easily adapted to synthesise the remaining members of the cephalosporolide family. At the commencement of these studies, only one synthetic study which resulted in the synthesis of enantiomers of cephalosporolides E 24 and F 25 (vide supra) had been reported in the literature.78

Due to the observed instability of the lactone functionality by Brimble et al.73 it was envisaged that cephalosporolides E 24 and F 25 would be synthesised by late stage installation of this reactive group (Scheme 39). It was anticipated that spiroacetal 159 could be obtained by the neutral deprotection of benzyl protected β-hydroxyketone 160 which in turn would be obtained from the Mukaiyama aldol reaction between methyl ketone 161 and aldehyde 162. Commercially available inexpensive propylene oxide 163 and (S)-malic acid 91 would be used to synthesise methyl ketone 161 and aldehyde 162 respectively.

![Scheme 39: Retrosynthesis of cephalosporolides E 24 and F 25.]

Upon the successful total synthesis of cephalosporolides E 24 and F 25 we could utilise the same strategy to synthesise other members of the cephalosporolide family. A common spiroacetal precursor 164 could be synthesised from the late stage installation of the lactone (Scheme 40). Deprotection of the β-hydroxyketone 165 formed by Mukaiyama aldol reaction between ketone 166 and aldehyde 167 would lead to the spiroacetal 164. Ketone 166 and aldehyde 167 in turn could be prepared from commercially available D-mannitol 168 and alcohol 169.
The strategy for the preparation of cephalosporolide H 28 would have the advantage over the Dudley et al.\textsuperscript{9} synthesis in that the side chain, which differentiates the members of the cephalosporolide family, would be installed in the final stage thus allowing the synthesis of the two natural products cephalosporolides H 28 and I 29 from a common precursor spiroacetal 164 (Scheme 40).
CHAPTER TWO: SYNTHESIS OF CEPHALOSPOROLIDES E AND F
2.1 Synthetic strategy

As discussed in the previous section, one of the primary focuses of this doctoral thesis is the synthesis of cephalosporolides E 24 and F 25. Since initial attempts by the Brimble group relying on the formation of (+)-bassianolone 35 intermediate proved unsuccessful, a novel synthetic strategy was developed (Scheme 41). The key steps of the revised pathway allow for lactonisation as the final step from the appropriately functionalised spiroacetal 159, itself obtained by the double deprotection and in situ spirocyclisation of β-hydroxyketone 160. Asymmetric aldol reaction between ketone 161 and aldehyde 162 would afford the key spirocyclisation precursor 160 with the desired syn-stereochemistry at C-3 and C-4. Ketone 161 and aldehyde 162 can be formed from readily available propylene oxide 163 and (S)-malic acid 91, respectively.

Scheme 41: Retrosynthesis of cephalosporolides E 24 and F 25.

This synthetic strategy exhibits obvious advantages compared to the existing syntheses previously described in Section 1.6. First of all, it allows the preparation of cephalosporolides E 24 and F 25 without the stereochemical redundancy observed in the synthesis by Ramana et al.66 therefore considerably decreasing the number of reaction steps. Furthermore, it enables the late stage formation of the lactone functionality which has proven problematic in previous syntheses by Fernandes et al.70 and by the Brimble group.73 Finally, a similar strategy could be employed for the preparation of other members of the cephalosporolide family.
2.2 **Synthesis of ketone 161**

As depicted in the retrosynthesis below (Scheme 42), ketone 161 can be obtained from alkene 170 which in turn could be formed from chiral epoxide 113 via ring opening at the terminal position by an allyl cuprate reagent and protection of the resultant alcohol as a benzyl ether 170. The chiral epoxide 113 can be obtained from inexpensive racemic epoxide 163 upon subjection to a Jacobsen’s hydrolytic kinetic resolution (HKR).

![Scheme 42: Retrosynthesis analysis of ketone 161.](image)

### 2.2.1 Jacobsen’s hydrolytic kinetic resolution

In order to obtain enantiopure epoxide 113, the hydrolytic kinetic resolution (HKR) of inexpensive propylene oxide 163 was carried out. Jacobsen *et al.* first established the resolution of terminal epoxides in 1997 to afford highly enantioenriched terminal epoxides and 1,2-diols. While Sharpless epoxidation and Shi epoxidation enables the synthesis of optically pure epoxides, only Jacobsen’s HKR enables access to enantiopure terminal epoxides. Mechanistic studies later carried out by Jacobsen *et al.* demonstrated that the cobalt catalyst complex 171 binds to both enantiomers with equal affinity giving 172 and 173. Therefore the high selectivity results from the selective reaction of one of the epoxide complexes with the salen-nucleophile complex 174 to afford the diol 175 via transition state 176 and the unreacted epoxide 177 (Scheme 43).

![Scheme 43: Kinetic parameters for the HKR reaction.](image)

This theory was confirmed by Schlörer *et al.* using NMR, titration experiments and quantum chemistry calculations. They showed that attack of the salen-nucleophile complex occur preferentially on one face of the salen-epoxide complex. Attack on the other face is strongly disfavoured by steric hindrance between the tert-butyl group of the catalyst and the R-group of the epoxide. Therefore only one enantiomer undergoes ring opening to the diol and the other enantiomer remains as the epoxide (Figure 16).
Features of the HKR reaction include: the use of water as the nucleophile for the epoxide ring opening; low loading (0.5 mol%) as well as recyclability of the catalyst; ease of separation of the epoxide and the 1,2-diol product; the use of inexpensive racemic epoxides and the ability to form either enantiomer with enantiomeric excess up to 99%. In addition, both enantiomers of the catalyst are commercially available as the inactive form and require activation by oxidation in the presence of a mild Bronsted acid (Scheme 44).

Scheme 44: Activation of the (R,R)-salen Co^{II} catalyst A.\textsuperscript{80}

The catalyst is commonly activated in one of the following two ways: 1) isolation of the active Co catalyst by stirring the salen Co^{II} complex in toluene with acetic acid (AcOH) under atmospheric conditions for 30 min followed by removal of all volatiles; and stirring the resultant brown solid in the presence of the epoxide and H\textsubscript{2}O for 12-18 h; 2) \textit{in situ} generation of the active catalyst by dissolving salen Co^{II} complex in the epoxide or epoxide/solvent mixture followed by addition of AcOH and H\textsubscript{2}O. Although both methods are reported to give good results the choice of method remains mostly substrate dependant with method 2 being more frequently used due to the obvious advantage of its one pot nature.
2.2.1.1 Jacobsen’s HKR of propylene oxide

Thus treatment of propylene oxide 163 with (R,R)-salen Co$^{II}$ complex A and AcOH according to method 1 described above, in which the active salen-Co$^{III}$ complex B is isolated before addition of propylene oxide 163 provided enantioenriched (R)-epoxide 113 (Scheme 45). The (S)-diol and the (R)-epoxide were separated by distillation at atmospheric pressure. In fact, thanks to the differences between the boiling point of the (R)-epoxide 113 (36 °C at atmospheric pressure) and the (S)-diol 178 (65 °C at 0.25 Torr), distillation conferred a reliable and practical separation of the two compounds. The reaction was carried out on scales up to 11.6 g of propylene oxide 163 to obtain yields ranging between 45-48%.

Reagents and conditions: a) (R,R)-salen Co$^{II}$ complex A; AcOH, toluene, rt, 30 min; H$_2$O, 0 °C to rt, 18 h, 45%.

Scheme 45: Preparation of epoxide 113 by HKR.$^{73}$

2.2.2 Cuprate addition

Next our attention turned to the ring opening and addition of an allyl substituent to the newly formed (R)-epoxide 113 (Scheme 46).

Reagents and conditions: a) CuI, allylMgBr, THF, -30 °C, 4 h; b) NaH, BnBr; THF, 0 °C to rt, 16 h, 60% over 2 steps.

Scheme 46: Synthesis of alkene 170.

In 1951, Tiefenthal and Huston reported that reactions of Grignard reagents with epoxides result in the formation of halohydrins 179 as the major product.$^{86}$ In the case of alkyl or aryl Grignard reagents, undesired epoxide ring opening catalysed by MgBr$_2$ is the likely pathway for bromohydrin 179 formation (Scheme 47). In this pathway the magnesium coordinates with the oxirane oxygen atom, thus withdrawing electron density from the ring and activating the epoxide for nucleophilic attack by the bromide anion.

Scheme 47: MgBr$_2$ Lewis acid pathway.
In order to minimise the amount of halohydrin side-product formed in the Grignard reaction, transmetallation of the Grignard reagent with copper (I) salt is commonly undertaken. Careful monitoring of the reaction temperature and adhering to a defined order of addition of the reagents is key to the success of the synthesis. Pre-complexation of copper with the Grignard reagent prior to the epoxide addition and use of cryogenic temperatures have been shown to minimise the formation of halohydrins.\(^{87}\)

The newly formed epoxide 113, derived from the HKR, was opened at the terminal position by the addition of an allyl cuprate reagent (Scheme 46). The latter was prepared by the addition of allylmagnesium bromide to copper iodide (CuI) at -30 °C in THF under inert atmosphere before the addition of the epoxide. The reaction takes place with high regioselectivity resulting in the formation of a secondary alcohol which was then protected as a benzyl ether 170 to give 60% yield over two steps. Gratifyingly, no formation of the halohydrin was observed. The (R)-stereochemistry was confirmed at this point by comparing the optical rotation value (\(\alpha_D\) value) with that reported in the literature. We obtained \([\alpha]_D -15.7 (c 1.10 \text{ in CHCl}_3)\) compared to the literature values of \([\alpha]_D +17.0 (c 1.10 \text{ in CHCl}_3)\) for the (S)-enantiomer.\(^{88}\)

### 2.2.3 Wacker oxidation

Next the newly formed alkene 170 was converted into our desired ketone 161 by way of a Wacker oxidation (Scheme 48).

\[\text{Me}_2\text{C} = \text{C} - \text{OBn} \xrightarrow{a} \text{Me}_2\text{C} = \text{C} - \text{OBn} \xrightarrow{\alpha} \text{Me}_2\text{C} = \text{C} = \text{O} - \text{Me} \]

**Scheme 48:** Synthesis of ketone 161.\(^{73}\)

The one-pot oxidation of olefins to the corresponding methyl ketones employing a catalytic amount of Pd\(^{II}\) salts is known as the Wacker oxidation. Although the reaction has been known for decades and it is a robust industrial process, a lot of controversy still surrounds its mechanism.\(^{89-90}\) One of the proposed reaction mechanisms shown below (Scheme 49) illustrates the catalytic cycle whereby the alkene is inserted into the Pd complex.\(^{91}\) Nucleophilic attack of water (H\(_2\)O) on the Pd\(^{II}\) species followed by \(\beta\)-hydride elimination and a further reductive elimination reaction affords methyl ketone and Pd\(^0\) species which can be reoxidised by CuCl\(_2\) to the active PdCl\(_2\), while CuCl\(_2\) itself can be restored by atmospheric oxygen. The oxidation of CuCl to CuCl\(_2\) is one of the fastest reactions in inorganic chemistry.\(^{92}\) Therefore CuCl is often employed in the reaction instead of CuCl\(_2\) in order to prevent the undesired chlorination of the carbonyl compound observed in the presence of CuCl\(_2\).

The reaction can also be carried out in the presence of other palladium species. Recently Kulkarni *et al.*\(^{93}\) used 10% Pd\(^0\)/C as the palladium species in the presence of catalytic amounts of CuCl\(_2\) in THF/H\(_2\)O to produce ketones in high yield. The catalyst can be recovered from the reaction and reused without loss of activity. Earlier this year the same group described a copper-free Wacker oxidation employing Pd\(^0\)/C in the presence of
potassium bromate (KBrO₃) as the oxidant. These reaction conditions improved the traditional Wacker oxidation in that a solid oxidant could be used instead of molecular oxygen and the absence of copper limits the toxic side products generated during the reaction.

Some of the general features of this methodology are: 1) the reaction is performed in the presence of H₂O, 2) external olefins react faster than internal olefins, 3) the reaction is tolerant to a large number of functional groups.

Scheme 49: Catalytic cycle for the Wacker oxidation.

The terminal olefin 170, formed from the previous cuprate addition, was subjected to a Wacker oxidation by stirring with PdCl₂ (0.5 eq) and CuCl (1.2 eq) in DMF/H₂O for 4 h under an oxygen atmosphere to afford the desired methyl ketone 161 in 69% yield (Scheme 48). An enantiomeric excess (ee) of 91% was determined by chiral HPLC analysis (Figure 17) using a Chiralpak® IC column.
HPLC, Chiralpak® IC, hexanes/isopropanol (65/35), ν = 1 mL min⁻¹, λ = 210 nm, retention time: 10.27 min (major), 10.27 min (minor).

**Figure 17:** Comparison of HPLC traces of chiral methyl ketone 161 with the racemic standard.

To summarise, ketone 161 was synthesised in 4 steps from commercially available propylene oxide 163 (Scheme 50). Jacobsen’s HKR of epoxide 163 to (R)-epoxide 113 was followed by allylcuprate addition and benzyl protection of the resultant secondary alcohol to afford alkene 170. Finally Wacker oxidation of alkene 170 afforded the desired methyl ketone 161, with an overall yield of 19% and 91% ee.

![Scheme 50: Synthesis of ketone 161.](image)

**Reagents and conditions:** a) (R,R)-salen Co²⁺ complex A; AcOH, toluene, rt, 30 min; H₂O, 0 °C to rt, 18 h, 45% b) CuI, allylMgBr, THF, -30 °C, 4 h; c) NaH, BnBr; THF, 0 °C to rt, 16 h, 60% over 2 steps; d) PdCl₂, CuCl, DMF, H₂O, O₂, rt, 4 h, 69%.

---

8 The racemic standard of 161 was synthesised from the racemic propylene oxide via an allylcuprate addition, benzyl protection and wacker oxidation.
2.3 Synthesis of aldehyde 162

The retrosynthetic strategy for the preparation of aldehyde 162, the second coupling partner for the aldol reaction is depicted in Scheme 51. Aldehyde 162 can be obtained from regioselective chelation-controlled reduction of methyl ester 180, which in turn could be formed from the benzyl protection of diester 181. The latter should be readily accessible by esterification of commercially available chiral pool (S)-malic acid 91.

Scheme 51: Retrosynthesis of aldehyde 162.

The first step in the synthesis was the bis-esterification of chiral pool (S)-malic acid 91 using acetyl chloride and MeOH (Scheme 52) following the procedure by Ley et al. After stirring at room temperature for 18h the desired product 181 was obtained in 80% yield.

Scheme 52: Synthesis of methyl ester 180.

Next, the base sensitive β-hydroxy group of ester 181 was protected as the corresponding benzyl ether 180 under acidic conditions. Reaction of freshly prepared benzyl trichloroacetimidate (BnTCA) 182 in the presence of a catalytic quantity of triflic acid (TfOH) for 2 days at room temperature afforded the desired benzyl protected ester 180. Benzyl trichloroacetimidate (BnTCA) itself was prepared by reaction of benzyl alcohol 183 with sodium hydride then trichloroacetonitrile 184 (Scheme 53).

Scheme 53: Preparation of benzyl trichloroacetimidate (BnTCA) 182.
2.3.1 Regioselective chelation-controlled reduction of ester 180

The next step in the synthesis of aldehyde 162 is the selective reduction of ester 180. There is literature precedent for this reduction involving a regioselective chelation-controlled reduction of ester 180 to the corresponding aldehyde 162,\(^{97}\) which can proceed via the mechanism depicted below (Scheme 54). The magnesium forms a chelate with the benzyl protected hydroxyl group and the carbonyl group of the ester α to the neighbouring alkoxy group. In fact, the protection of the hydroxyl group as a benzyl ether provides a regioselective reduction with the aluminium species. It has been shown by Reetz that the regioselectivity of the reaction is the result of faster formation of the five-membered transition state compared to the less stable six-membered ring complex that forms from chelation of the magnesium to the methyl ester β to the neighbouring alkoxy group.\(^{99}\) As shown in Scheme 54 one equivalent of DIBAL-H should lead to the desired aldehyde 162. However in our case, use of 1.0 equivalent of DIBAL-H resulted in no reaction and the use of 1.2 equivalents of DIBAL-H as demonstrated by Keck et al.\(^{97}\) led to a mixture of aldehyde 162 and the over-reduced product alcohol 185. The sensitive nature of the aldehyde 162, which has been previously reported,\(^{97}\) rendered separation of this mixture difficult and only the alcohol 185 could be isolated. It was therefore decided to directly prepare the alcohol 185 by employing an excess of DIBAL-H and oxidise it to the desired aldehyde 162 in an extra step. Since it was noted by Reibig et al.\(^{100}\) that the quality of the magnesium reagent used strongly impacts the outcome of the reaction, the magnesium bromide diethyl etherate (MgBr\(_2\)·OEt\(_2\)) used was freshly prepared before each reaction. MgBr\(_2\)·OEt\(_2\) was obtained by stirring magnesium turnings with 1,2-dibromoethane in diethyl ether, and added to a solution of ester 180 at -90 °C. The chelate thus formed was treated with 2.0 eq of DIBAL-H dropwise over 90 min thus affording the desired alcohol 185 in 53% yield.

Scheme 54: Mechanism for selective chelation controlled reduction of ester 180 to alcohol 185.

Unfortunately oxidation of the primary alcohol 185 using conditions such as pyridinium chlorochromate (PCC), Swern, 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) proved unsuccessful. Aldehyde 162 was finally obtained using a TEMPO-catalysed oxidation procedure and used in the ensuing aldol reaction without further purification.
The mechanism for the TEMPO-catalysed oxidation is shown below (Scheme 55). TEMPO is first oxidised to the oxoammonium salt 186, which interacts with the alcohol to form adduct 187. A Cope-like cyclic elimination reaction occurs to afford the desired aldehyde and hydroxylamine 188, which can be oxidised back to TEMPO.

Scheme 55: TEMPO oxidation mechanism where [O] is the co-oxidant and B is the base.

The reaction of alcohol 185 was carried out at -5 °C employing trichloroisocyanuric acid (TCIA) as the co-oxidant and sodium bicarbonate as the mild base (Scheme 56). This reaction allows for a mild and efficient synthesis of aldehyde 162 with a very simple purification step eliminating the problems previously encountered with the DIBAL-H reduction.

Reagents and conditions: a) TEMPO, TCIA, EtOAc, NaHCO₃, -5 °C, 1 h, 70%.

Scheme 56: Synthesis of aldehyde 159.

Aldehyde 162 was thus synthesised in five steps (Scheme 57) as follows; bis-esterification of (S)-malic acid 91 followed by benzyl protection afforded ester 180, reduction of the ester 180 to alcohol 185 using DIBAL-H and subsequent oxidation of the newly formed alcohol 185 with TEMPO afforded aldehyde 162, in a 21.9% overall yield.
Chapter Two: Cephalosporolides E and F

2.4 Aldol reaction of methyl ketone 161 and aldehyde 162

With aldehyde 162 and ketone 161 in hand, our focus turned to the next step, the aldol reaction. Aldol reactions are one of the most powerful and versatile methods for the construction of carbon-carbon bonds. The mechanism of the reaction involves the formation of an enolate 189, from reaction of a ketone 190 with either a strong base or a Lewis acid and an amine base, which then undergoes nucleophilic attack on an aldehyde 191 to form a new C-C bond and a hydroxyl group. Four stereoisomeric β-hydroxy carbonyl products are possible (Scheme 58).

\[
\begin{align*}
\text{Scheme 58: Schematic of the aldol reaction with the four possible outcomes.}
\end{align*}
\]

Over the years, both the issues of regioselectivity and stereoselectivity in aldol reactions have been reviewed. The nature of the metal enolates has been widely accepted as the major contributing factor to the relative stereochemical outcome of reactions under kinetic control. In general, E-enolates react with an aldehyde to form 1,2-anti products and Z-enolates deliver mainly 1,2-syn adducts. This generalisation stems from the Zimmerman-Traxler model whereby a metal ion chelates to both the enolate and the carbonyl substrate, forming a well-defined, cyclic six-membered transition state.

Considering the reaction of enolate 192 and aldehyde 191, four Zimmerman-Traxler transitions states may arise from reaction at each face (Re or Si) of both the aldehyde and enolate coupling partners. Thus two syn and two anti products may arise. However, experimentally, only two of the four possible isomers are observed. This stereocontrol can be rationalised by examining the individual transition states resulting from the reaction of aldehyde 191 with both E-enolate 192a and Z-enolate 192b. As shown in Scheme 59, transition state 193, leading to syn-194, encounters severe 1,3-diaxial strain between substituents R\(^1\) and R\(^3\), hence the alternative transition state 195 leading to anti-196 is more favourable than transition state 193. Conversely, for Z-enolate...
transition state $197$ experiences similar unfavourable 1,3-diaxial interactions, thus aldol adduct $198$ is formed predominantly.

Scheme 59: Zimmerman-Traxler transition states model for the aldol reaction with both $E$ and $Z$ enolates.\textsuperscript{105}

Many reviews have been published on developing methodology to address the issue of the stereoselectivity of the aldol reaction.\textsuperscript{106-109} As seen by the Zimmerman-Traxler model (Scheme 59) under kinetic control the relative stereochimistry is determined by the conformation of the metal enolate ($E$ or $Z$) formed. The control of the absolute stereochemistry can be achieved in one of three ways.\textsuperscript{110}

1. Induction from the aldehyde
2. Induction from the enolate
   a. Substrate-mediated
   b. Ligand-mediated
   c. Auxiliary controlled
3. Induction from a chiral Lewis acid using a Mukaiyama aldol reaction

2.4.1 Induction from the aldehyde

Asymmetric induction in aldol reactions requires significant stereodifferentiation of the $\pi$-faces of the enolate and the aldehyde. An aldol reaction between an achiral enolate and a chiral aldehyde is one of the most straightforward methods of forming $\beta$-hydroxy carbonyl compounds diastereoselectively.\textsuperscript{110}
The Felkin-Ahn model can be used to predict the stereochemistry of the aldol reaction. This model has proven to be accurate for the aldol reaction between an E-enolate with a chiral aldehyde (Scheme 60), where the substituents on the aldehyde are defined as medium (M) and large (L). The unfavourable syn-pentane interaction between the R^M group on the aldehyde and the equatorial R^2 substituent of the enolate can be observed in the anti-Felkin-Ahn transition state 199, making anti-product 200 formation favourable.

Scheme 60: Felkin-Ahn transition states for E-enolate.

The Z-enolate aldol reaction experiences similar syn-pentane interacts in the Felkin-Ahn transition state 201 between the R^M group on the aldehyde and the R^2 substituent on the enolate, making the anti-Felkin-Ahn transition 202 more favourable (Scheme 61), thus giving the syn-product 203 predominantly.

Scheme 61: Felkin-Ahn transition states for Z-enolate.

The asymmetric induction from the chiral aldehyde alone is generally insufficient to lead to a high level of stereoselectivity for any given β-hydroxy carbonyl compound. Therefore, other methods are more often employed.
2.4.2 Induction from the enolate

The stereochemistry in the aldol reaction can also be introduced from the enolate component either from substrate-mediated induction, ligand-mediated induction or auxiliary controlled induction.

2.4.2.1 Substrate-mediated

Similar to the aldehyde directed approach, chiral substituents in close proximity to the carbonyl functional group of the ketone can direct the stereochemistry of the aldol reaction.

Substrate mediated control of chiral ketone 204 in the aldol reaction with achiral aldehyde 205 resulted in 1,4-syn induction with boron or titanium enolates via transition states 206 and 207 (Scheme 62). Theoretical studies carried out by Goodman et al.\textsuperscript{112} identified that transition state 206 for the boron enolate is stabilised by the H-bond between the β-oxygen atom and the neighbouring hydrogen of the aldehyde. In the case of the titanium enolate favourable interaction between the β-oxygen atom and the metal, seen in transition state 207 gives rise to 1,4-syn product 208.\textsuperscript{113} In both instances the selectivity arises from favourable interactions between the β-oxygen atom and the metal or a nearby hydrogen atom.

\begin{align*}
\text{Reagents and conditions: a) } & \text{Cy}_2\text{BCl, NEt}_3, \text{Et}_2\text{O, } -78 \text{°C; b) } \text{TiCl}_4, \text{iPr}_2\text{NEt CH}_2\text{Cl}_2, -78 \text{°C.}
\end{align*}

\textbf{Scheme 62:} Substrate-mediated aldol reaction.\textsuperscript{112-113}
2.4.2.2 Ligand-mediated

The ligand-mediated aldol reactions have an advantage over the substrate-mediated reactions as the chiral moiety used to install the diastereoselectivity is present on the Lewis acid rather than the substrate. Work in this area mainly consists of chiral boron reagents such as diisopinocampheylboron triflate \( \text{209} \). Paterson \textit{et al.} \textsuperscript{114} have demonstrated that the use of Ipc\(_2\)BOTf \( \text{209} \) in the aldol reaction between ketone \( \text{190} \) and aldehyde \( \text{191} \), proceeds \textit{via} attack on the \textit{Si}-face of the aldehyde. This is explained by transition states \( \text{210} \) and \( \text{211} \) for the \( \text{Z} \)-enolate, which is formed predominantly in this reaction, the severe steric interactions between the methyl group of the Ipc ligand and the enolate substituent make transition state \( \text{210} \) more favourable thus leading to the formation of \( \text{syn} \) \( \beta \)-hydroxyketone \( \text{198} \) (Scheme 63).

\[
\begin{align*}
\text{R}^1 & \text{R}^2 \\
\text{O} & \text{OH} \\
\text{R}^3 & \text{R}^4
\end{align*}
\]

Reagents and conditions: Ipc\(_2\)BOTf, CH\(_2\)Cl\(_2\), \( \text{iPr}_2\)NEt.

Scheme 63: The use of chiral (Ipc)\(_2\)BOTf in aldol reaction. \textsuperscript{114}

2.4.2.3 Auxiliary-mediated aldol reaction

An alternative method for controlling the diastereofacial selectivity of the aldol reaction is attachment of a chiral auxiliary to the enolisable coupling partner. Evans \textit{et al.} \textsuperscript{115} pioneered the use of oxazolidinones such as \( \text{212} \) (Scheme 64) for use in \( \text{syn} \) aldol reactions. \( \text{Z} \)-enolate \( \text{213} \) will react via a chair-like transition state \( \text{214} \), whereby the steric interactions of the ligand on the boron and the chiral auxiliary are minimised, to give \( \text{syn} \) aldol product \( \text{215} \).
Heathcock et al.\textsuperscript{116} discovered that upon addition of a bulky Lewis acid such as diethylaluminium chloride (Et\textsubscript{2}AlCl), \textit{anti} aldol products rather than \textit{syn} products are obtained. In this case, the aldol reaction proceeds through an open transition state (Scheme 65). If the Lewis acid is small the reaction proceeds through transition state \textbf{216} to form the \textit{syn} product \textbf{217} predominantly. When a large Lewis acid is employed the reaction proceeds through transition state \textbf{218} where the steric interaction between the Lewis acid and R\textsuperscript{1} is minimised giving rise to the \textit{anti}-product \textbf{219}.

The advantages of auxiliary-mediated aldol reactions are that the chiral auxiliaries are: 1) easily synthesised; 2) can induce high levels of stereocontrol; and 3) are easily cleaved under mild conditions and can be recycled.\textsuperscript{110}
2.4.3 Induction from preformed enolate

The Mukaiyama aldol reaction\textsuperscript{117} is a variation of the aldol reaction in which the enolate is pre-formed as a silyl enol ether (Scheme 66). In contrast to most of the previously mentioned chiral inductions, the Mukaiyama aldol reaction does not proceed through the Zimmerman-Traxler chair transition state but through an open chain transition state. The geometry of the enolate formed does not have a direct effect on the stereochemistry of the reaction. High levels of desired diastereoselectivity can be obtained by careful choice of substrate and reaction conditions.

\[
\begin{align*}
\text{R}^1\text{CH} = \text{O} + \text{R}^2\text{R}^3\text{SiX}_3 & \rightarrow \text{R}^1\text{CH} = \text{O} \text{R}^2\text{R}^3 \quad \text{syn-diastereoisomer} \\
\text{X} = \text{alkyl, aryl} & \quad \text{anti-diastereoisomer}
\end{align*}
\]

Scheme 66: Mukaiyama aldol reaction.

There are six possible transition states that may form either the \textit{syn} or \textit{anti} aldol product from the Z-enolate (Scheme 67). Transition states B and F are disfavoured due to steric interactions between \(\text{R}^3\) and the Lewis acid (LA), transition states C and G are disfavoured due to unfavourable dipole-dipole interactions of the carbon-oxygen bonds. High \textit{anti} selectivity is obtained from transition state A when \(\text{R}^2\) is small and \(\text{R}^3\) is bulky affording 220. When \(\text{R}^2\) is large \textit{syn} stereochemistry 221 predominates in the aldol reaction (TS E).

For \(E\)-enol silanes, the preferred transition state is D as it avoids steric interactions between the bulky silyl group and the aldehyde oxygen atom as well as the \(\text{R}^3\) group. The use of aldehydes that can participate in chelation in the Mukaiyama aldol reaction gives high levels of \textit{syn} selectivity as shown in transition state H.

\[
\begin{align*}
\text{Transition states for Z-enolates} & \quad \text{Transition state for E-enolate} \\
\text{A} & \quad \text{B} \\
\text{C} & \quad \text{D} \\
\text{E} & \quad \text{F} \\
\text{G} & \quad \text{H}
\end{align*}
\]

Scheme 67: Transition states for the Mukaiyama aldol reaction.\textsuperscript{117}

Work is being carried out on the design of new chiral Lewis acids which can be used in sub-stoichiometric quantities. The rationale behind this approach is that catalytic amounts of the desired Lewis acid, which will
coordinate to the aldehyde, will hinder approach of an enolate to one side of the prochiral carbonyl compound to ensure high enantioselectivity in the aldol reaction.

A review by Mahrwald\textsuperscript{117} details the various Lewis acids and their uses in the aldol reaction. Among the catalysts reviewed are chiral boron\textsuperscript{222}\textsuperscript{118}, tin\textsuperscript{223}\textsuperscript{119} and copper complex\textsuperscript{224} (Figure 18).\textsuperscript{120}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure18.png}
\caption{Examples of chiral catalysts used in the Mukaiyama aldol reaction.\textsuperscript{118-120}}
\end{figure}
2.5 **Synthesis of β-hydroxyketone 160**

With aldehyde 162 and ketone 161 in hand, we next turned our attention to the aldol reaction (Scheme 68). In light of the abundant literature dealing with asymmetric induction in aldol reactions, we endeavoured to choose the most appropriate method for our particular substrate. Among the previously mentioned induction techniques, one was immediately discarded, namely the substrate mediated induction from the enolate. In fact, due to the distance between the reactive centre and the chiral centre, the latter would not have a significant influence on the diastereofacial selectivity of the reaction. On the other hand the proximity of the chiral centre on the aldehyde coupling partner 162 (α to the aldehyde functional group), prompted us to attempt to install the stereochemistry using induction from the chiral aldehyde.

![Scheme 68: Aldol reaction between ketone 161 and aldehyde 162.](image)

The ketone 161 was first converted to the lithium enolate *in situ* by reacting with lithium diisopropylamide (LDA) for 30 min at -78 °C. Next, aldehyde 162 was added and the reaction allowed to slowly warm to room temperature overnight. Disappointingly, the desired β-hydroxyketone 160 was not detected by TLC analysis or from the crude NMR spectrum and only ketone 161 could be observed. This suggests that aldehyde 162 may decomposed during the reaction. A slightly milder base LiHMDS (pKₐ of 26 in THF compared to a pKₐ of 35 for LDA) was therefore used to synthesise the lithium enolate. The reaction was stirred for 16 h and after work-up both the aldehyde 162 and ketone 161 were detected in the crude NMR spectrum but none of the desired β-hydroxyketone 160 was observed. Due to the sensitive nature of aldehyde 162, only ketone 161 could be isolated from the reaction.

These initial attempts proved to be problematic, so a change in strategy was initiated. Therefore the ligand mediated aldol reaction which had been employed by Paterson *et al.*[^121] in synthetic studies towards peloruside A (Scheme 69) was next attempted. The ligand-mediated aldol conditions they developed relied on the use of (Ipc)₂BCl and triethylamine (NEt₃). Paterson *et al.*[^121] successfully coupled acetone 225 with aldehyde 226 using these conditions to give a 90:10 mixture of 227 and 228.

![Scheme 69: Synthetic studies towards peloruside A.](image)

---

[^121]: Paterson et al., Synthetic Studies towards Peloruside A.
Hoping that these reaction conditions could also be used on a more complex system, methyl ketone 158 was reacted with (Ipc)_2BCl and NEt_3 in Et_2O at -78 °C. Aldehyde 162 was added and the reaction mixture warmed to -5 °C overnight. Unfortunately no β-hydroxyketone 160 was obtained. Although both ketone 161 and aldehyde 162 were detected by TLC, only ketone 161 was recovered from the reaction. Attempts to increase the reaction rate by allowing the reaction mixture to warm to room temperature did not improve the reaction outcome and none of the desired β-hydroxyketone 170 was observed.

2.5.1 Mukaiyama aldol reaction of aldehyde 162 and methyl ketone 161

Since no reaction was observed using lithium enolates (LDA and LiHMDS) and the chiral Lewis acid (Ipc)_2BCl reagent, our focus next turned to the Mukaiyama aldol reaction. Aldehyde 162 had previously been employed in a Mukaiyama aldol reaction with a simpler silyl enol ether 229. In this case aldehyde 162 was treated with BF_3·OEt_2 in CH_2Cl_2 at 0 °C before the addition of silyl enol ether 229 giving a 53:47 mixture of β-hydroxyketones 230 and 231 (Scheme 70) which upon purification and treatment with hydrochloric acid produced lactones 232 and 233 in 61% yield with the same 53:47 ratio.

![Scheme 70: Mukaiyama aldol reaction of aldehyde 162 with silyl enol ether 229.]

Reagents and conditions: a) aldehyde 162, BF_3·OEt_2, CH_2Cl_2, 0 °C, 15 min, then silyl enol ether 229, 0 °C, 1 h, 50% aq. H_2SO_4, rt, 30 min; b) HCl, CH_2Cl_2, rt, 1 h, 61%.

In the same publication it was noted that the use of titanium tetrachloride (TiCl_4) in the place of BF_3·OEt_2 in the above reaction afforded cis-lactone 233 predominantly upon purification (Scheme 71). This transformation demonstrated that chelate formation governs the selectivity of this reaction as no selectivity was observed when BF_3·OEt_2 (no chelation possible) was employed in the same reaction.

![Scheme 71: Mukaiyama aldol reaction of aldehyde 162 with silyl enol ether 229.]

Reagents and conditions: a) aldehyde 162, TiCl_4, CH_2Cl_2, 0 °C, 15 min, then silyl enol ether 229, 0 °C, 1 h, 50% aq. H_2SO_4, rt, 30 min, 61%.
The synthesis of β-hydroxyketone 160 using a Mukaiyama aldol reaction was next attempted (Table 1). Firstly, we required the preparation of silyl enol ether 234. Our initial attempts utilising LiHMDS, trimethylsilyl chloride (TMSCl) and NEt₃ according to a procedure by Evans et al.¹²² were successful but not reliable so we decided to use the more reactive TMSOTf in combination with NEt₃. This change in silylating reagents enabled formation of silyl enol ether 234 in a reliable manner. Full conversion was observed by TLC with reaction times as short as 30 min.

With the synthesis of the desired silyl enol ether 234 in hand, focus turned to the Mukaiyama aldol reaction itself. Our various attempts to effect the Mukaiyama aldol reaction are summarised in Table 1. In all instances the aldehyde coupling partner 162 was added to a solution of the Lewis acid to induce pre-complexation prior to exposure to silyl enol ether 234. Boron trifluoride diethyl etherate (BF₃·OEt₂) was first employed as the Lewis acid for the reaction of silyl enol ether 234 with aldehyde 162 (Table 1, entry 1). As the literature reaction of aldehyde 162 gave low selectivity at 0 °C, the BF₃·OEt₂ reaction was carried out at -78 °C and slowly warmed to room temperature overnight. The NMR spectrum of the crude reaction mixture showed none of the desired β-hydroxyketone 160, but revealed both aldehyde 162 and ketone 161 starting materials. As expected only ketone 161 was isolated from the reaction.

Next we attempted the TiCl₄ reaction at 0 °C. No formation of the β-hydroxyketone 160 was observed at 0 °C, hence the reaction was warmed to rt over 2 h. The sensitive aldehyde 162 decomposed and only ketone 161 was detected upon workup (Table 1, entry 2). Disappointingly, none of the desired β-hydroxyketone 160 was observed.

Literature precedence for a chelation-controlled Mukaiyama aldol reaction employing MgBr₂·OEt₂ in the synthesis of natural product azaspiracid 235 (Scheme 72)¹²² encouraged to use this Lewis acid. In their synthesis of azaspiracid 235, Evans et al. achieved the formation of β-hydroxyketone 236 as a single diastereomer in 93% yield with a 95:5 diastereomeric ratio (dr). The silyl enol ether 237 for the Mukaiyama aldol reaction was formed by treating the ketone 238 with LiHMDS, TMSCl and NEt₃. This newly formed enol ether 237 was then reacted with a pre-complexed mixture of aldehyde 239 and MgBr₂·OEt₂ to deliver the β-hydroxyketone 236, which underwent further reactions to afford the natural product 235.
Chapter Two: Cephalosporolides E and F

Reagents and conditions: a) LiHMDS, TMSCl, Et$_3$N, THF, -78 °C, 89%; b) MgBr$_2$·OEt$_2$, CH$_2$Cl$_2$, 0 °C, 93%, >95:5 dr.

Scheme 72: Towards the total synthesis of azaspiracid 235.

Pleasingly, when the chelating agent MgBr$_2$·OEt$_2$ was used for the reaction between silyl enol ether 234 and aldehyde 162 the desired syn β-hydroxyketone 160 was formed in 35 % yield with >95% diastereomeric excess (de) (Table 1, entry 3). Furthermore, the remaining ketone 161 could also be recovered.

Table 1: Mukaiyama aldol conditions surveyed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>BF$_3$OEt$_2$</td>
<td>recovered ketone only</td>
</tr>
<tr>
<td>2$^a$</td>
<td>TiCl$_4$</td>
<td>recovered ketone only</td>
</tr>
<tr>
<td>3$^b$</td>
<td>MgBr$_2$·OEt$_2$</td>
<td>35% aldol product</td>
</tr>
</tbody>
</table>

Conditions for the formation of silyl enol ether x: a) LiHMDS, TMSCl, NEt$_3$, CH$_2$Cl$_2$, -78 °C, 1 h; or b) NEt$_3$, TMSOTf, CH$_2$Cl$_2$, 0 °C, 30 min; c) aldehyde 162 stirred with Lewis acid before addition of silyl enol ether 234.

The diastereomeric excess of the newly formed β-hydroxyketone 160 could not immediately be determined by $^1$H NMR spectroscopy due to overlapping resonances for the hydroxyl group. Conversion of the hydroxyl group to an acetyl group 240 (Scheme 73) resulted in the downfield shift of H-4 in the desired aldol product 160 from δ 4.05-3.99 ppm to δ 5.51-5.47 ppm (Figure 19). H-3 also shifted downfield from δ 3.81-3.78 to δ 4.15-4.11 ppm. The H-3 and H-4 shifts were assigned with the aid of 2D COSY and HSQC spectra. Thereby confirming that only one diastereomer was formed in the reaction.

Reagents and conditions: a) DMAP, pyridine, Ac$_2$O, rt, 1 h, 56 %.

Scheme 73: Protection of the newly formed β-hydroxyketone 160.
Figure 19: Comparison of $^1$H NMR spectra of aldol product 160 and acetate 240.
As observed by Reibig et al.\(^{100}\) the strong stereoselectivity obtained may be the result of the chelating properties of the Lewis acid. As discussed in Section 2.4.3 chelation-control can be used to direct the stereochemistry in the Mukaiyama aldol reaction. Chelation of the Lewis acid with the \(\alpha\)-heteroatom and the carbonyl group forces the substrate into a rigid conformation and facilitates nucleophile attack on the less sterically hindered face of the aldehyde (Scheme 74). The preferred formation of the \(\text{syn}\)-aldol product 106 can be rationalised by the Cram-chelate model.

![Scheme 74: Cram chelate model for aldol reaction.](image)

### 2.5.2 Super silyl aldol reaction

In parallel to the Mukaiyama aldol reaction, super silyl aldol reactions were carried out. In 2009 a review article was published\(^{123}\) detailing the reactivity of the tris(trimethylsilyl)silyl (TTMSS) in the aldol reaction and the high levels of diastereoselectivity obtained for the \(\beta\)-hydroxy carbonyl compound. A key feature of this methodology is the large steric size of the tris(trimethylsilyl)silyl (TTMSS) group which restricts the conformation of the molecule. The advantage of this strategy would be the isolation of a stable bulky enol ether 241 which should react with aldehyde 242 with high diastereoselectivity to give \(\beta\)-hydroxyketone 243 with the resultant hydroxyl group protected as a TTMS ether (Scheme 75).

![Scheme 75: Super silyl aldol reaction.](image)

The super silyl enol ether 241 can be synthesised in two ways; a) a metal-halogen exchange of silver triflate (Ag\(_2\)OTf) and tris(trimethylsilyl)silyl chloride (TTMSSCl) to form the silyl triflate which reacts with ketone 244 to form silyl enol ether 241 or b) the reaction of tris(trimethylsilyl)silyl hydride with triflic acid thereby generating the silyl triflate \textit{in situ}.

The reaction mechanism for the aldol reaction of the newly formed silyl enol ether 241 with aldehyde 242 is shown in Scheme 76 employing triflimide (HNTf\(_2\)) and a Brønsted acid (BH). In this case triflimide acts as a precatalyst with TTMSNTf\(_2\) acting as the true catalyst.\(^{123}\) The preformed super silyl enol ether 238 reacts with triflimide to afford the true catalyst TTMSNTf\(_2\) which reacts with the aldehyde 242 to form the intermediate 245. Another molecule of the super silyl enol ether reacts with this intermediate to form the \(\beta\)-hydroxyketone 243.
We first focused on the preparation of the TTMS enol ether (Scheme 77). Tris(trimethylsilyl)silyl hydride (TTMSSH) was reacted with triflic acid (TfOH) in CH$_2$Cl$_2$ and stirred for 1 h. Ketone 161 and triethylamine were added dropwise to the solution with precautions taken to release the pressure from the liberated hydrogen gas. Disappointingly, no desired super silyl enol ether 246 was detected. We therefore moved to the metal-halogen exchange reaction. Unfortunately, stirring of tris(trimethylsilyl)silyl chloride (TTMSSCl) with silver triflate in CH$_2$Cl$_2$ overnight followed by the addition of ketone 161 and triethylamine also failed to afford the desired silyl enol ether 246. It should be noted that to date only aldehydes and simple ketones such as acetone have been used to form super silyl enol ethers.$^{123-124}$ This might shed some light on the difficulties we encountered during our attempts to effect the synthesis of the super silyl enol ether of ketone 161.

**Scheme 76: Mechanism of the super silyl aldol reaction.$^{123}$**

**Scheme 77: Attempted synthesis of super silyl enol ether 246.**

Reagents and conditions: a) TfOH, TTMSSH, CH$_2$Cl$_2$, rt, 1 h, then ketone 161, NEt$_3$, CH$_2$Cl$_2$, rt, 30 min; b) TTMSSCl, CH$_2$Cl$_2$, Ag$_2$OTf, rt, overnight, then ketone 161, NEt$_3$, CH$_2$Cl$_2$, rt, 6 h.

At this point the desired β-hydroxyketone 160 had been synthesised albeit in low 35% yield employing MgBr$_2$·OEt$_2$ in a Mukaiyama aldol reaction hence use of the TTMS pathway was abandoned.
2.7 Spirocyclisation

With the desired β-hydroxyketone 160 in hand, only a few steps remained to complete the synthesis of cephalosporolides E 24 and F 25. Initial attempts to deprotect the benzyl group of β-hydroxyketone 160 over 10% Pd/C under an atmosphere of hydrogen at ambient temperature proved unsuccessful with only starting material 160 been isolated after 16 h. Fortunately, double deprotection of the benzyl groups using a Parr hydrogenator with 10% Pd/C at 60 psi followed by in situ cyclisation of the resultant diol mixture delivered a 1:1 mixture of spiroacetals 159a and 159b. The diastereomeric mixture was inseparable by column chromatography hence this mixture was used in the next step.

Reagents and conditions: a) Pd/C, H₂, MeOH, 60 psi, 12 h; b) Amberlyst-15®, CH₂Cl₂, rt, 12 h, 86% over 2 steps, 3:2 24:25.

Scheme 78: Synthesis of cephalosporolides E 24 and F 25.71

The final acid-catalysed lactonisation of the 1:1 mixture of hydroxyesters 159a and 159b using Amberlyst-15® in CH₂Cl₂ furnished a 3:2 mixture of lactones 24 and 25 after stirring for 12 h. The two diastereoisomers were carefully separated by column chromatography on deactivated silica.** Comparison of the optical rotation (αD) values and the ¹H and ¹³C NMR data with that reported in the isolation paper35 and the ¹H and ¹³C NMR spectra reported by Ramana et al.,66 confirmed the structures of the natural products cephalosporolides E 24 and F 25 (Table 2 and 3). The characteristic signal corresponding to the spiro-carbon resonated at δ 115.0 ppm in the NMR spectrum for cephalosporolide E 24 and at δ 115.5 ppm in the NMR spectrum for cephalosporolide F 25. The ¹H NMR spectrum for cephalosporolide E 24 displayed a triplet for H-4 at δ 5.15 ppm. This characteristic signal was first found in the structure of ent-cephalosporolide E 85 (Figure 20).66 In cephalosporolide F 25 H-4 resonates as a doublet of doublet of doublets at δ 5.08 ppm with coupling constants J = 2.1, 4.4, 6.6 Hz (Table 3). All other protons were found to match the isolation paper.35

There is a great deal of variation in the reported values for the αD of cephalosporolides E 24 and F 25.66,70,71 This variance may relate to the propensity of both diastereomers to rapidly epimerize at the spiroacetal center.71

The αD for cephalosporolide E 24 was +27.3 (c 0.41, CHCl₃) compared with αD +51.3 (c 0.41, CHCl₃)35 for the isolation paper while αD +49.2 (c 0.25, CHCl₃)70 and αD +35.0 (c 0.41, CHCl₃)71 were reported for synthetic

**The silica gel was deactivated by the addition of 0.1% NEt₃ to the eluent to reduce the possibility of equilibration by acid catalysed ring-opening of the spiroacetal during column chromatography.
cephalosporolide E 24 by Fernandes et al.\textsuperscript{70} and Britton et al.\textsuperscript{71} respectively. However, the $\alpha_D$ we obtained for cephalosporolide F 25 $\alpha_D$ -33.9 (c 0.79, CHCl$_3$) was in agreement with the isolation value of $\alpha_D$ -33.3 (c 0.79, CHCl$_3$).\textsuperscript{35}

A molecular ion at $m/z$ 221.0792 in the high resolution EI mass spectrum (221.0784 calculated for MNa$^+$) provided evidence for the successful formation of the cephalosporolide E 24. Similarly, a $m/z$ 221.0790 in the high resolution EI mass spectrum (221.0784 calculated for MNa$^+$) indicated the presence of cephalosporolide F 25.

Table 2: Comparison of the NMR data for the synthetic cephalosporolide E 24 with that in the isolation paper.\textsuperscript{35}

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Figure 20: $^1$H NMR spectral comparison between ent-cephalosporolide E 85 and synthetic cephalosporolide E 24.
Table 3: Comparison of NMR values for synthetic cephalosporolide F and isolation paper.

![Cephalosporolide F 25](image)

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<td>14.7, 6.6</td>
<td>36.9</td>
<td>2.27</td>
<td>dd</td>
<td>15.0, 7.0</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.33</td>
<td>dd</td>
<td>14.9, 2.2</td>
<td></td>
<td>2.46</td>
<td>dd</td>
<td>15.0, 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td></td>
<td>115.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>115.3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.18-1.95</td>
<td>m</td>
<td>-</td>
<td>36</td>
<td>2.05</td>
<td>m</td>
<td>-</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2.18-1.95</td>
<td>m</td>
<td>-</td>
<td>32.4</td>
<td>1.67</td>
<td>m</td>
<td>-</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.80+1.70</td>
<td>m</td>
<td>-</td>
<td>32.4</td>
<td>2.05</td>
<td>m</td>
<td>-</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4.25-4.15</td>
<td>m</td>
<td>-</td>
<td>76.5</td>
<td>4.15</td>
<td>m</td>
<td>-</td>
<td>76.5</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.28</td>
<td>d</td>
<td>6.1</td>
<td>22.7</td>
<td>1.23</td>
<td>d</td>
<td>6</td>
<td>22.6</td>
<td></td>
</tr>
</tbody>
</table>
Synthetic $^1$H NMR spectra from Ramana et al.$^{66}$ for ent-cephalosporolide F $^86$

Figure 21: $^1$H NMR spectra comparison of ent-cephalosporolides F $^86$ and cephalosporolide F $^25$.$^{66,73}$
2.8 Summary

In summary we have synthesised the natural products cephalosporolides E 24 and F 25 in 12 steps from propylene oxide 163 and (S)-malic acid 91 in an overall yield of 3.1 and 2.1% respectively (Scheme 79). A diastereoselective Mukaiyama aldol reaction was used to establish the syn-hydroxy stereocentre in β-hydroxyketone 160 which upon benzyl deprotection under neutral conditions cyclised to afford hydroxyesters 159a and 159b. Finally acid-catalysed lactonisation completed the synthesis of the spiroacetals 24 and 25 giving NMR spectra in agreement with the isolation paper and with the spectra for the enantiomers of cephalosporolides E 85 and F 86 by Ramana et al. 66

Reagents and conditions: a) (R,R)-salen CoII complex A, AcOH, toluene, rt, 30 min; H2O, 0 °C to rt, 18 h, 45% b) Cu, allylMgBr, THF, -30 °C, 4 h; c) NaH, BnBr; THF, 0 °C to rt, 16 h, 60%; d) PdCl2, CuCl, DMF, H2O, O2, rt, 4 h, 69%; e) MeOH, AcCl, rt, 18 h, 80%; f) BnTCA, CH2Cl2, cyclohexane, TiOH, rt, 24 h, 74%; g) DIBAL-H, CH2Cl2, MgBr2·OEt2, -78 °C to 0 °C, 2 h, 53%; h) TEMPO, TCIA, EtOAc, NaHCO3, -5 °C, 1 h, 70%; i) TMSOTf, NEt3, CH2Cl2, 30 min, 0 °C then aldehyde 162, CH2Cl2, MgBr2·OEt2, -78 °C to 0 °C, 2 h, 35%; j) Pd/C, H2, MeOH, 60 psi, 12 h; k) Amberlyst-15®,

Scheme 79: Summary of synthesis of cephalosporolides E 24 and F 25.
CHAPTER THREE: SYNTHETIC STUDIES TOWARDS CEPHALOSPOROLIDES H AND I
3.1 Synthetic strategy

With the successful synthesis of cephalosporolides E 24 and F 25 accomplished, attention turned to the other members of the cephalosporolide family. At the commencement of this project no previous synthesis of cephalosporolide H 28 had been reported and the absolute stereochemistry of the isolated natural products had not been established (Figure 22). During the course of this work syntheses of the natural product cephalosporolide H 28 by Dudley et al. and Fernandes et al., have suggested that the stereochemistry at C-6 be reassigned to that of spiroacetal 144. We planned our synthesis to allow for the isolation of diastereoisomers of the spiroacetal about C-6, which could be used to confirm the absolute stereochemistry of the natural product. In contrast to the previous syntheses, our route aims to allow for the late stage installation of the side chain, thus giving access to both natural products cephalosporolides H 28 and I 29 from a common precursor spiroacetal.

![Initial cephalosporolide H 28](image1)

![Cephalosporolide I 29](image2)

![Reassigned cephalosporolide H 144](image3)

Figure 22: Reported structures of cephalosporolides H 28 and I 29 and reassigned structure of cephalosporolide H 144.

There are many possible routes that could be employed to synthesise cephalosporolides H 28 and I 29, a few of which are featured in Scheme 80. All methods to assemble the benzyl protected hydroxymethyl substituted spiroacetal 164 are based on construction of the acyclic precursor 247. The different synthetic routes therefore only differ in the approach taken to afford this spirocyclisation precursor 247. These routes include: use of an aldol reaction of methyl ketone 166 and aldehyde 167 to give β-hydroxyketone 247, a nitrile oxide cycloaddition reaction between oxime 248 and alkene 249, to afford a cycloadduct that can be reduced to β-hydroxyketone 247; use of a pinacol coupling of aldehydes 250 and 251; and use of a dithiane coupling of dithiane 252 and allyl bromide 253, which following a Sharpless asymmetric dihydroxylation and deprotection will afford spirocyclisation precursor 164. Alternatively, β-hydroxyketone 247 can be derived from olefin 254 which in turn can be prepared using one of the following methods: an allylation reaction between bromide 253 and aldehyde 255; an alkyne coupling between epoxide 256 and alkyne 257; a Horner-Wadsworth-Emmons (HWE) reaction between phosphonate 258 and aldehyde 251; or a cross metathesis reaction between olefins 259 and 260. All of the described routes were investigated and it was decided to first attempt the nitrile oxide cycloaddition reaction as it was one of the most direct routes to the spirocyclisation precursor 247.
Scheme 80: Possible routes to cephalosporolides H and I
3.2 Nitrile oxide cycloaddition pathway

Originally the Mukaiyama aldol reaction was to be employed as the key step to install the stereochemistry about C-3 and C-4 of the lactone in spiroacetal 164. However, due to the low yields obtained in the previous synthesis it was decided to change the synthetic strategy and to employ a nitrile oxide cycloaddition reaction as the key step (Scheme 81). Cephalosporolides H and I would be obtained from the common precursor spiroacetal 164, by functionalisation of the hydroxyl group on C-10. Spiroacetal 164 can itself be obtained from acid-catalysed deprotection of TBS-protected β-hydroxyketone 247 which is expected to promote the formation of the 5,5-spiroacetal as well as the intramolecular esterification to install the γ-lactone functionality. β-Hydroxyketone 247 should be available from reduction of the isoxazoline 261, formed from the nitrile oxide cycloaddition between oxime 248 and alkene 249. Oxime 248 and alkene 249 would be obtained from D-mannitol 168 and commercially available alcohol 169, respectively.

Scheme 81: Retrosynthetic analysis of cephalosporolides H and I.

3.2.1 Background

1,3-Dipolar nitrile oxide cycloaddition (NOC) reactions are a convenient method for the construction of five-membered heterocycles, such as isoxazoline 262 (Scheme 82). The resultant isoxazoline 262 can be transformed into a variety of other functional groups including β-hydroxyketones and γ-amino alcohols.\textsuperscript{125}

Scheme 82: 1,3-Dipolar cycloaddition for isoxazoline synthesis.\textsuperscript{125}
Nitrile oxides are usually unstable and prone to dimerisation. Therefore, they are most often generated \textit{in situ} by either i) dehydrogenation of primary nitro compounds or ii) dehydrohalogenation of hydroximoyl chlorides or bromides (Scheme 83).\textsuperscript{125-126} Hydroximoyl chlorides can be synthesised from oximes by chlorination with chlorine, N-chlorosuccinimide or sodium hypochlorite. Elimination of hydrochloric acid (HCl) by treatment with a base leads to the formation of the nitrile oxide for reaction with an alkene to give isoxazoline.\textsuperscript{126}

\[
\begin{array}{c}
\text{OH} \\
\text{R} \\
\text{Cl or Br} \\
\end{array} \xrightarrow{\text{dehydrohalogenation}} \begin{array}{c}
\text{R} \\
\text{C} = \text{N} \\
\text{O} \\
\end{array} \xrightarrow{\text{dehydration}} \begin{array}{c}
\text{R} \\
\text{\text{NO}_2} \\
\end{array}
\]

\textbf{Scheme 83: Nitrile oxide formation.}\textsuperscript{125}

Two pathways have been proposed for the mechanism of the 1,3-dipolar cycloaddition reaction (Scheme 84). Pathway 1 proposed by Huisgen involves a concerted mechanism in which the two bonds are partially formed in a single transition state.\textsuperscript{127} The second pathway proposed by Firestone involves biradical intermediates and represents a two step pathway.\textsuperscript{128}

\[
\begin{array}{c}
a \\ b \\ c \\ d \\ e \\
\end{array} \xrightarrow{\text{Pathway 1}} \begin{array}{c}
a \\ b \\ c \\ d \\ e \\
\end{array}
\]

\[
\begin{array}{c}
a \\ b \\ c \\ d \\ e \\
\end{array} \xleftarrow{\text{Pathway 2}} \begin{array}{c}
a \\ b \\ c \\ d \\ e \\
\end{array}
\]

\textbf{Scheme 84: Proposed mechanisms for 1,3-dipolar cycloaddition by Huisgen\textsuperscript{127} and Firestone.}\textsuperscript{128}

The controversy over these two mechanisms was resolved in 1978 by Huisgen et al.\textsuperscript{129} The high stereoselectivity observed in the reaction between diazomethane 263 and methyl tiglate 264 (Scheme 85) excludes the possibility of biradical intermediate formation.

\[
\begin{array}{c}
\text{H}_2\text{C} = \text{N} \\
\text{263} \\
\text{Me} \\
\text{Me} \\
\end{array} \xrightarrow{+} \begin{array}{c}
\text{H}_2\text{C} \xrightarrow{\text{C}} \text{Me} \\
\text{CO}_2\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} \text{Me} \text{Me}
\]

\textbf{Scheme 85: 1,3-Dipolar cycloaddition reaction between diazomethane 263 and methyl tiglate 264.}\textsuperscript{129}

The regioselectivity of this reaction has been thoroughly investigated by many groups.\textsuperscript{125} Recently Rastelli \textit{et al.}\textsuperscript{130} carried out the cycloaddition between nitrile oxide 265 and alkene 266 giving cycloadduct 267 as the major product (Scheme 86). This experimental data was supported by DFT calculations thus this model can be employed to predict the outcome of other cycloaddition reactions.
3.2.2 Synthesis of oxime 248

The synthesis of the oxime fragment 248 began with commercially available D-mannitol 168. Protection of the bis-terminal diols as acetonides was accomplished using ZnCl₂ and acetone to afford 268 (Scheme 87).¹³¹ Oxidative cleavage between the unprotected diol gave aldehyde 269 which underwent a HWE reaction with triethylphosphonoacetate 270 to give ester 271.¹³¹ The HWE reaction¹³²-¹³³ has recently been reviewed by Bisceglia et al.¹³⁴ and involves the reaction of an aldehyde with a phosphonate carbanion to produce an alkene. This reaction predominantly generates the trans olefin geometry.

Reduction of the E-alkene 271 with 10% Pd/C in a hydrogen atmosphere afforded ester 272.¹³⁵ The ester 272 was reduced to aldehyde 273 which reacted with hydroxylamine hydrochloride in ethanol to form oxime 274.

![Scheme 86: Nitrile oxide cycloaddition between nitrile oxide 265 and alkene 266.¹³⁰](image)

**Reagents and conditions:**
a) acetone, ZnCl₂, 0 °C to rt, o/n, K₂CO₃ 0 °C, 1 h, 80%; b) NaHCO₃, NaIO₄, CH₂Cl₂, <25 °C, 2 h, 42%; c) K₂CO₃, H₂O, 0 °C, 22 h, 83%; d) 10% Pd/C, EtOH, H₂, rt, 3 h, 89%; e) DIBAL-H, CH₂Cl₂, -78 °C, 1 h, 94%; f) NH₂OH·HCl, EtOH, pyridine, rt, 2 h, 84%.

**Scheme 87: Synthesis of oxime 274.**

It was planned that the acetonide of 272 would be deprotected to reveal a diol which could be orthogonally protected as the TBS and benzyl ethers respectively. Protection of the primary alcohol of 275 as a TBS ether was successful affording ester 276. Benzylaion of the secondary alcohol 276 to give ester 277 was attempted and a range of acidic, basic and neutral reaction conditions were screened (Table 4). Acid-catalysed protection employing benzyl trichloroacetimidate (entry 1) and Ag₂O mediated benzyl bromide protection (entry 2) both proved unsuccessful. The lack of reactivity of the secondary alcohol was attributed to steric hindrance afforded by the bulky silyl ether protecting group and therefore a modification of the protecting group strategy was required.
Chapter Three: Cephalosporolides H and I

Table 4: Benzylation conditions surveyed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>Reagents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂, hexane</td>
<td>48 h</td>
<td>BnTCA, TfOH</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>16 h</td>
<td>BnBr, Ag₂O</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>20 h</td>
<td>NaH, TBAI, BnBr</td>
<td>Recovered starting material</td>
</tr>
</tbody>
</table>

a) TBSCI, DMAP, imidazole, CH₂Cl₂, 0 °C, 18 h, 72%.

Benzyl protected lactone [278] was therefore obtained by reacting diol [275] with dibutyltin oxide in toluene under Dean & Stark conditions (Scheme 88).

The lactone [278] was then opened and trapped as methyl ester [279]. TBS protection of the resultant secondary alcohol afforded [280]. Ester [280] was then reduced to aldehyde [255] and reacted with hydroxylamine hydrochloride in DMF with a catalytic amount of pyridine to afford the orthogonally protected oxime [248].

Scheme 88: Synthesis of oxime [248].

Due to the lengthy nature of the route to oxime [248], a change in strategy was needed to make the synthesis more efficient. Towards that end, commercially available glycidol [281] was protected as a benzyl ether [282] (Scheme 89). Jacobsen’s HKR, discussed in Section 2.2.1, involved the treatment of the protected epoxide [282] with (R,R)-salen Co⁷ complex A affording enantiomeriched (R)-epoxide [283] which can easily be separated from the (S)-diol by column chromatography. The newly formed epoxide [283] was opened at the terminal position by the addition of an allyl cuprate reagent, formed by reacting CuI with allylMgBr in THF at -40 °C, to afford secondary alcohol [284] which was then protected as a TBS ether [285]. Ozonolysis of the resulting alkene [285] gave aldehyde [255], which was converted to the corresponding oxime [248] using the previously established conditions of hydroxylamine hydrochloride in DMF.
Chapter Three: Cephalosporolides H and I

3.2.3 Synthesis of alkene coupling partner 249

The synthesis of alkene 249 (Scheme 90), the second coupling partner of the nitrile oxide cycloaddition reaction, started with a Swern oxidation of commercially available alcohol 169 to aldehyde 251.\(^{139}\) As aldehyde 251 is volatile it was taken on to the next step without further purification. Racemic alkene 286 was obtained from Grignard addition of vinylmagnesium bromide to aldehyde 251.

Reagents and conditions: a) DMSO, (COCl)\(_2\), CH\(_2\)Cl\(_2\), -78 °C, 1 h, NEt\(_3\), rt, 89%; b) vinylMgBr, THF, 0 °C, 3 h, 73%.

Scheme 90: Synthesis of alkene 286.

3.2.3.1 Enzymatic kinetic resolution

It was envisaged that enzymatic kinetic resolution reaction of alkene 286 could afford a chiral alcohol 249, the coupling partner for the NOC reaction. An enzyme kinetic resolution is a reaction of a racemate in which one of the enantiomers reacts more rapidly than the other, in ideal cases only one enantiomer reacts and the other remains unchanged.\(^{140}\) To achieve high enantioselectivity the reaction must be rapid and irreversible (Scheme 91).

\[
\begin{align*}
{\text{(R)-ROH}} & \quad \xrightarrow{\text{enzyme}} \quad {\text{(R)-ROAcyl}} \\
{\text{(S)-ROH}} & \quad \xrightarrow{\text{acyl donor}} \quad {\text{(S)-ROH}}
\end{align*}
\]

Scheme 91: Kinetic resolution of alcohols by enzymatic acylation.

This improved synthesis allowed access to the desired oxime 248 in six steps and was able to be performed on multi-gram scale.
Kazlauskas et al.\textsuperscript{141} postulated an empirical rule with regards the resolution of secondary alcohols to determine the relative configuration of the fast acting enantiomer based on the relative sizes of the substituents about the alcohol (Figure 23). This rule relies on the substituents having a large difference in size. The disadvantage of this methodology is its maximum theoretical yield of 50%.

![Diagram of substituents](image)

**Figure 23:** The fast acting enantiomer when L is large.\textsuperscript{141}

Our attempts to resolve racemic alcohol 286 and isolate the enantiopure (S)-acetate 287 by enzymatic kinetic resolution were unfortunately unsuccessful. Using conditions based on unpublished work carried out in the Brimble group that involved stirring lipase acrylic resin from *Candida antarctica* (Cal-B) with alcohol 286 and vinyl acetate in hexane at 60 °C in the microwave for 6-24 h, only resulted in recovery of starting material 286. Although the adverse effect of mechanical agitation of the enzyme was considered, shaking rather than stirring the reaction over 24 h at 32 °C did not improve the outcome.

### 3.2.3.2 Aldol reaction

As we were unable to obtain chiral alcohol 249 from the enzymatic kinetic resolution our approach was modified to use an auxiliary-mediated aldol reaction (Scheme 92). It was envisaged that chiral alkene 249 could be obtained from mono-methylated alkene 288, which in turn can be formed from the cleavage of auxiliary 289. The aldol reaction between oxazolidinone 290 and commercially available acrolein 291 would install the desired (S)-stereochemistry.

![Scheme 92](image)

**Scheme 92:** Retrosynthesis for alkene 249.

Initially, we synthesised the opposite auxiliary 292 due to the expensive nature of the D-phenylalanine starting material required for 290. This would allow us to establish optimal conditions for the reaction before employing the more expensive substrate. Oxazolidinone 292 was synthesised from commercially available L-phenylalanine 293 (Scheme 93) which was converted into its corresponding amino alcohol by reacting with
iodide and sodium borohydride. The resultant alcohol 294 was treated with diethyl carbonate in the presence of NEt₃ for 2 h followed by base hydrolysis under reflux for a further 2 h. Treatment of the resulting oxazolidinone 295 with nBuLi and propionyl chloride gave oxazolidinone 292.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} & \quad \text{b,c} & \quad \text{O} & \quad \text{NH} & \quad \text{c} & \quad \text{O} & \quad \text{N} & \quad \text{Me}\n293 & \quad \rightarrow & \quad 294 & \quad \rightarrow & \quad 295 & \quad \rightarrow & \quad 296 & \quad \rightarrow & \quad 292
\end{align*}
\]

Reagents and conditions: a) NaBH₄, THF, 0 °C, I₂, 0 °C to reflux, 24 h, quant; b) THF, (EtO)₂CO, NEt₃, 0 °C to rt, 2 h; c) NaOH, THF, reflux, 2 h, 68% over 2 steps; d) nBuLi, THF, -78 °C, propionyl chloride, -78 °C-rt, 2 h, 92%.

Scheme 93: Synthesis of oxazolidinone x.

With the oxazolidinone 292 in hand, the aldol reaction with commercially available acrolein 291 was carried out to afford β-hydroxyketone 296 in 67% yield (Scheme 94). Cleavage of the auxiliary by sodium methoxide gave methyl ester 297 and the regenerated auxiliary 295. Next, introduction of the desired second methyl group via α-alkylation was attempted. The alkylation was tried by deprotonation with either LDA or LiHMDS with and without HMPA, followed by addition of methyl iodide and in most cases warming the reaction from -78 °C to room temperature overnight. HMPA was added as it is known to improve the rate of metalation with lithium bases by solvating the counterion, thereby providing a “naked” and more reactive anion nucleophile. Unfortunately, these reactions did not yield the desired product 298.

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{Me} & \quad \text{a} & \quad \text{O} & \quad \text{N} & \quad \text{Me} & \quad \text{b} & \quad \text{MeO} & \quad \text{Me} & \quad \text{b} & \quad \text{MeO} & \quad \text{Me} & \quad \text{MeO} & \quad \text{Me}
292 & \quad + & \quad 291 & \quad \rightarrow & \quad 296 & \quad \rightarrow & \quad 297 & \quad \rightarrow & \quad 298
\end{align*}
\]

Reagents and conditions: a) TiCl₄, CH₂Cl₂, DIPEA, 0 °C, 1 h; acrolein, -78 °C, 1 h, 67%; b) NaOMe, MeOH, 0 °C, 45 min, 44%.

Scheme 94: Attempted synthesis of alkene 298.

As attempts to obtain the geminal dimethyl group on alkene 297 after the aldol reaction proved unsuccessful, efforts were made to install this functional group during the aldol reaction. Oxazolidinone 299 could be obtained from auxiliary 295 by treatment with nBuLi and isobutryl chloride (Scheme 95). The aldol reaction between the newly formed oxazolidinone 299 and acrolein 291, however, was not successful using the same conditions as previously employed in the above aldol. This is presumably due to the steric crowding around the isopropyl enolate.
Reagents and conditions: a) nBuLi, THF, isobutryl chloride, -78 °C, 2.5 h, 92%.

**Scheme 95:** Attempted synthesis of alkene 298.

### 3.2.2.3 Reformatsky aldol

A better alternative to the traditional aldol reaction was therefore sought. The Reformatsky aldol reaction involves the metal induced reaction of α-carbonyl halides with aldehydes to form β-hydroxyketones. This reaction is a good alternative as the enolate is formed under neutral conditions and highly substituted ketones such as bromide 300 are well tolerated. A recent review into the use of the Reformatsky reaction in the synthesis of natural products highlights the useful diastereoselectivity that can be obtained.\(^{148}\) It also highlights some literature precedence for the employment of oxazolidinone 300.\(^{149}\) The auxiliary 295 could be utilised again in the synthesis of bromide 300. In this case, reaction of oxazolidinone 295 with chloride 301, which was synthesised from commercially available 2-bromo-2-methylpropanoic acid by stirring with oxalyl chloride in dichloromethane overnight, afforded bromide 300 (Scheme 96). Unfortunately attempted aldol reactions of the newly formed bromide 300 with acrolein 291, mediated by titanium tetrachloride (TiCl₄) in dichloromethane resulted in the formation of the debrominated product 299 and none of the desired β-hydroxyketone 302 was observed.

Reagents and conditions: a) nBuLi, THF, -78 °C, 20 min, bromide 301, -78 °C, 2 h, 49%.

**Scheme 96:** Attempted synthesis of alkene 298.

As attempts to obtain the desired chiral alcohol 298 proved unsuccessful it was decided to move forward to the nitrile oxide cycloaddition with the racemic alcohol 286 to find the optimum conditions for this key coupling step.

### 3.2.4 Nitrile oxide cycloaddition

With all the fragments in hand, focus turned towards the nitrile oxide cycloaddition itself. The acetonide protected oxime 274 and alkene 286 coupling was tried first. Attempts to form the chloride 303 in situ using sodium hypochlorite (NaOCl) failed to produce cycloadduct 304. Therefore hydroximoyl chloride 303 was
synthesised by reaction with \( N \)-chlorosuccinimide (NCS) and isolated before reacting with triethylamine (NE\(_3\)) in the presence of alkene 286 to afford isoxazoline 304 in 50% yield (Scheme 97).

Reagents and conditions: a) NCS, EtOH, pyridine, rt, 3 h, 95%; b) NE\(_3\), CH\(_2\)Cl\(_2\), -40 °C to rt, o/n, 50%.

Scheme 97: Nitrile oxide cycloaddition of oxime 274 and alkene 286.

Although there is little or no literature precedent for this reaction employing an alkene containing a quaternary centre β to the alkene,\(^{150}\) this promising result prompted attempts to be made employing these conditions for the synthesis of isoxazoline 305. The conditions used for the formation of hydroximoyl chloride 303 could not be used for the synthesis of chloride 306 due to the labile nature of the TBS protecting group. DMF was used as an alternative solvent to give chloride 306 in good yield (Table x).

The previously established conditions of NE\(_3\) in CH\(_2\)Cl\(_2\) were employed in the synthesis of cycloadducts 305-309. The best yields were obtained for the NOC reaction of alkene 286 and chloride 306 affording cycloadduct 305 in 35% yield (Table 5, entry 1). Different alkenes were selected in an attempt to improve the yields of the reaction. It was envisaged that employing alkene 297, synthesised earlier by the aldol reaction, could improve the yield and allow for ready access to cycloadduct 305 at a later stage. Unfortunately the yield of the reaction was only 32% (Table 5, entry 2). Changes to the alkene substituent by removing the steric bulk of the geminal dimethyl group to afford alkene 310 surprisingly resulted in a low yield of 12% (Table 5, entry 3). The ester functionality was also removed and substituted as a silyl protected alcohol 311. In this case, a low yield of only 8% was obtained when the NOC reaction was attempted (Table 5, entry 4).
Table 5: Different alkenes surveyed in the nitrile oxide cycloaddition reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime $x$</th>
<th>Alkene</th>
<th>Result $b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnO$\text{Cl}$ OH OTBS 306</td>
<td>$\text{Me Me Me}$</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>BnO$\text{Cl}$ OH OTBS 306</td>
<td>297</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>BnO$\text{Cl}$ OH OTBS 306</td>
<td>$\text{Me Me}$</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>BnO$\text{Cl}$ OH OTBS 306</td>
<td>311</td>
<td>8%</td>
</tr>
</tbody>
</table>

a) NCS, DMF, rt, 2 h, 83%; b) NEt$_3$, CH$_2$Cl$_2$, -40 °C to rt, o/n.

Alkene 310 (Table 5, entry 3) was synthesised by aldol reaction between acrolein 291 and ethyl acetate 312 (Scheme 98). This alkene was synthesised with the aim that removal of the steric bulk by way of the double methyl group would allow for easier access to the nitrile oxide cycloaddition product 308 and the methyl substituents could be introduced at a later stage.

Reagents and conditions: a) EtOAc 312, LiHMDS, THF, -78 °C, 15 min, aldehyde 291, THF, -78 °C, 2 h, 45%.

Scheme 98: Synthesis of alkene 310.

Alkene 311 (Table 5, entry 4) was obtained from neopentyl glycol 313 by mono protection as a TBS ether 314 followed by Swern oxidation of the remaining alcohol to afford aldehyde 291. Grignard addition of vinylmagnesium bromide afforded alkene 311 in 91% yield (Scheme 99). The aim in synthesising this alkene was to remove H-bonding between the ester functionality and the free alcohol of 286 by using a protected alcohol in which less H-bonding can occur.
Reagents and conditions: a) imidazole, DMAP, TBSCl, CH$_2$Cl$_2$, rt, 12 h, 80%; b) DMSO, CH$_2$Cl$_2$, (COCl)$_2$, -78 °C, 1 h, NEt$_3$, rt, 88%; c) vinylMgBr, THF, 0 °C, 1 h, 91%.

Scheme 99: Synthesis of alkene 311.

Several other conditions were surveyed in an attempt to improve the yield of the reaction to access isoxazoline 305 (Table 6). Changing the base from triethylamine to potassium carbonate improved the yield slightly to 42% (Table 6, entry 1). Attempts to synthesise the chloride 306 in situ by reacting oxime 248 with tert-butyl hypochlorite (tBuOCl) proved unsuccessful with the isolation of oxime 248 and alkene 286 in both cases (Table 6, entry 2-3). Hypervalent iodine-induced cycloaddition was investigated using either (diacetoxyiodo)benzene (DIB) or phenyl iodine bis(trifluoroacetate) (PIFA). Recently it was reported that treatment of oximes with hypervalent iodine led to the rapid development of the nitrile oxide directly. This is an advantage for the reaction as it can be executed in one pot without isolation of chloride 306 and short reaction times are necessary. Unfortunately the desired cycloadduct 305 was not detected in the complex mixtures of products obtained (Table 6, entry 4-5).

Table 6: Conditions tried for the nitrile oxide cycloaddition of 248 and 286.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime x</th>
<th>Conditions</th>
<th>Temperature and Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>N-Chloro-313</td>
<td>K$_2$CO$_3$, CHCl$_3$</td>
<td>0 °C to rt, 16 h</td>
<td>42% 305</td>
</tr>
<tr>
<td>2</td>
<td>248</td>
<td>tBuOCl, NaI, 2,6 lutidene, dioxane</td>
<td>rt, 18 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>3</td>
<td>248</td>
<td>tBuOCl, iPrOH, iPrMgBr, CH$_2$Cl$_2$</td>
<td>-78 °C to rt, 16 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>4</td>
<td>248</td>
<td>DIB, MeOH, TFA,</td>
<td>rt, 4 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>248</td>
<td>PIFA, dioxane, H$_2$O</td>
<td>rt, o/n</td>
<td>complex mixture, no 305</td>
</tr>
</tbody>
</table>

a) NCS, DMF, rt, 2 h, 83%;
3.2.5 Reduction of nitrile oxide cycloadduct 305

With the isoxazoline 305 in hand, albeit in moderate yield, focus next turned to the reduction of the isoxazoline 305 to β-hydroxyketone 247. This reaction can be carried out by different methods (Scheme 100). The most common method involves reduction over Raney nickel (Raney-Ni) in the presence of an acid. This procedure however, can sometimes promote acid-catalyzed elimination to form enone 316. Cycloadduct 317 can also be opened by molybdenum hexacarbonyl to afford the β-hydroxyketone 318.\cite{126}

![Scheme 100: Reduction of isoxazoline 317.\cite{126}](image)

The reduction of isoxazoline 305 using molybdenum hexacarbonyl was attempted first (Table 7, entry 1). However none of the desired β-hydroxyketone 247 was obtained. It had been previously observed by Furstner et al.\cite{153} that the presence of a free hydroxyl group adjacent to the heterocycle prohibited the use of Mo(CO)\(_6\). Attention therefore turned to carrying out the reduction over Raney-Ni with an acid (Table 7, entries 2-5). Unfortunately the use of Raney-Ni with several different acidic conditions resulted in complex mixtures that contain elimination product 319 (Table 7, entry 5). The use of iron metal in place of Raney-Ni led to decomposition of the isoxazoline 305 (Table 7, entry 6).\cite{154}

![Table 7: Attempted reduction of cycloadduct 305 to β-hydroxyketone 247.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Solvent</th>
<th>Acid</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mo(CO)(_6)</td>
<td>MeCN/H(_2)O</td>
<td>None</td>
<td>Reflux, 4 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>2</td>
<td>Raney-Ni</td>
<td>THF/H(_2)O</td>
<td>B(OH)(_3)</td>
<td>H(_2) atmosphere, rt, 16 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>3</td>
<td>Raney-Ni</td>
<td>THF/H(_2)O</td>
<td>HCl</td>
<td>H(_2), rt, 16 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>4</td>
<td>Raney-Ni</td>
<td>MeOH/H(_2)O</td>
<td>AcOH</td>
<td>H(_2), H-cube*, 20 psi, 1 mL/min, rt</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Raney-Ni</td>
<td>MeOH/H(_2)O</td>
<td>AcOH</td>
<td>H(_2), rt, 4 h</td>
<td>Complex mixture containing 319</td>
</tr>
<tr>
<td>6</td>
<td>Fe</td>
<td>EtOH/H(_2)O</td>
<td>NH(_3)Cl</td>
<td>80 °C, 1 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
3.3 **Aldol reaction pathway**

As the nitrile oxide cycloaddition pathway proved problematic in accessing the desired β-hydroxyketone 247, it was decided to attempt the aldol reaction as the key step in the construction of cyclisation precursor to the cephalosporolides H and I. Conveniently, the required aldol coupling components had been synthesised previously as starting materials for the aforementioned isoxazoline route (Scheme 101). Cephalosporolides H and I would be obtained from the common spiroacetal precursor 164, which itself can be obtained by the double deprotection of β-hydroxyketone 165. The cyclisation precursor 165 could be obtained from an aldol reaction between methyl ketone 166 and aldehyde 320. A Wacker oxidation of previously synthesised alkene 285 should afford methyl ketone 166. Aldehyde 320, the other coupling partner could be obtained via ozonolysis of alkene 286, synthesised previously from alcohol 169.

![Scheme 101: Revised retrosynthetic analysis of cephalosporolide H and I.](image)

The aldol reaction would allow access to the desired β-hydroxyketone 165 without the problematic reduction step from the NOC pathway. This pathway was originally discarded due to the low yields obtained in the reaction when employed in the synthesis of cephalosporolides E 24 and F 25. However as we were unable to obtain the desired β-hydroxyketone 165 from the NOC pathway, the next logical pathway was to attempt the aldol reaction as we could easily prepare the coupling partners from existing alkenes 285 and 286.
3.3.1 Synthesis of ketone 166

Ketone 166 was first synthesised from glycidol 281, while alkene 285 was synthesised via the established route used in the aforementioned NOC pathway. Benzyl protection followed by Jacobsen’s HKR enabled access to enantiopure epoxide 283 (Scheme 102). Terminal ring opening with allyl cuprate reagent and TBS protection of the resultant alcohol led to alkene 285. Wacker oxidation of the terminal alkene 285 employing the reaction conditions established in the previous chapter (Section 2.2.3) afforded methyl ketone 166 in 64% yield.

Reagents and conditions: a) BnBr, NaH, DMF, 0 °C to rt, o/n, 84%; b) AcOH, THF, H₂O, (R,R)-salen Co II complex A, 0 °C to rt, 16 h, 48%; c) CuI, allylMgBr, THF, -40 °C to rt, 3 h, 70%; d) TBSCl, imidazole, CH₂Cl₂, rt, 16 h, 70%; e) PdCl₂, CuCl, DMF, H₂O, O₂, rt, 4 h, 64%.

Scheme 102: Synthesis of ketone 166.

3.3.2 Synthesis of aldehyde 320

Alkene 286 was previously synthesised for the NOC pathway via Swern oxidation of commercially available alcohol 169 followed by Grignard addition to the resultant aldehyde 251. Protection of the secondary alcohol of alkene 286 as a TBS ether 321 followed by ozonolysis afforded aldehyde 320 (Scheme 103).

Reagents and conditions: a) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, 1 h, NEt₃, rt, 89%; b) vinylMgBr, THF, 0 °C, 3 h, 73%; c) imidazole, DMAP, TBSCl, DMF, 0 °C to rt, o/n, 61%; d) O₃, CH₂Cl₂, DMS, -78 °C to rt, o/n, 91%.

Scheme 103: Synthesis of aldehyde 320.

Aldehyde 322 was also prepared using a similar method (Scheme 104). Alkene 286 was protected by chloromethyl ethyl ether (EMCl) to afford 323, followed by ozonolysis to afford aldehyde 322.

Reagents and conditions: a) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, 1 h, NEt₃, rt, 89%; b) vinylMgBr, THF, 0 °C, 3 h, 73%; c) DIPEA, EMCl, CH₂Cl₂, rt, 12 h, 69%; d) O₃, CH₂Cl₂, DMS, -78 °C to rt, o/n, 90%.

Scheme 104: Synthesis of aldehyde 322.

The TBS and EM protecting groups were chosen for the aldehyde as they would allow for the acid catalysed double deprotection and in situ cyclisation of the newly formed β-hydroxyketone to spiroacetal 164 (Scheme 105).
3.3.3 Aldol reaction

With aldehydes 320, 322 and methyl ketone 166 in hand, attention turned to the aldol reaction (Scheme 106). This reaction is similar to the reactions carried out in the previous chapter and therefore optimised conditions for the previous transformation were first attempted. Disappointingly, use of the previously established conditions employing MgBr₂·OEt₂ in dichloromethane with either TBS or EM protected aldehydes 320 and 322 (Table 8, entry 1-2) failed to produce the desired β-hydroxyketone and both starting ketone 166 and aldehydes 320 and 322 were recovered.

A variety of other conditions were surveyed in an attempt to effect the synthesis of β-hydroxyketone 324 and 325 (Table 8). Use of BF₃·OEt₂ as the Lewis acid for the Mukaiyama aldol reaction also afforded no reaction (Table 8, entry 3-4). As the protected hydroxylaldehydes 320 and 322 were used as racemates, the stereoselectivity of the aldol reaction was no longer of concern and more reactive conditions were investigated. The in situ generation of a lithium enolate by reaction of ketone 166 with LDA before addition of either aldehyde 320 or 322, unfortunately only led to the isolation of ketone 166 after work up (Table 8, entry 5-6). The in situ formation of the boron enolate was next attempted by reacting ketone 166 with dicyclohexylboron chloride (cy₂BCl) in Et₂O at -78 °C followed by the addition of either aldehyde 320 or 322 and allowing the reaction to warm to room temperature overnight. In both cases, ketone 166 and aldehyde 320 or 322 were the only products detected (Table 8, entry 7-8).
Table 8: Aldol conditions screened.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone 166 or silyl enol ether</th>
<th>Aldehyde R=TBS or EM</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS enol ether 326</td>
<td>TBS</td>
<td>CH₂Cl₂, MgBr₂·OEt₂, -78 °C to rt o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>2</td>
<td>TMS enol ether 326</td>
<td>EM</td>
<td>CH₂Cl₂, MgBr₂·OEt₂, -78 °C to rt o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>3</td>
<td>TMS enol ether 326</td>
<td>TBS</td>
<td>CH₂Cl₂, BF₃·OEt₂, -78 °C to rt, 4 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>4</td>
<td>TMS enol ether 326</td>
<td>EM</td>
<td>CH₂Cl₂, BF₃·OEt₂, -78 °C to rt, 4 h</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>5</td>
<td>Ketone 166</td>
<td>TBS</td>
<td>LDA, THF, -78 °C, 2 h</td>
<td>Ketone 166 only</td>
</tr>
<tr>
<td>6</td>
<td>Ketone 166</td>
<td>EM</td>
<td>LDA, THF, -78 °C to rt, o/n</td>
<td>Ketone 166 only</td>
</tr>
<tr>
<td>7</td>
<td>Ketone 166</td>
<td>TBS</td>
<td>Cy₂BCl, NEt₃, Et₂O, -78 °C to rt o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>8</td>
<td>Ketone 166</td>
<td>EM</td>
<td>Cy₂BCl, NEt₃, Et₂O, -78 °C to rt, o/n</td>
<td>Recovered starting material</td>
</tr>
</tbody>
</table>

a) TMSOTf, NEt₃, CH₂Cl₂, 30 min, 0 °C.

3.4 Barbier-type allylation reaction pathway

Our initial retrosynthesis relied upon the installation of the β-hydroxyketone 247 at the key coupling step. In view of the above disappointing results for the aldol reaction, a re-evaluation of the available options was needed (Scheme 80). It was decided to try a new revision hinging on the coupling of aldehyde 255 and bromide 327 to afford alcohol 328 (Scheme 106). Oxidation of the secondary alcohol followed by asymmetric dihydroxylation should install the desired syn stereochemistry of the β-hydroxyketone 329, the cyclisation precursor for cephalosporolides H and I. This strategy would allow for the late stage installation of the diol at C-3 and C-4, thereby removing some of the steric bulk about the reactive centre.
Before the allylation reaction could be attempted the starting materials, bromide 327 and aldehyde 255, needed to be synthesised.

### 3.4.1 Synthesis of bromide 327

Bromide 327 was synthesised from aldehyde 315, which in turn was synthesised via the aforementioned NOC pathway from neopentyl glycol 313 by mono protection of the diol followed by Swern oxidation (Scheme 107). HWE reaction of aldehyde 315 with triethyl phosphonoacetate 270 afforded ester 330 which was reduced by DIBAL-H to the corresponding alcohol 331. Bromination of alcohol 331 with carbon tetrabromide and triphenylphosphine then afforded the desired coupling partner bromide 327.

**Scheme 107:** Synthesis of bromide 327.

*Reagents and conditions: a) imidazole, DMAP, TBSCl, CH₂Cl₂, rt, 12 h, 80%; b) DMSO, CH₂Cl₂, (COCl)₂, -78 °C, 1 h, NEt₃, rt, 88%; c) triethyl phosphonoacetate, NaH, THF, 0 °C to rt, o/n, 63%; d) DIBAL-H, CH₂Cl₂, -78 °C, 3 h, 94%; e) PPh₃, CB₃, CH₂Cl₂, 0 °C, 20 min, 62%.*
3.4.2 Allylation reaction

As aldehyde 255 has been previously synthesised for the NOC pathway, the coupling between aldehyde 255 and bromide 327 was next investigated (Scheme 108).

![Scheme 108: Synthesis of alcohol 255.](image)

Different metals were surveyed to facilitate the synthesis of alcohol 328 (Table 9). The first reaction conditions attempted (Table 9, entry 1) involved use of indium in aqueous DMF. A recent review on the use of indium in organic synthesis illustrated the versatility of indium metal in the Barbier type allylation reaction. The advantage of indium in this system is that the reaction can be performed in the presence of water and the metal does not require activation by sonification or acid catalysis. Unfortunately when the reaction was performed using aldehyde 255 and bromide 327, no desired alcohol 328 was obtained and the starting materials were isolated exclusively.

Next, chromium dichloride (CrCl₂) in THF was tried allowing the reaction to warm from 0 °C to room temperature overnight (Table 9, entry 2). These conditions were chosen based on the report by Taddei et al. for the synthesis of alcohol 332 from aldehyde 333 with bromide 334 (Scheme 109). Unfortunately no desired alcohol 328 was observed when this method was applied to our synthesis.

![Scheme 109: Synthesis of alcohol 332.](image)

Our next attempt was based on literature precedence by Loh et al. in which the metal-mediated allylation reaction was attempted in aqueous media. The allylation reaction of aldehyde 335 with cinnamyl bromide 336 in the presence of tin and H₂O afforded alcohol 337 exclusively in 80% yield (Scheme 110). Disappointingly, when the same conditions were applied to our reaction decomposition of the reagents was the result (Table 9, entry 3).

![Scheme 110: Synthesis of alcohol 337.](image)
The next metal tried was samarium diiodide (SmI₂) in THF (Table 9, entry 4). A commercial solution of SmI₂ (0.1 M in THF) was tested and the best results were obtained with multiple additions of 5 mol % SmI₂ over 6 h. Unfortunately this procedure only led to the isolation of 10% alcohol 328.

The last two metals surveyed were magnesium and zinc (Table 9, entries 5-10). The magnesium metal was activated for the reaction by the addition of iodine and 1,2-dibromoethane before addition of the bromide 327. The solution was stirred for 15-20 min at -78 °C and aldehyde 255 was added. The reaction was then allowed to warm to rt overnight. Unfortunately no desired alcohol 328 was detected.

The allylation reaction carried out in the presence of zinc had more promising results. Activation of the metal by sonication in the presence of cerium chloride gave a 12% yield of the desired alcohol 328 (Table 9, entry 6). Changing the activation conditions to LiCl, 1,2-dibromoethane and TMSCl resulted in the formation of the TBS deprotected alcohol, again in low yield.

Donnelly et al. recently described the reaction of bromide 338 with aldehyde 339 in the presence of zinc and bismuth triiodide (BiI₃). This afforded alcohol 340 in 63% yield (Scheme 111). The Bi(0) salt was formed first by stirring zinc powder and BiI₃ in THF at room temperature for 1 h. Bromide 338 and aldehyde 339 were added and the reaction stirred at reflux for 2 h.

Reagents and conditions: a) Zn, BiI₃, THF, rt, 1 h, bromide 338, aldehyde 339, reflux, 2 h, 63%.

Scheme 111: Synthesis of alcohol 340.

As BiI₃ was not readily available in our laboratory bismuth tribromide (BiBr₃) was used in its place (Table 9, entry 8). The reaction of 327 and 255 using BiBr₃ however did not afford the desired alcohol 328 and only the starting bromide 327 and aldehyde 255 were obtained. Heating the reaction to reflux led to decomposition of aldehyde 255.
The best results were achieved by activating the Zn by stirring with a crystal of iodine in THF until the solution turned colourless (Table 9, entry 9). The bromide 327 was added and the reaction was stirred for 10-15 min, at which point aldehyde 255 was added and the reaction stirred at room temperature overnight. Unfortunately the yield of this reaction was only 25% and in trying to scale up the reaction from 50 mg to 200 mg no product 328 was formed. Also, the reaction was not reliable and the results varied significantly with every attempt. The solvent was changed to DMF in an attempt to improve the yield but although alcohol 328 was formed the yield was only 23% (Table 9, entry 10).

Table 9: Allylation conditions attempted.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Solvent</th>
<th>Activation</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In</td>
<td>DMF/H2O</td>
<td>None</td>
<td>rt, o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>2</td>
<td>CrCl2</td>
<td>THF</td>
<td>None</td>
<td>0 °C to rt o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>3</td>
<td>Sn, CH2Cl2/H2O</td>
<td>None</td>
<td>rt, o/n</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SmI3</td>
<td>THF</td>
<td>None</td>
<td>0 °C, 6 h</td>
<td>10% yield 328</td>
</tr>
<tr>
<td>5</td>
<td>Mg Et2O</td>
<td>I2, 1,2-dibromoethane</td>
<td>-78 °C to rt o/n</td>
<td>Recovered starting material</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Zn</td>
<td>THF</td>
<td>CeCl3, sonication</td>
<td>rt, o/n</td>
<td>12% yield 328</td>
</tr>
<tr>
<td>7</td>
<td>Zn</td>
<td>THF</td>
<td>LiCl, 1,2-dibromoethane, TMSCl</td>
<td>rt, o/n</td>
<td>TBS deprotection</td>
</tr>
<tr>
<td>8</td>
<td>Zn</td>
<td>THF</td>
<td>BiBr3</td>
<td>rt, o/n</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>9</td>
<td>Zn</td>
<td>THF</td>
<td>I2</td>
<td>rt, o/n</td>
<td>25% yield 328</td>
</tr>
<tr>
<td>10</td>
<td>Zn</td>
<td>DMF</td>
<td>I2</td>
<td>rt, o/n</td>
<td>23% yield 328</td>
</tr>
</tbody>
</table>
3.5 **Dithiane reaction pathway**

The inconsistent results associated with the above allylation reaction prompted the investigation of yet another reaction pathway to access β-hydroxyketone 329. It was next decided to try umpolung alkylation chemistry for the construction of the cyclisation precursor (Scheme 112). Bromide 327 from the previous pathway could be coupled to dithiane 252 to afford dithiane 341. This resultant dithiane 341 could be converted to the desired β-hydroxyketone 329 in two steps; Sharpless asymmetric dihydroxylation and dithiane conversion to the corresponding ketone. Further deprotection and cyclisation reactions would afford the desired spiroacetal precursor 164.

![Scheme 112: Retrosynthetic analysis of cephalosporolides H and I.](image)

3.5.1 **Synthesis of dithiane 252**

The aldehyde 255 synthesised for the NOC pathway above (Scheme 89) was converted into 1,3-dithiane 252 using conditions established in the Brimble group which require the use of CoCl$_2$ and freshly distilled 1,3-propanedithiol in acetonitrile (Scheme 113).

![Scheme 113: Synthesis of dithiane 252.](image)

**Reagents and conditions:** a) 1,3-propanedithiol, CoCl$_2$, MeCN, rt, 2 h, 57%.

3.5.2 **Dithiane reaction**

To investigate the viability of 1,3-dithiane 252 as an umpolung alkylation agent, deuterium exchange experiments were performed to determine the ease and extent of its lithiation. The reactions were carried out in THF and quenched with deuterated water (D$_2$O) at times indicated in Table 10. Comparison of the integral for H-4 in dithiane 252 before and after the reaction allowed determination of the extent of lithiation. Both nBuLi
Ceephalsporolides H and I

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(Table 10, entry 1-5) and tBuLi (Table 10, entry 6-8) were attempted with addition of HMPA or DMPU at different temperatures and reaction times. Lithiation attempts employing DMPU as an additive afforded only 12% of 342 (Table 10, entry 4). The absence of deuterium incorporation was attributed to a suspected short lifetime of the intermediate anion. The use of a mixture of nBuLi-Bu₂Mg (4:1), which has been shown to lengthen the lifetime of the lithiated species, unfortunately gave 0% deuteration (Table 10, entries 9, 10).

Table 10: Conditions attempted for the lithiation of dithiane 252.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base used</th>
<th>Additives</th>
<th>Temperature</th>
<th>Time</th>
<th>% Deuteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nBuLi</td>
<td>None</td>
<td>-78 °C</td>
<td>30 min</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>nBuLi</td>
<td>None</td>
<td>-20 °C</td>
<td>15 min</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>nBuLi</td>
<td>None</td>
<td>0 °C</td>
<td>5 min</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>nBuLi</td>
<td>DMPU</td>
<td>0 °C</td>
<td>15 min</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>nBuLi</td>
<td>HMPA</td>
<td>-78 °C</td>
<td>30 min</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>tBuLi</td>
<td>None</td>
<td>-78 °C</td>
<td>30 min</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>tBuLi</td>
<td>HMPA</td>
<td>-78 °C</td>
<td>10 min</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>tBuLi</td>
<td>HMPA</td>
<td>-78 °C</td>
<td>30 min</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>nBuLi-Bu₂Mg</td>
<td>None</td>
<td>rt</td>
<td>20 min</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>nBuLi-Bu₂Mg</td>
<td>None</td>
<td>rt</td>
<td>1 h</td>
<td>0</td>
</tr>
</tbody>
</table>

As the best yield for the deuteration experiments was 12% (Table 10, entry 4) it was decided to try a different dithiane coupling reaction. 1,3-Dithiane 343 is commercially available and has been employed in a wide variety of umpolung reactions. In our case 1,3-dithiane 343 was lithiated by nBuLi at -20 °C for 1 h before the addition of bromide 327 (Scheme 114). Unfortunately none of the desired dithiane 344 was observed and only starting materials were recovered from the reaction. Deuterium exchange experiments showed that 1,3-dithiane 343 was lithiated during the reaction with no visible sign of H-1 in the NMR spectrum suggesting >90% deuteration. This implies that fault may lie with the bromide allylation partner.

Scheme 114: Alternative dithiane coupling.
3.6 Cross metathesis pathway

Our strategy was revised as indicated in Scheme 115, where one of the five-membered rings of the spiroacetal is formed prior to the coupling step. Spiroacetal 164, the precursor to the natural products cephalosporolides H and I, can be obtained via oxidative radical cyclisation of lactone 345. The stereochemistry at C-3 and C-4 of the lactone could be obtained by Sharpless asymmetric dihydroxylation of alkene 346, which in turn can be introduced via cross metathesis of alkene 347 with alkene 260. Glycidol 281 and alcohol 169 can again be employed for the synthesis of alkenes 347 and 260, respectively.

Scheme 115: Revised retrosynthesis.
3.6.1 Cross metathesis background

The cross metathesis reaction involves an intermolecular exchange of alkylidene groups between two alkenes catalysed by a transition metal.\textsuperscript{163} A variety of possible products can be synthesised due to the lack of a dominant driving force (Scheme 116).

![Scheme 116: Possible products from the cross metathesis reaction.\textsuperscript{163}](image)

The availability of catalysts such as Grubbs’ I \textsuperscript{348} and II \textsuperscript{349} as well Schrock’s molybdenum catalyst \textsuperscript{350} (Figure 24) has expanded the variety of functional groups amenable to the cross metathesis reaction.

![Figure 24: Structures of cross metathesis catalysts Grubbs’ I \textsuperscript{348}, Grubbs’ II \textsuperscript{349} and Schrock’s molybdenum catalyst \textsuperscript{350}](image)

Therefore, due to the lack of stereoselective and chemoselective control in this reaction, a general model was needed. Grubbs and co-workers\textsuperscript{164} developed a general model based on the ability of alkenes to homodimerise. Therefore, alkenes can be classed into four groups

1. **Type 1**: rapid homodimerisation with the resultant homodimer available for further reactions.
2. **Type 2**: slow homodimerisation with homodimers slightly reactive
3. **Type 3**: no homodimerisation
4. **Type 4**: spectators- do not take part in the cross metathesis reaction but also do not deactivate the catalyst.

Overall there is a decrease in alkene reactivity from type 1 to type 4. However how the alkenes are classified greatly depends on the catalyst employed (Table 11).
### Alkene classification for selective cross metathesis

<table>
<thead>
<tr>
<th>Olefin Type</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Terminal alkenes</td>
<td>● Terminal alkenes</td>
<td>● Terminal alkenes</td>
<td>● Vinyl nitro alkenes</td>
</tr>
<tr>
<td></td>
<td>● 1° Allylic alcohols</td>
<td>● Ally silanes</td>
<td>● 3° Allyl amines</td>
<td>● 1,1-Disubstituted alkenes</td>
</tr>
<tr>
<td></td>
<td>● Esters</td>
<td>● 1° Allylic alcohols</td>
<td>● Vinyl siloxanes</td>
<td>● Disubstituted α,β-unsaturated carbonyls</td>
</tr>
<tr>
<td></td>
<td>● Allyl boronate esters</td>
<td>● Ethers</td>
<td>● 3° Allyl amines</td>
<td>● Vinyl nitro alkenes</td>
</tr>
<tr>
<td></td>
<td>● Allyl halides</td>
<td>● Ethers</td>
<td>● 3° Allyl amines</td>
<td>● Trisubstituted allyl alcohols (protected)</td>
</tr>
<tr>
<td></td>
<td>● Styrenes (small ortho subs.)</td>
<td>● Ally boronate esters</td>
<td>● 3° Allyl amines</td>
<td>● 1,1-Disubstituted alkenes</td>
</tr>
<tr>
<td></td>
<td>● Allyl silanes</td>
<td>● Ally halides</td>
<td>● 3° Allyl amines</td>
<td>● Disubstituted α,β-unsaturated carbonyls</td>
</tr>
<tr>
<td></td>
<td>● Allyl silanes</td>
<td>● Ally halides</td>
<td>● 3° Allyl amines</td>
<td>● Vinyl nitro alkenes</td>
</tr>
<tr>
<td></td>
<td>● Allyl sulphides</td>
<td>● Ethers</td>
<td>● 3° Allyl amines</td>
<td>● Trisubstituted allyl alcohols (protected)</td>
</tr>
<tr>
<td></td>
<td>● Allyl sulphides oxides</td>
<td>● Ethers</td>
<td>● 3° Allyl amines</td>
<td>● 1,1-Disubstituted alkenes</td>
</tr>
<tr>
<td></td>
<td>● Protected allyl amines</td>
<td>● Ethers</td>
<td>● 3° Allyl amines</td>
<td>● 1,1-Disubstituted alkenes</td>
</tr>
</tbody>
</table>

**Note:** The table outlines different types of olefins and their associated classes based on the selective cross metathesis process.
With respect to our current objectives, it has been observed that alkenes with fully substituted \( \alpha \)-quaternary centres primarily give *trans* selectivity in the cross metathesis reaction when Grubbs’ II is employed.\(^{164}\)

An example of this is seen in the synthesis of olefin 351 (Scheme 1).\(^{165}\) The cross metathesis was carried out with multiple additions of Grubbs’ II catalyst and afforded olefin 351 and dimer 352. The dimer 352 itself could be recycled to give olefin 351. Due to the steric hindrance abundant in both alkenes a large quantity of the Grubbs’ II catalyst was employed in this reaction.

\[ \text{Reagents and conditions: a) 20 mol\% Grubbs’ II, dibenzyl ether, 23 °C, 49 h, 61\% olefin 351, 22\% dimer 352; b) 31 mol\% Grubbs’ II, dibenzyl ether, 23 °C, 42 h, 65\%.} \]

**Scheme 117:** Synthesis of olefin 351.\(^{165}\)

### 3.6.2 Synthesis of alkene 347

Alkene 347, the first coupling partner for the cross metathesis reaction, could be synthesised utilising available starting material alkene 284, synthesised previously for the NOC pathway in three steps from glycidol 281. Ozonolysis of alkene 284 gave the tetrahydrofuran 353 as a 1:1 mixture of cis/trans isomers which was reacted with allyl trimethylsilane (allylTMS) to install the desired allyl side-chain of 347 as a 1:1 mixture.

\[ \text{Reagents and conditions: a) BnBr, NaH, DMF, 0 °C to rt, o/n, 84\%; b) AcOH, THF, H}_2\text{O}, (R,R)-salen Co\(^{II}\)A, 0 °C to rt, 16 h, 48\%; c) CuI, allylMgBr, THF, -40 °C to rt, 3 h, 70\%; d) O}_3, \text{CH}_2\text{Cl}_2, \text{MeOH}, \text{PPh}_3, -78 °C to rt 15 h, 71\%; e) allylTMS, \text{CH}_2\text{Cl}_2, BF}_3\cdot\text{OEt}_2, \text{rt}, 3 h, 83\%.} \]

**Scheme 118:** Synthesis of alkene 347.
3.6.3 Synthesis of alkene 260

Next attempted was the synthesis of alkene 260 from previously synthesised aldehyde 251 using a Wittig reaction (Scheme 119). The Wittig reaction was carried out on aldehyde 251 in the presence of methyltriphenylphosphonium bromide in THF at 0 °C and allowed to warm to room temperature over 2 h. Unfortunately the resulting alkene 260 was volatile and though was visible by TLC and crude NMR, attempts to purify it resulted in evaporation of the product.

Scheme 119: Attempted synthesis of alkene 261.

It was decided to synthesise alkene 354 that contains a larger UV-active benzyl ester substituent rendering it less volatile than methyl ester 260 (Scheme 120). Commercially available ester 169 was deprotected to give the acid 355 which underwent benzyl protection to 356. Swern oxidation of alcohol 356 afforded aldehyde 357 which was reacted in a Wittig olefination reaction to yield alkene 354.

Scheme 120: Synthesis of alkene 354.

In parallel, aldehyde 315 had already been prepared from neopentyl glycol 313 (Scheme 121), hence alkene 358 was also prepared. Wittig reaction of aldehyde 315 using LiHMDS and methyltriphenylphosphonium bromide afforded alkene 358 in moderate yield for use in the planned cross metathesis reaction.

Scheme 121: Synthesis of alkene 358.
3.6.4 Cross metathesis

With alkenes 347 and 358 in hand, the cross metathesis was attempted (Table 12). Grubbs’ II catalyst was employed due to the known propensity towards trans selectivity in the cross metathesis reaction with olefins containing an α-quaternary centre.\textsuperscript{164} All the reactions were carried out with a four-fold excess of alkene 358. The first reaction conditions attempted involved use of Grubbs’ II catalyst in dichloromethane by portionwise addition of 5 mol% of catalyst at 12 h intervals. After 48 h and the addition of 10 mol% Grubbs’ II, only 4% of the desired alkene 359 was obtained (Table 12, entry 1).

Previous cross metathesis studies carried out by a member of the Brimble group indicated an improvement in yield by carrying out the reaction neat. However, when the same conditions were applied only 3% yield of the desired alkene 359 was obtained (Table 12, entry 2).

A change of solvent to dichloroethane, which has a higher boiling point of 83 °C compared to 40 °C for dichloromethane, allowed for the reaction to be attempted at 80 °C with 20 mol% Grubbs’ II added portionwise over 48 h and afforded 11% of the desired alkene 359 (Table 12, entry 3). Use of the same conditions stirring the reaction at 80 °C for an extra 24 h increased the yield slightly to give 13% of 359 (Table 12, entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol %)\textsuperscript{a}</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield of heterodimer 359</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 Grubbs’ II</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>48 h</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>10 Grubbs’ II</td>
<td>Neat</td>
<td>rt</td>
<td>72 h</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>20 Grubbs’ II</td>
<td>C\textsubscript{2}H\textsubscript{4}Cl\textsubscript{2}</td>
<td>80 °C</td>
<td>48 h</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>20 Grubbs’ II</td>
<td>C\textsubscript{2}H\textsubscript{4}Cl\textsubscript{2}</td>
<td>80 °C</td>
<td>72 h</td>
<td>13%</td>
</tr>
</tbody>
</table>

a) 5 mol% loading of catalysis every 12 h.
In parallel, alkene 354 was synthesised and employed in the cross metathesis reaction (Table 13). The reaction was carried out in dichloroethane at 80 °C with the addition of 5 mol% catalyst portionwise over 48 h. These conditions afforded an 8% yield of alkene 360 (Table 13, entry 1). The reaction was then attempted neat with 15 mol% Grubbs’ II catalyst at 50 °C to afford 13% yield of the desired alkene 360 (Table 13, entry 2). The same amount of catalyst was employed in dichloroethane at 50 °C in the microwave over 6 h to afford the alkene 360 in 11% yield (Table 13, entry 3).

Recently, Abell et al.168 found that the addition of 10 mol% of the Lewis acid dicyclohexylboron chloride (cy2BCl) in the ring closing metathesis greatly improved the yield of the reaction. These conditions were applied to the cross-metathesis reaction between alkene 347 and alkene 354 in dichloroethane in the microwave at 50 °C over 8 h afforded 17% yield of the desired heterodimer 360 (Table 13, entry 4). Changing the solvent to toluene at 90 °C in the microwave with Lewis acid cy2BCl and 10 mol% Grubbs’ II afforded the best yield of 22% yield. Finally the reaction was attempted with 10 mol% Hoveyda-Grubbs’ II catalyst in an attempt to improve the yield, but unfortunately, no desired alkene 360 was detected.

**Table 13**: Cross metathesis conditions tried.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol %)</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Additives</th>
<th>Yield of heterodimer 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 Grubbs’ II</td>
<td>C2H4Cl2</td>
<td>80 °C</td>
<td>48 h</td>
<td>none</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>15 Grubbs II</td>
<td>Neat</td>
<td>50 °C</td>
<td>72 h</td>
<td>none</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>15 Grubbs II</td>
<td>C2H4Cl2</td>
<td>microwave, 50 °C</td>
<td>6 h</td>
<td>microwave</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>20 Grubbs’ II</td>
<td>C2H4Cl2</td>
<td>microwave, 50 °C</td>
<td>8 h</td>
<td>cy2BCl</td>
<td>17%</td>
</tr>
<tr>
<td>5</td>
<td>10 Grubbs’ II</td>
<td>toluene</td>
<td>microwave, 90 °C</td>
<td>2 h</td>
<td>cy2BCl</td>
<td>21%</td>
</tr>
<tr>
<td>6</td>
<td>10 Hoveyda-Grubbs’ II</td>
<td>C2H4Cl2</td>
<td>80 °C</td>
<td>72 h</td>
<td>none</td>
<td>Recovered starting materials</td>
</tr>
</tbody>
</table>
The low yields observed in our reactions are not surprising considering similar work recently published by Fernandes et al. They attribute the steric crowding in the vicinity of the olefin bond by the dimethyl group in olefin 361 to be the reason for no formation of the desired olefin 362 upon attempted cross-metathesis with olefin 151 (Scheme 122).

![Scheme 122: Attempted synthesis of olefin 362 by Fernandes et al.]

The removal of this dimethyl group allowed for easy access to olefin 156 in 75% yield and 7:1 (E/Z) ratio with low catalyst loading (Scheme 123).

![Scheme 123: Synthesis of olefin 156 by Fernandes et al.]

In our case, having the tetrahydrofuran ring system in alkene 347 has a beneficial effect on the cross metathesis reaction. Also a change from a chlorinated solvent (CH$_2$Cl$_2$ or C$_2$H$_4$Cl$_2$) to a less polar solvent (toluene) and the higher temperature employed, improved the yield from 17% to 21% and allowed for the recovery of alkene 354.
3.7 Pinacol coupling

In parallel with the cross metathesis reaction, the pinacol coupling reaction of 363 with 357 was also attempted (Scheme 124). Aldehyde 357 has been synthesised in the cross metathesis pathway (Scheme 120). Ozonolysis of the alkene 347 also formed in the cross metathesis pathway afforded aldehyde 363, the second coupling partner for the pinacol coupling reaction.

The pinacol reaction involves the formation of 1,2-diols 364 from the coupling of carbonyl compounds (Scheme 125). The mechanism is thought to proceed through one of two pathways shown below; either through one-electron reduction of carbonyl 365 to a ketyl radical anion 366 (pathway A) or less likely through a two-electron reduction to give 367 (pathway B). The radical pathway (A) can also be split into two with another radical reaction or the trapping of 366 with another carbonyl compound 368. In pathway B dianionic species 367 acts as a nucleophile and attacks a carbonyl compound 365 to give diol 364. The pathway that a given reaction will proceed through greatly depends on a variety of factors including pH, the metal and the type of solvent used.
The conditions used for the pinacol coupling were based on literature precedence by Pedersen et al.\textsuperscript{171} who described the coupling of a similar aldehyde 369 with aldehyde 370 giving high diastereofacial selectivity for diol 371 (Scheme 126). As the reaction often resulted in an inseparable mixture of diol 371 and lactone 372, the diol was not isolated but converted directly to the lactone.

\begin{center}
\begin{tabular}{ccc}
\textbf{Scheme 126: Pinacol coupling as described by Pederson et al.}\textsuperscript{171} & & \\
\end{tabular}
\end{center}

\textit{Reagents and conditions:} a) VCl\textsubscript{3}·(THF)\textsubscript{3}, Zn, CH\textsubscript{2}Cl\textsubscript{2}, rt, 2 d, 10% aq. sodium tartrate, rt, 6-15 h; b) benzene, PTSA, 1-2 h, 72%.

Unfortunately when the same conditions were applied to the attempted reaction of 363 and 357, the best yield obtained was 9% of the desired coupling product 373 and isolation of starting materials (Scheme 127). The reaction was not reliable and more often than not resulted in isolation of only starting materials.

\begin{center}
\begin{tabular}{ccc}
\textbf{Scheme 127: Pinacol coupling between aldehydes 365 and 357.} & & \\
\end{tabular}
\end{center}

\textit{Reagents and conditions:} a) Zn, VCl\textsubscript{3}·(THF)\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, 1 h, aldehydes 365 and 357, rt, o/n, 9%.

As at this stage, we had succeeded in obtaining alkene 360 from the cross metathesis reaction, albeit in low yield. Hence, it was decided to abandon the pinacol coupling and focus instead on the Sharpless dihydroxylation of alkene 360.
3.8 **Sharpless asymmetric dihydroxylation**

The Sharpless asymmetric dihydroxylation reaction to install the desired syn-diols 374 and 375 from alkene 360 (Scheme 128) was critical to the success of the project.

![Scheme 128: Sharpless asymmetric dihydroxylation of alkene 360.](image)

The dihydroxylation of alkenes utilising osmium tetroxide (OsO₄) is accelerated and proceeds in an asymmetric fashion by the addition of a chiral tertiary amine ligand to the reaction mixture to afford an enantiopure diol. The structures (DHQD)₂PHAL and (DHQ)₂PHAL shown below in Figure 25 are examples of commonly used ligands for this purpose.

![Figure 25: Cinchona alkaloid derivatives for the Sharpless asymmetric dihydroxylation.](image)

The reaction medium (Figure 26) is a biphasic system in that the active oxidant OsO₄ persists in the organic layer co-ordinated to the ligand while the re-oxidant, typically potassium ferricyanide or N-methyl morpholine N-oxide (NMO), persists in the aqueous layer. Following oxidation of the alkene, hydrolysis of the resulting osmate ester releases the diol, the ligand and the molecule of polar osmium (VI) glycolate which migrates to the aqueous layer upon hydrolysis. The use of methanesulfonamide is thought to accelerate the reaction at 0 °C which can improve selectivity.
Figure 26: Catalytic cycle for asymmetric dihydroxylation using K₃Fe(CN)$_6$ as co-oxidant in biphasic conditions.$^{172}$

The enantioselectivity can be determined by the mnemonic in Figure 27. If the alkene is orientated in the same way as depicted with the largest substituent on the southwest quadrant, oxidation from the top or $\beta$ face by DHQD ligands leads to diol 376. Oxidation from the bottom or $\alpha$-face affords diol 377. This diastereomeric interaction between the alkene substituents and ligand-osmium complex give rise to olefin diastereofacial selectivity and consequently the reaction relies on a significant steric difference between the olefin substituents.

Figure 27: Enantiofacial selectivity of the Sharpless asymmetric dihydroxylation reaction.$^{172}$
The mnemonic when applied to alkene 360 (Figure 28) demonstrates the products that should form in the Sharpless asymmetric dihydroxylation of alkene 360. Attack from the top or β-face by the (DHQD)$_2$PHAL ligand should afford the cis diols 374 and 375. Therefore, changing to the (DHQ)$_2$PHAL ligand should afford the opposite stereochemistry, diols 378 and 379, as attack is from the bottom or α-face is favoured.

Figure 28: Enantiofacial selectivity of the Sharpless asymmetric dihydroxylation of alkene 360.

Sharpless asymmetric dihydroxylation was carried out on the (E)-alkene 360 with (DHQD)$_2$PHAL ligand (Scheme 129). The expected result was the isolation of diols 374 and 375 and the TLC of the reaction mixture looked promising with two separable spots being observed during the reaction. Work up and isolation of these two spots did not give the expected diols but instead afforded lactones 345a and 345b (Scheme 129). Not surprisingly, the H-6 to H-9 nOe correlation remained inconclusive, so that the relative configuration of the tetrahydrofuran methine carbons C-6 and C-9 remain ambiguous. The $^1$H NMR spectra confirmed that the H-6 and H-9 methine protons were in different environments but pinning down the relative configuration of the tetrahydrofuran with respect to the lactone proved difficult due to the conformational flexibility about the bridging methylene.

Reagents and conditions: a) 5 mol% (DHQD)$_2$PHAL, methanesulfonamide, K$_2$CO$_3$, K$_3$Fe(CN)$_6$, OsO$_4$, rBuOH, H$_2$O, rt, 15 h, 73%, 1:1 mixture of diastereomers (345a:345b).

Scheme 129: Synthesis of lactones 345a and 345b.
To resolve this ambiguity the Sharpless asymmetric dihydroxylation of alkene 360 was performed in the presence of the opposite ligand (DHQ)_2PHAL (Scheme 130). Again lactones 380 and 381 were believed to have formed in 76% yield as a 1:1 mixture of diastereomers.

![Chemical structure of 360, 380, and 381](image)

**Reagents and conditions:** a) 5 mol% (DHQ)_2PHAL, methanesulfonamide, K$_2$CO$_3$, K$_3$Fe(CN)$_6$, OsO$_4$, tBuOH, H$_2$O, rt, 15 h, 76%, 1:1 mixture of diastereomers (380:381).

**Scheme 130:** Synthesis of lactones 380 and 381.

### 3.8.1 Stereochemistry

Comparisons were drawn between the $^1$H and $^{13}$C NMR spectra of all four lactones 345a, 345b, 380 and 381 as well as optical rotation values ($\alpha_D$ values) (Table 14). Firstly the $\alpha_D$ values for all four compounds are very different; the lactones formed using the (DHQD)$_2$PHAL ligand both have a positive $\alpha_D$ value, and the opposite is true of the lactones afforded from use of the (DHQ)$_2$PHAL ligand. The $^1$H NMR spectra also illustrate the differences between all four compounds. As previously mentioned in Chapter 1, five-membered rings are known to exhibit rapid pseudorotation and deformation in which the ring and its substituents may assume a continuous set of conformations, which make it difficult to assign the stereochemistry about the tetrahydrofuran ring. The position of the free hydroxyl group at C-3 of the lactone in correlation to the oxygen atom of the tetrahydrofuran ring has an influence on the conformation of the lactone, as H-bonding can possibly exist in some conformations. The position of the benzyl protecting group in space can also influence this interaction. There are some similarities between lactones 345a and 380 as shown in Table 14, H-6 as well as H-9 are both multiplets with similar chemical shift, whereas in lactones 345b and 381 the H-6 and H-9 multiplets are overlapping. Therefore they are in different environments. Also different are H-3 and H-4, in lactone 345b formed by using (DHQD)$_2$PHAL ligand, H-3 is a doublet at $\delta$ 3.95 ppm ($J = 3.4$ Hz) whereas in 345a the chemical shift of H-3 overlaps with H-6 at $\delta$ 5.40-4.00 ppm. A similar observation is present in the (DHQ)$_2$PHAL-derived lactones 380 and 381 where H-3 of lactone 381 is a triplet ($\delta$ 3.92 ppm, $J = 3.6$ Hz) and this same proton in lactone 380 overlaps with H-6 at $\delta$ 4.07-4.00 ppm.

By comparison of all the above data it was deduced that lactones 345a and 345b are indeed cis/trans diastereomers about the tetrahydrofuran ring respectively, but unfortunately the relative configuration of the tetrahydrofuran could not be determined.
Table 14: $^1$H and $^{13}$C NMR spectroscopic data for lactones.

![Structures of 345a, 345b, 380, and 381]

<table>
<thead>
<tr>
<th>Position</th>
<th>345a (400 MHz, CHCl$_3$)</th>
<th>345b (400 MHz, CHCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta^1$H (ppm)</td>
<td>Multiplicity</td>
</tr>
<tr>
<td>3</td>
<td>4.07-4.00</td>
<td>m</td>
</tr>
<tr>
<td>4</td>
<td>4.54-4.50</td>
<td>m</td>
</tr>
<tr>
<td>5</td>
<td>2.21-2.13</td>
<td>m</td>
</tr>
<tr>
<td>6</td>
<td>4.07-4.00</td>
<td>m</td>
</tr>
<tr>
<td>7</td>
<td>1.18-1.59</td>
<td>m</td>
</tr>
<tr>
<td>8</td>
<td>2.08-1.97</td>
<td>m</td>
</tr>
<tr>
<td></td>
<td>1.18-1.59</td>
<td>m</td>
</tr>
<tr>
<td>9</td>
<td>4.27-4.21</td>
<td>m</td>
</tr>
<tr>
<td>10</td>
<td>3.48</td>
<td>dtd 12.5, 10.2</td>
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<table>
<thead>
<tr>
<th>Position</th>
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<th>381 (400 MHz, CHCl$_3$)</th>
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<tbody>
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<td>Multiplicity</td>
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<tr>
<td>3</td>
<td>4.07-4.00</td>
<td>m</td>
</tr>
<tr>
<td>4</td>
<td>4.54-4.50</td>
<td>m</td>
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<tr>
<td>5</td>
<td>2.17-2.04</td>
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<td>6</td>
<td>4.07-4.00</td>
<td>m</td>
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<td>7</td>
<td>2.17-2.04</td>
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<tr>
<td>10</td>
<td>3.52</td>
<td>dd 10.0, 3.6</td>
</tr>
</tbody>
</table>
Crystallisation of lactone 380 from CH$_2$Cl$_2$/hexanes resulted in the isolation of thin white needles. X-ray crystallography analysis could only be obtained with 13% accuracy but suggests that the cis isomer was formed for lactone 380 (Figure 29).

Figure 29: Crystal structure of lactone 380 from (DHQ)$_2$PHAL reaction.

All the lactones were taken through to the cyclisation step with the objective that confirmation of the structure could be made at this point.
3.9 Oxidative radical cyclisation

The oxidative cyclisation approach provides a valuable alternative to the traditional acid-catalysed spirocyclisation of dihydroxyketones used for the synthesis of spiroacetals. It is particularly useful when acid-labile or sensitive substrates are involved. This method often facilitates the synthesis of what would be the kinetic products of a traditional spiroacetalisation reaction. The reaction mechanism of the intramolecular hydrogen abstraction has been reviewed\(^{59}\) and a modified version is shown in Scheme 131.

The proposed mechanism (Scheme 131) involves initial alkoxy radical formation by homolytic cleavage of the O-I bond in hypoiodite 63, which is formed by reacting alcohol 64 with iodosobenzene diacetate and iodine. The mechanism for formation of 5-membered rings proceeds through a 6-membered transition state 65. Hydrogen abstraction by the oxygen atom generates a new carbon radical 382, which upon oxidation to the cation intermediate 383 undergoes ring closure to form spiroacetal 3.

\[ 64 \xrightarrow{2\text{AcO}I} \xrightarrow{\text{PhI(OAc)}_2 + I_2} 63 \xrightarrow{\text{hv}} 65 \xrightarrow{I_2} 382 \xrightarrow{e^-} 383 \xrightarrow{H^+} 3 \]

**Scheme 131:** Mechanism for the oxidative radical cyclisation modified from Brimble *et al.*\(^{59}\)
3.9.1 Oxidative radical cyclisation of lactone 345a, 345b

The above mechanism when applied to lactone 345a (Scheme 132) affords a mixture of spiroacetals 164a and 164b. Hypoiodite 384b, formed by reacting lactone 345a with Phl(OAc)$_2$ and iodine, undergoes a photochemical homolytic cleavage of the O-I bond to form radical 385. Hydrogen abstraction by the oxygen atom of radical 385 generates a new carbon radical 386. This radical 386 is then oxidised to the cation intermediate 387 that is trapped by the C-3 hydroxyl group from either the α-face or β-face affording a 1:1 mixture of spiroacetals 164a and 164b. As the stereocentre at C-6 is destroyed in the cation intermediate lactones 345a and 345b should afford the same 1:1 mixture of spiroacetals 164a and 164b.

Pleasingly, the oxidative cyclisation of alcohols 345a and 345b proceeded with relative ease, to give, as expected, a 1:1 mixture of spiroacetals 164a and 164b. Lactone 345a, derived from the (DHQD)$_2$PHAL mediated dihydroxylation reaction, was treated with Phl(OAc)$_2$ and iodine in a CH$_2$Cl$_2$/hexane mixture to afford a 1:1 mixture of spiroacetals 164a and 164b in 51% yield (Scheme 133). When the same procedure was carried out on lactone 345b, also derived from the (DHQD)$_2$PHAL reaction, the same 1:1 mixture of spiroacetals 164a and 164b was obtained in 51% yield. This provides further evidence that the two diastereomeric lactones 345a and 345b, derived from the Sharpless asymmetric dihydroxylation differ only in the stereochemistry about C-6 of the tetrahydrofuran ring.

Scheme 132: Mechanism for the oxidative radical cyclisation of lactone 345a.
Chapter Three: Cephalosporolides H and I

Reagents and conditions: a) PhI(OAc)$_2$, I$_2$, CH$_2$Cl$_2$, hexane, 75 W, 1 h, 51%, 1:1 mixture of diastereomers; b) PhI(OAc)$_2$, I$_2$, CH$_2$Cl$_2$, hexane, 75 W, 1 h, 51%, 1:1 mixture of diastereomers.

Scheme 133: Synthesis of spiroacetals 164a and 164b.

To further illustrate this theory, the lactones 380 and 381 derived from the Sharpless dihydroxylation employing the opposite (DHQ)$_2$PHAL ligand were reacted in the oxidative radical cyclisation reaction (Scheme 134). Similar results were obtained with the isolation of a 1:1 mixture of diastereomeric spiroacetals 388 and 389 when lactone 380 was treated with the above procedure. The use of the other diastereomeric lactone 381 in the reaction also afforded a 1:1 mixture of diastereomeric spiroacetals 388 and 389.

Reagents and conditions: a) PhI(OAc)$_2$, I$_2$, CH$_2$Cl$_2$, hexane, 75 W, 1 h, 51%, 1:1 mixture of diastereomers; b) PhI(OAc)$_2$, I$_2$, CH$_2$Cl$_2$, hexane, 75 W, 1 h, 52%, 1:1 mixture of diastereomers.

Scheme 134: Synthesis of spiroacetals 388 and 389.
3.9.2 Stereochemistry

To determine the stereochemistry of the newly formed spiroacetals 164a, 164b, 388 and 389, we first need to examine the stereochemistry of the previously synthesised natural products of the cephalosporolide family (Figure 30). There is a distinct coupling pattern for H-4 in all the described spiroacetals. In synthetic cephalosporolide E 24 and ent-cephalosporolide E 85, H-4 resonates as a triplet at δ 5.17 ppm and δ 5.09 ppm respectively, which is attributed to the relationship between C-6 and C-4 having 6S,4S or 6R,4R stereochemistry. Conversely, in synthetic cephalosporolide F 25 and ent-cephalosporolide F 86 containing 6R,4S and 6S,4R stereochemistry respectively, H-4 resonates as a distinct doublet of doublet of doublets at δ 5.08 ppm and δ 5.02 ppm respectively. The absolute stereochemistry of cephalosporolides E 24 and F 25 and their enantiomers 85 and 86 have been confirmed by comparison of the αD values of all the synthetic spiroacetals to those of the isolated natural products. The X-ray crystal structures ent-cephalosporolide F 86 and of the precursor to ent-cephalosporolide E (2-hydroxycephalosporolide E 99) were obtained, further confirming their stereochemistry.

![Figure 30: Previously synthesised members of the cephalosporolide family.](image)

Recently, the stereochemistry of cephalosporolide H 144 and its C-6 epimer 28 (Figure 30), synthesised by Dudley et al. and Fernandes et al. have been determined based upon similarity to the spiroacetal structure of ent-cephalosporolides E 85 and F 86. In cephalosporolide H 144, the (R)-stereochemistry at C-4 was installed via a stereoselective reduction leaving only the stereochemistry at the spirocentre unknown. The spirocentre was
assigned as (S) due to the characteristic doublet of doublet of doublets splitting pattern observed for H-4 that resonated at $\delta$ 5.03 ppm ($J = 6.4, 3.8, 1.6$ Hz). As expected, H-4 in the epimer 28 resonates as a triplet at $\delta$ 5.07 ppm ($J = 4.9$ Hz). The spirocentre at C-6 was therefore assigned as 6$R$ similar to that of ent-cephalosporolide E 86. Two further diastereomers of cephalosporolide H, 390 and 391 were recently synthesised by Dudley et al. and differ from 28 and 144 only in the stereochemistry of the side-chain at C-9. Both diastereomers contain similar coupling patterns at C-4 to ent-cephalosporolides E 85 and F 86 and were therefore assigned as 6$S$ and 6$R$ respectively. Interestingly, the absolute stereochemistry of the natural product cephalosporolide H first assigned as (4$R$,6$R$) by Li et al. remains ambiguous as no X-ray crystal structure data for the individual diastereomers or conclusive NOESY correlations have been obtained. Nevertheless, Dudley et al. recently reassigned the stereochemistry of the isolated cephalosporolide H 28 to that of the synthetic 144. Their conclusions were primarily based on $\alpha_D$ values and comparison of the coupling pattern of H-4 with the known structures of ent-cephalosporolides E 85 and F 86.

The same approach was used to determine the stereochemistry of spiroacetals 164a-164b, synthesised in the current study (Table 15). Spiroacetals 164a and 164b differ only in the stereochemistry about the spirocentre (Figure 31). The stereochemistry could be determined using the characteristic coupling pattern for H-4. The (R)-stereochemistry at C-4 was installed via a Sharpless asymmetric dihydroxylation using (DHQD)$_2$PHAL. In spiroacetal 164a, H-4 resonates as a doublet of doublet of doublets at $\delta$ 5.02 ppm with a coupling constant of $J = 6.4, 3.7, 1.6$ Hz, suggesting 164a exhibits (S)-stereochemistry at the spirocentre. Conversely, the $^1$H NMR data of spiroacetal 164b exhibits a triplet at $\delta$ 5.06 ppm ($J = 4.8$ Hz) assigned as H-4 suggests (R)-stereochemistry at the spirocentre.

Figure 31: Spiroacetals 164a and 164b and cephalosporolide H 28 and 144.

Spiroacetals 388 and 389 (Table 15) contain the same core as the natural products penisporolides A 26 and B 27 (Figure 32) and are diastereomers of spiroacetals 164a and 164b. In these spiroacetals, the (3$S$,4$S$) stereochemistry of the lactone is similar to the stereochemistry of the natural products cephalosporolides E 24 and F 25. The (S)-stereochemistry at C-4 was installed via a Sharpless asymmetric dihydroxylation using (DHQ)$_2$PHAL. Again comparison of the $^1$H NMR coupling patterns observed for H-4 to cephalosporolide E 24 and F 25 can be used to assign the stereochemistry at C-6. In spiroacetal 388, H-4 resonates as a triplet at
δ 5.10 ppm ($J = 5.2$ Hz) supporting 6$\delta$ stereochemistry. Spiroacetal 389 can be assigned as 4$S$,6$R$ due to H-4 at δ 5.00 ppm resonating as a doublet of doublet of doublets with coupling constants $J = 6.3, 3.9, 1.5$ Hz.

![Image of spiroacetals 389 and 390]

**Figure 32:** Spiroacetals 388 and 389 and corresponding natural products penisporolides A 26 and B 27.

### 3.9.3 Assignment of stereochemistry

In summary the stereochemistry of the spiroacetals 164a, 164b, 388 and 389 has been assigned based on the following.

- The Sharpless asymmetric dihydroxylation reaction was carried out on a 1:1 mixture of olefin 360 using (DHQD)$_2$PHAL affording a 1:1 mixture of lactones 345a and 345b. Similarly (DHQ)$_2$PHAL gave lactones 380 and 381 as a 1:1 mixture of diastereomers. This suggests that the reactions afforded *cis/trans* isomers about the tetrahydrofuran ring (Figure 33).
- Each individual lactone when cyclised gave a 1:1 mixture of spiroacetals which differ only in the stereochemistry at the spiroacetal centre C-6, again implying a selective Sharpless dihydroxylation reaction.
- $^1$H NMR comparisons between all four spiroacetals show similar characteristic coupling patterns about H-4 to that of cephalosporolides E 24 and F 25 and to the newly synthesised cephalosporolide H 144 and its epimer 28.

All this information combined suggests that spiroacetals 164a and 164b differ only in the stereochemistry about the spirocentre with spiroacetal 164a being assigned as (3$R$,4$R$,6$\delta$,9$\delta$) and spiroacetal 164b as (3$R$,4$R$,6$R$,9$\delta$). The stereochemistry of spiroacetals 388 and 389, only differ in the stereochemistry at C-6 and have been assigned as (3$S$,4$S$,6$\delta$,9$\delta$) for spiroacetal 388 and (3$S$,4$S$,6$R$,9$\delta$) for spiroacetal 389 (Figure 33).
Figure 33: Stereochemical assignment of the four lactones 345a, 345b, 380 and 381 and their corresponding spiroacetals 164a, 164b, 388 and 389.
Table 15: $^1$H and $^{13}$C NMR data for spiroacetals 164a, 164b, 388 and 389.

<table>
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<td></td>
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</table>
Figure 34: $^1$H NMR spectra of spiroacetals 164a and 164b from the DHQD$_2$PHAL pathway.
Figure 35: $^1$H NMR spectra of spiroacetals 389 and 388 from the (DHQ)$_2$PHAL pathway.
Figure 36: $^1$H NMR spectra for initial cephalosporolide H 28 and reassigned cephalosporolide H 144.

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Chapter Three: Cephalosporolides H and I
3.9.4 *Spiroacetal deprotection*

The final steps carried out were the deprotection of spiroacetals 388 and 389. Spiroacetal 388 was deprotected using 10% Pd/C in EtOAc to give the corresponding primary alcohols 392 (Scheme 134). Similarly, spiroacetal 393 was obtained from the deprotection of spiroacetal 389. Further elaboration of spiroacetals 392 and 393 should afford the natural products penisporolides A 26 and B 27.

*Reagents and conditions:* a) 10% Pd/C, EtOAc, H₂, 18 h, 87%; b) 10% Pd/C, EtOAc, H₂, 16 h, 68%.

**Scheme 135:** Synthesis of spiroacetals 392 and 393.
3.10 Summary of final synthesis of spiroacetals 164a-164b

In summary, through a great deal of experimentation the spiroacetal core of cephalosporolides H and I has been successfully synthesised (Scheme 136). The key steps of this synthesis are the cross metathesis of alkene 347 with alkene 354 followed by Sharpless asymmetric dihydroxylation to install the stereocchemistry about C-3 and C-4 of the lactone ring. Oxidative ring closure by intramolecular hydrogen abstraction elegantly afforded the tricyclic core as a separable mixture of epimers about the quaternary spiroacetal centre.

Reagents and conditions: a) BnBr, NaH, DMF, 0 °C to rt, o/n, 84%; b) AcOH, THF, H2O, (R,R)-salen CoII complex A, 0 °C to rt, 16 h, 48%; c) CuI, allylMgBr, THF, -40 °C to rt, 3 h, 70%; d) O3, CH2Cl2, MeOH, PPh3, -78 °C to rt, 15 h, 71%; e) allyl TMS, CH2Cl2, BF3·OEt2, rt, 3 h, 83%; f) LiOH, THF, MeOH, H2O, 0 °C to rt, 1.5 h, 73%; g) BnBr, DMF, K2CO3, rt, 5 h, 86%; h) DMSO, CH2Cl2, (COCl)2, -78 °C, 1 h, then NEt3, 82%; i) LiHMDS, MePPh3Br, THF, 0 °C to rt, o/n, 46%; j) Grubbs’ II, toluene, cy2BCl, 90 °C, mw, 9 h, 22%; k) 5 mol% (DHQD)2PHAL, methanesulfonamide, K2CO3, K3Fe(CN)6, OsO4, tBuOH, H2O, rt, 15 h, 73%, 1:1 mixture of diastereomers; l) PhI(OAc)2, I2, CH2Cl2, hexane, 75 W, 1 h, 51%, 1:1 mixture of diastereomers.

Scheme 136: Synthetic summary of the spiroacetal cores of cephalosporolides H and I.

As there has been some disagreement about the stereochemistry of cephalosporolide H 144,9, 72, 75, 77 our synthesis allows for the synthesis of both diastereomers about the spirocentre and enables access to both natural products cephalosporolides H and I.
The spiroacetal core of penisporolides A 26 and B 27 could also be synthesised from the same precursor olefin 360 (Scheme 137). Sharpless asymmetric dihydroxylation employing the opposite ligand (DHQ)$_2$PHAL afforded the stereochemistry at C-3 and C-4 for these natural products. Oxidative radical cyclisation of the newly formed lactones afforded the spiroacetals 388 and 389. Deprotection of the benzyl group gave spiroacetals 392 and 393.

Reagents and conditions: a) BnBr, NaH, DMF, 0 °C to rt, o/n, 84%; b) AcOH, THF, H$_2$O, (R,R)-salen Co$^{II}$ complex A, 0 °C to rt, 16 h, 48%; c) CuI, allylMgBr, THF, -40 °C to rt, 3 h, 70%; d) O$_3$, CH$_2$Cl$_2$, MeOH, PPh$_3$, -78 °C to rt, 15 h, 71%; e) allyl TMS, CH$_2$Cl$_2$, BF$_3$-OEt$_2$, rt, 3 h, 83%; f) LiOH, THF, MeOH, H$_2$O, 0 °C to rt, 1.5 h, 73%; g) BnBr, DMF, K$_2$CO$_3$, rt, 5 h, 86%; h) DMSO, CH$_2$Cl$_2$, (COCl)$_2$, -78 °C, 1 h, then NEt$_3$, 82%; i) LiHMDS, MePPh$_3$Br, THF, 0 °C to rt, o/n, 46%; j) Grubbs’ II, toluene, cy$_3$BCl, 90 °C, mw, 9 h, 22%; k) 5 mol% (DHQ)$_2$PHAL, methanesulfonamide, K$_2$CO$_3$, K$_3$Fe(CN)$_6$, OsO$_4$, tBuOH, H$_2$O, rt, 15 h, 76%, 1:1 mixture of diastereomers; l) Phl(OAc)$_2$, I$_2$, CH$_2$Cl$_2$, hexane, 75 W, 1 h, 52%, 1:1 mixture of diastereomers; m) 10% Pd/C, EtOAc, H$_2$, 18 h, 87%; n) 10% Pd/C, EtOAc, H$_2$, 16 h, 68%.

Scheme 137: Synthetic summary of the spiroacetal cores of penisporolides A and B.
### 3.11 Future work

Although we have succeeded in synthesising the desired spiroacetal core of the cephalosporolide family the current route has the disadvantage of a low yielding cross-metathesis coupling step, thereby limiting the amount of the desired spiroacetal that can be obtained. Therefore, an alternative route would be desirable.

The HWE reaction had proven successful for formation of the C-C bond adjacent to the quaternary centre, in the coupling of aldehyde 315 with triethylphosphonoacetate. Therefore, the HWE reaction could be employed as the key coupling step for the synthesis of alkene fragment 346, one option is shown in Scheme 138. Alkene 284, previously synthesised from glycidol 281, could be employed in the following route to afford tetrahydrofuran 394 over two steps; cross metathesis with known (S)-carbonate 395 followed by palladium catalysed cyclisation.\textsuperscript{173} A regioselective hydroboration-oxidation of the newly formed alkene 394 could be carried out employing conditions that have proven successful on a similar alkene.\textsuperscript{173} A further oxidation step should afford ketone 396, the HWE precursor. The newly formed phosphonate 396 could be reacted with aldehyde 251 to afford alkene 397. Removal of the carbonyl group of this alkene by reduction to the alcohol followed by Barton-McCombie deoxygenation should afford alkene 346. Sharpless asymmetric dihydroxylation and radical cyclisation according to the current synthesis should afford the desired spiroacetal core for the cephalosporolide family.

\[ 
\begin{align*}
\text{HO} & \quad \text{BnO} & \quad \text{OH} & \quad \text{MeO} & \quad \text{P(O)OMe} & \quad \text{O} & \quad \text{CO}_2\text{Me} & \quad \text{BnO} & \quad \text{OH} & \quad \text{MeO} & \quad \text{P(O)OMe} & \quad \text{O} & \quad \text{CO}_2\text{Me} \\
281 & \quad 284 & \quad \text{395} & \quad \text{394} & \quad \text{396} & \quad 251 & \quad \text{397} & \quad \text{346}
\end{align*}
\]

**Scheme 138:** Possible alternative route to alkene 346.
The side chain of the spirowalactone in cephalosporolides H and I also needs to be attached to C-10 of the core spirowalactones prepared above. This can be achieved in a variety of ways, one of which is shown in Scheme 139.

The side chain of cephalosporolide H could be attached employing a Wittig reaction by first deprotection of the benzyl group to afford alcohol 398, oxidation of the primary alcohol into aldehyde 399 that is then reacted with the known phosphorus ylide 400. Reduction of the resultant double bond in 401 should afford the desired diastereomeric mixture for cephalosporolide H 28 and 144. A similar method could be employed for the synthesis of cephalosporolide I 29. Wittig reaction of aldehyde 399 with known phosphorus ylide 402 should afford alkene 403. Reduction of the resultant double bond should then afford cephalosporolide I 29.

Scheme 139: Possible pathways for the formation of cephalosporolides H and I.
In a similar manner to the cephalosporolides, penisporolides A 26 and B 27 can be synthesised from spiroacetal 392/393 using a Wittig reaction. Oxidation of alcohol 392/393 to aldehyde 404 gives access to a common precursor for the Wittig reaction. Penisporolide A 26 can be formed by reaction of aldehyde 404 with known phosphorus ylide 405.\textsuperscript{176} Reduction of the double bond of 406 followed by selective reduction of the ketone to enantiopure (S)-alcohol should afford the natural product 26. Penisporolide B 27 can be synthesised \textit{via} a Wittig reaction between aldehyde 404 and known phosphorus ylide 407.\textsuperscript{177} Reduction of the resultant double bond of 408 should afford the desired natural product 27.

\textbf{Scheme 140:} Possible pathways for the formation of penisporolides A 26 and B 27.
CHAPTER FOUR: BIOLOGICAL EVALUATION OF ANTI-*HELICOBACTER PYLORI* COMPOUNDS
4.1 Bacterial infectious diseases

The following chapter describes the testing of spiroacetals against infectious diseases. Diseases caused by pathogenic microbial agents including bacteria, viruses, fungi and protozoa are classified as infectious diseases. The steady outbreak of new infectious diseases and the re-emergence of old infectious ones have had a huge impact on human health and the global economy. Bacterial resistance to antibiotics and vaccines and the ability of people to move great distances has allowed opportunities for these pathogens to spread and multiply. Recently it has been estimated that infectious diseases kill more than 17 million people each year, and are the second leading cause of death worldwide.

4.2 Development of drug resistance

The first natural antibiotic (Figure 37), penicillin 409 was discovered in 1929 by Sir Alexander Fleming while the first synthetic antibiotic prontosil 410 was reported by Gerhard J. P. Domagk in 1935. They have been used extensively for the treatment of bacterial infectious diseases and as synthons in the development of new antibiotics.

Figure 37: Structures of the first natural and synthetic antibiotics.

An antibiotic can work by a variety of methods such as: 1) inhibition of cell wall synthesis, 2) inhibition of DNA or RNA synthesis, 3) inhibition of protein synthesis, 4) inhibition of folate synthesis and 5) depolarisation of membrane potential. All these methods inhibit essential processes for bacterial function and development. Since traditional antibiotics cause premature death of bacterial cells, bacteria are placed under significant pressure to develop resistance in order to survive. Clatworthy et al. have developed a timeline illustrating the deployment of antibiotics and the evolution of resistance to these same antibiotics (Figure 38). The inappropriate overuse of antibiotics over the years has accelerated the development of antibiotic resistance. To date most strains of bacteria have acquired resistance to at least one antibiotic.

It is estimated that there is an average of 8 years from Phase 1 trials to launching any drug. With the increase in the occurrence of bacterial infections especially in hospital environments, there is an increasing need for the development of new antibiotics preferably with a different mode of action than those in the current market to minimise the growth of resistance.
The infectious pathogen which is the target of our work is *Helicobacter pylori* (*H. pylori*). It is the bacterium responsible for stomach ulcers and gastritis and was classified as a class 1 carcinogen in 1994.

### 4.3 Helicobacter pylori

The infectious pathogen which is the target of our work is *Helicobacter pylori* (*H. pylori*). It is the bacterium responsible for stomach ulcers and gastritis and was classified as a class 1 carcinogen in 1994.

#### 4.3.1 Discovery and isolation of *H. pylori*

The initial discovery of *H. pylori* occurred in 1875 when German scientists found spiral bacteria in the stomach lining of human stomachs, however they were unable to culture the microorganism. Jaworski found the rod-like bacteria in 1899 which he named *Vibrio rugula* and included his discovery in the Polish handbook of gastric diseases. Subsequently these results were largely forgotten for decades. In 1979 Robin Warren visualised the bacteria in the stomach of gastric ulcer patients and managed to isolate the microorganism with his colleague Barry Marshall. By 1983, Warren and Marshall had isolated the spiral bacterium and successfully cultured the organism. They found it inhabited the interface between the gastric epithelium and the semi-permeable gastric mucus layer. Warren and Marshall proposed that most stomach ulcers and gastritis are caused by the infection of these bacteria and not from stress and poor diet as previously proposed. They went on to show that antibiotics are effective in many cases of gastritis and in 2005 were awarded the Nobel Prize for Medicine and Physiology.
4.3.2 Morphology of *H. pylori*

*H. pylori* are a Gram-negative, micro-aerophilic spiral rod shaped bacterium that colonise the stomach (Figure 39). Each bacterium is approximately 2.5-3.0 µm in length and 0.5 µm in width and usually possess up to five sheathed flagella at one end of the cell. These flagella enable the bacterium to penetrate and colonise the gastric mucosal lining of the stomach. The flagella provide a powerful movement of the organism while secretion of HP0169, a putative collagenase enzyme and other substances act to decrease the mucosal viscosity and therefore allow better movement of the bacterium. The spiral rod shape of the bacterium also offers the bacterium resistance to peristalsis (the contraction and relaxation of smooth muscles).

![Electron microscope images of *H. pylori*](image)

The stomach is an extremely harsh environment with gastric juice containing ~0.17M hydrochloric acid. Therefore penetration of the mucosal layer, which acts as a shield to the gastric epithelium, would offer a safer environment for the survival of *H. pylori*. The bacterium produces the enzyme urease, which catalyses the hydrolysis of urea into carbon dioxide and ammonia. The ammonia produced buffers the acidic environment around the bacteria allowing the bacteria to reach a more neutral environment (ie gastric mucosa).

4.3.3 Inflammation and immune response

The precise mechanism by which *H. pylori* causes inflammation is not well understood. The accepted mechanism is due to the toxic components produced by the bacterium; HP-NAP (*H. pylori* neutrophil-activating protein), cagA (cytotoxic associated gene A), vac A (vacuolating toxin) and urease, which are all antigens in the immune response.

*H. pylori* infection triggers a host immune response involving the release of various antigens. Neutrophils and monocytes are sent by the immune system towards the site of infection where they are unable to pass through the epithelial cells to reach and eliminate the source of the infection. HP-NAP recruits theses neutrophils and monocytes which adhere to the epithelial cells and promote the release of cytotoxins which can cause tissue damage.

The strains of *H. pylori* can be divided into cytotoxic (cag A-positive) and non-cytotoxic (cag A-negative) strains. The cagA-positive strains of *H. pylori* can translocate the cagA protein into epithelial cells causing a
cascade of specific cellular responses inducing greater inflammation thus increasing the risk of gastric cancer.\textsuperscript{200} The vacA produced by \textit{H. pylori} causes large vacuole formation in epithelial cells leading to ulceration and tissue damage.\textsuperscript{201-202}

\textbf{4.3.4 Pathology}

\textit{H. pylori} is estimated to affect about 50\% of the population and is thought to be acquired during childhood, however only a small portion of these patients develop symptoms.\textsuperscript{196, 203} If left untreated \textit{H. pylori} persists chronically and can lead to chronic gastritis, peptic ulcer disease and in some individuals gastric cancer.\textsuperscript{198} The main differences in the effect of the infection are attributed to the severity of the immunological reaction of the host, the strain of the organism and environmental factors.\textsuperscript{204}

Most cases of peptic ulcer disease, gastric mucosal associated lymphoid tissue (MALT) lymphoma and distal stomach cancer are caused by the progression of \textit{H. pylori} infection (Figure 40).\textsuperscript{205} The progression of chronic superficial gastritis into atrophic gastritis is considered as a precursor to gastric cancer. Gastric cancer is the second most prevalent cancer worldwide. \textit{H. pylori} was classified as a class 1 carcinogen in 1994 by the International Agency for Research on Cancer (IARC), a division of the World Health Organisation.\textsuperscript{188}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure40.png}
\caption{A model of \textit{H. pylori} infection and gastroduodenal pathology, reproduced from Suerbaum and Michetti.\textsuperscript{205}}
\end{figure}
4.3.5 Treatment of H. pylori

The main aim of the current treatments for *H. pylori* is the eradication of the bacteria. In the case of gastric or duodenal ulcers the eradication of the bacteria has a cure rate of ~90%. Current treatment involves the triple therapy of a proton pump inhibitor (PPI), antibiotics clarithromycin 411 and amoxicillin 412 with an elimination success rate of ~80% (Figure 41).206 Amoxicillin 412 acts by inhibiting the synthesis of the bacterial cell wall, but the drug has some side effects such as diarrhea. Clarithromycin 411 inhibits protein synthesis of the bacteria and is acid stable and well absorbed by the stomach. Unfortunately it is also one of the more expensive drugs available for the treatment of *H. pylori*. Proton-pump inhibitors such as omeprazole 413 inhibit gastric acid secretion and therefore increase the pH of the stomach making antibiotics such as amoxicillin more effective.

![Figure 41: The standard treatment against H. pylori.](image)

In the case of failure of the triple therapy, a quadruple therapy is often employed in which bismuth salts are added in combination with the proton pump inhibitor, metronidazole 414 and tetracycline 415 (Figure 42). In all cases antibiotics not used in the first line or triple therapy should be used in the quadruple therapy. A summary of the current treatments available was published in 2013 illustrating the advantages and disadvantages of the currently available therapies.207

![Figure 42: Quadruple therapy agents.](image)

4.3.6 Rescue therapies

In cases where the first and second line therapies fail to eliminate the bacterium there are rescue therapies or salvage therapies available (Figure 43). The main reason for the failure of the previous triple or quadruple therapies is usually due to drug resistance. Therefore it would be good practice to carry out antimicrobial susceptibility testing to design a specific therapy to individual patients. However this is not always possible due to high cost of testing as well as sensitivity issues (not 100% sensitive). In most cases especially in areas of
clarithromycin resistance a triple therapy involving levofloxacin 416, a fluoroquinolone, amoxicillin 412 and a PPI are employed.208

Tinazole 417 has a similar structure to metronidazole 414 and has been shown to be effective in conjunction with tetracycline 415 and a bismuth salt as a second or third line therapy.209

Plaunotol 418 is an acyclic diterpene alcohol originally isolated from the plau-noi tree in Thailand and has been shown to be effective in vivo studies in nude mice as a triple therapy with amoxicillin 412 and metronidazole 414.210

Rifabutin 419 is a very expensive anti-mycobacterial drug that can be used in combination with amoxicillin 412 and a PPI to eliminate H. pylori in an estimated 50% of patients where standard triple and quadruple therapies have failed.211 The expensive nature of this drug as well as the possibility of developing resistance implies that this therapy should be restricted to the third or fourth line of defence in treating H. pylori. Rifaximin 420 is a member of the rifabutin family of antibiotics but has a lower risk of developing resistance as it is not readily absorbed by the gastric and intestinal mucosa.212

![Chemical structures of levofloxacin, tinidazole, plaunotol, rifabutin, and rifaximin](image)

Figure 43: Rescue therapies against H. pylori.208-212

### 4.3.7 Limitations of current treatment

One major disadvantage of the current therapy is non-compliance. This is mainly due to the complicated schedule for drug administration and the amount of drugs that need to be added in combination. There are also a large range of side effects associated with the treatment including nausea, diarrhea and taste disturbances. In 2003 a single capsule containing bismuth biskalcitrate, metronidazole 414 and tetracycline 415 was prepared and trialled in combination with the proton-pump inhibitor omeprazole 413.213 This reduced the failure of treatment due to noncompliance but does not completely eliminate the problem.
There is, as mentioned earlier the possibility of drug resistance when these drugs are used over a long period. Clarithromycin resistance is very common as this antibiotic is also used in the treatment of other infectious diseases, mainly upper respiratory tract infections. The bacteria have therefore already come into contact with this antibiotic and can develop a resistance to it.

The quadruple therapy involving the administration of bismuth salts is often used when the triple therapy fails and can be highly efficient and has shown good results even in clarithromycin resistant populations. However, there are drawbacks to this therapy as well. Bismuth salts are not available everywhere, and can be quite toxic if taken long term.
4.4 Novel anti *Helicobacter pylori* compounds

As a consequence of the limitations in the current therapies available, there is a need for the development of a new safe and reliable mono-therapy that can achieve almost total eradication of *H. pylori* as a first course of treatment. There are several natural products which display anti-*Helicobacter pylori* activity some of which are discussed in this section.\textsuperscript{214-215}

4.4.1 Sesquiterpenes

Several novel natural compounds 421-431 have been isolated from *Santalum album*, in 2005 which display anti-*H. pylori* activity (Figure 44).\textsuperscript{216} The anti-*Helicobacter pylori* activity of these compounds was tested against two strains of *H. pylori* (ATCC43504 and SS-1) based on a disk diffusion method with amoxicillin and AMPC as positive controls. The results indicated that compound 431 is the most potent.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{natural_products.png}
\caption{Natural products isolated from *Santalum album*.\textsuperscript{216}}
\end{figure}
4.4.2 Quinolones

Eight novel quinolones 432-439 were isolated from Pseudocardia sp. with MIC values up to 0.1 ng/mL and were labelled as CJ compounds (Figure 45). The compounds were tested by Dekker et al. against H. pylori 41 strain with CJ-13, 564 435 being the most potent and CJ-13, 567 438 being the least active. All eight compounds are selective for H. pylori with no visible inhibition of any of the other bacteria tested.

![Quinolone anti-H. pylori compounds](image)

**Figure 45:** Quinolone anti-*H. pylori* compounds.
4.4.3 Pyloricidins A-D

Another class of natural products with anti-\textit{H. pylori} activity are the pyloricidins A-D 440-445 which were isolated from \textit{Bacillus} sp. (Figure 47).\textsuperscript{218} The anti-Helicobacter activity of all the compounds were tested against \textit{H. pylori} NCTC 11637 with pyloricidins A 440, A\textsubscript{1} 441 and B 443 being the most active with MIC values of 0.0625 \(\mu\)g/mL. The pyloricidins appear to be selective for \textit{H. pylori} with no inhibition of several other bacteria tested.

\textbf{Figure 46:} Pyloricidin natural products.\textsuperscript{218}

4.4.4 Spirolaxine and the CJ compounds

Our research group has a keen interest in biologically relevant spiroacetal-containing natural products. One such natural product is spirolaxine 446 and its methyl ether 447 which were isolated from a strain of white rot fungi \textit{Sporotrichum laxum}, as well as from \textit{S. pruinosum} and \textit{Phanerochaete chrysosporium}.\textsuperscript{219-220} Spirolaxine 446 contains a 7-methyl-5-hydroxyphthalide linked through a polymethylene chain to a 6,5-spiroacetal group and differs from the methyl ether 447 only in the methoxy substituent on the 5 position of the phthalide (Figure 47).

\textbf{Figure 47:} Structures of spirolaxine 446 and spirolaxine methyl ether 447.

Spirolaxine 446 was not tested against \textit{H. pylori} upon its isolation but was later tested in a screening programme by Dekker \textit{et al.}\textsuperscript{221} as well as several new phthalide compounds isolated from the basidiomycete \textit{Phanerochaete velutina} CL6387 and also named the CJ compounds (Figure 48). The absolute stereochemistry of these compounds was not defined thereby limiting the construction of analogues of these natural products with similar structural activity relationships.
Figure 48: The seven CJ compounds 448-454 isolated from Phanerochaete velutina CL6387.²²¹

The anti H. pylori activity of these compounds was tested giving the MIC (minimum inhibitory concentration) and the MBC (minimum bactericidal concentration) by two different strains of the bacteria. Dekker et al.²²¹ tested compounds 446-454 employing H. pylori 41 whereas Brimble et al.²²² employed the H. pylori type strain 11637. The results shown in Table 16 are the results obtained by the Brimble group but are comparable to the results obtained by Dekker et al.²²¹ All the natural products tested contain significant activity but the presence of a spiroacetal increases the activity compared to the open chain phthalides. All the natural products were tested against a panel of other microorganisms such as Bacillus searothermophilis, Micrococcus luteus, Staphylococcus aureus and Pasteurella haemolytica by Dekker et al.²²¹ and did not display any activity against these bacteria. This high level of selectivity suggests that the CJ compounds may exhibit fewer side effects and may not produce resistance in non-target organisms.

The 5,5-spiroacetals 448 and 449 (Table 16, entry 1-2) when tested by Dekker et al.²²¹ displayed very potent activity against H. pylori. Unfortunately when there were synthesised by Brimble et al.²²² the separation of the individual epimers about the spiroacetal was not possible due to the rapid equilibration of the 5,5-spiroacetal. Therefore only a 1:1 mixture of spiroacetals 448 and 449 could be tested. The open chain phthalides (Table 16, entry 3-6) showed some activity but were less active than the spiroacetal natural products.

Brimble et al.²²³ synthesised the natural product spirolaxine methyl ether 446 as well as its (2′S)-diastereoeomer 455 which upon testing proved to be four times more active than the natural product. This result suggests that the exact stereochemistry of the 6,5-spiroacetal ring system is an important structural feature in the anti-H. pylori activity of these compounds. Spirolaxine methyl ether 447 was just as active as spirolaxine 446 itself, therefore the phenol is not necessary for the inhibitory activity of this compound.
In the quest to obtain biologically active analogues of the CJ compounds it was envisaged that the indole heterocycle would be a good bioisostere for the phthalide while simultaneously simplifying the structure by removing the stereogenic centre at the C3 position.\textsuperscript{224} The results are shown in Table 17 for the analogues of the open chain intermediates 456-461.\textsuperscript{222, 224} Unfortunately the activity of these compounds proved to be less active than the natural phthalides with the exception of 460, which is a shortened chain length indole of CJ-13,108 453. Shortening the chain length improved the activity 2-fold. The addition of a 6,6-spiroacetal to the shorter chain indole did not improve the activity (Table 17, entry 6).

Table 16: Anti \textit{H. pylori} of the natural CJ compounds 448-453, spirolaxine 446, spirolaxine methyl ether 447 and the unnatural spirolaxine methyl ether 455.\textsuperscript{222}

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Anti \textit{H. pylori} activity (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJ-12,954 448</td>
<td>Me</td>
<td></td>
<td>0.3 / 0.3</td>
</tr>
<tr>
<td>CJ-13,014 449</td>
<td>Me</td>
<td></td>
<td>0.3 / 0.3</td>
</tr>
<tr>
<td>CJ-13,015 450</td>
<td>Me</td>
<td></td>
<td>2.5 / 5</td>
</tr>
<tr>
<td>CJ-13,102 451</td>
<td>Me</td>
<td></td>
<td>1.25 / 2.5</td>
</tr>
<tr>
<td>CJ-13,104 452</td>
<td>Me</td>
<td></td>
<td>12.5 / 50</td>
</tr>
<tr>
<td>CJ-13,108 453</td>
<td>Me</td>
<td></td>
<td>10 / 10-20</td>
</tr>
<tr>
<td>Spirolaxine 446</td>
<td>H</td>
<td></td>
<td>0.2 / &gt;2</td>
</tr>
<tr>
<td>Spirolaxine methyl ether 447</td>
<td>Me</td>
<td></td>
<td>0.5 / 1</td>
</tr>
<tr>
<td>unnatural spirolaxine methyl ether 455</td>
<td>Me</td>
<td></td>
<td>0.125 / 0.125</td>
</tr>
</tbody>
</table>

Table 17: Anti-\textit{H. pylori} activity of indole analogues 456-461.\textsuperscript{222}
4.5 Biological evaluation of the compounds prepared

The observation that the shortened chain length for the indole analogue 460 is more potent than its parent phthalide 453 led to the development of analogues of the unnatural spirolaxine methyl ether 455 by Ivaylo Dimitrov from the Brimble group. Eight analogues were synthesised in total, three indole analogues with variable chain lengths, three oxindole analogues with the same chain lengths and two analogues of unnatural spirolaxine methyl ether 455 with a shorter and a longer chain length than the natural product.

Figure 49: Unnatural spirolaxine methyl ether 455 and its synthetic analogues 462-469.

4.5.1 Biological Testing

All of these newly synthesised spiroacetals have been evaluated using the same strain of *H. pylori* and methodology as previously described by Brimble *et al.* thereby allowing for easy comparison between the synthetic analogues and the natural products previously examined.
4.5.2 Methods

The \textit{H. pylori} type strain NCTC11637 was used to determine the MIC and MBC of each of the eight analogues and the results are displayed in Table 18. The biological testing was carried out by the following procedure: \textit{H. pylori} was cultured overnight in a microaerophilic atmosphere at 37 °C, 70 rpm in Brucella Broth supplemented with 2.5% foetal bovine serum. The test compounds were weighed out on day of testing and dissolved in dimethyl sulfoxide (DMSO) at 10 mg/mL. Compounds were diluted in Brucella broth. The highest concentration used for testing was 100 μg/mL. The baseline absorbance of the \textit{H. pylori} culture was measured at A_{570} and bacterial numbers enumerated by plating serial 10-fold dilutions of the culture onto quarter sections of Brucella agar and cultured face-up at 37 °C for 5 days. \textit{H. pylori} was transferred into small petri dishes (2 mL/dish) and 0.5 mL compound added. Equivalent amounts of DMSO or Brucella broth alone were included as controls. Cultures were incubated for 24h. A_{570} was measured for each condition tested. The MIC value is defined as the lowest concentration of compound at which there is no visible growth of the bacteria. The \textit{H. pylori} was plated in serial 10-fold dilutions of the culture onto quarter sections of Brucella agar and cultured face-up for 5 days at 37 °C. The colony forming units (CFU/ml) were calculated to determine the MBC after the five day culture time by screening the plates to identify the highest dilution factor with visible single colonies and enumerate the colonies (Table x). The MBC value was defined as the lowest concentration able to kill 99% of the bacteria. The analogues were tested in two independent experiments and the same MIC and MBC values were obtained in both experiments.

4.5.2 Results and conclusion

The results in Table 18 illustrate the \textit{H. pylori} activity of the indole and oxindole analogues synthesised by Ivaylo Dimitrov. The general trend for the indole analogues (Table 18, entry 2, 4, 9) shows that by decreasing the chain length there is an increase in anti-\textit{H. pylori} activity. There is less correlation between the chain length and activity of the oxindole (Table 18, entry 5, 6, 8) with oxindoles 467 and 468 having the same inhibition. Increasing the chain length further however decreased the anti-\textit{H. pylori} activity (Table 18, entry 8). The same trend is not observed in the phthalide analogues 462 and 463 with the longer chain phthalide 463 having a greater activity than the shorter chain.
The two most active analogues are the short chain indole analogue 464 and the long chain phthalide analogue 463 which both have a MIC value of 3 µg/mL. This is similar to the inhibitory activity of the natural product 447 (2 µg/mL) but unfortunately not more potent.
CHAPTER FIVE: EXPERIMENTAL
5.1 General details

All reactions were carried out in flame- or oven-dried glassware under a dry nitrogen or argon atmosphere unless otherwise stated. Tetrahydrofuran (THF) and diethylether (Et₂O) were freshly distilled from sodium/benzophenone directly before use. Dichloromethane (CH₂Cl₂), triethylamine (Et₃N), disopropylethylamine (iPr₂NEt), 2,6-lutidine, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and acetonitrile (MeCN) were distilled from calcium hydride. Reactions performed at low temperature were either cooled with an acetone–dry ice bath to reach –78 °C, MeCN–dry ice bath to reach -40 °C or using a water–ice bath to reach 0 °C. Flash chromatography was carried out using 0.063 – 0.1 mm Riedel-de-Häen silica gel with the denoted solvent.

Thin-layer chromatography (TLC) was carried out using 0.2 mm Kieselgel F254 (Merck) silica gel plates and compounds were visualised using UV irradiation at 365 nM and/or staining with: vanillin in methanolic sulfuric acid or a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid. Preparatory TLC was carried out on 500 μm, 20 x 20 cm UniplateTM (Analtech) silica gel thin layer chromatography plates. Optical rotations were measured with a Perkin Elmer 341 polarimeter, using the sodium-D line (589 nm), with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrometer on a film ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm⁻¹) and recorded using a range of 450 to 4000 cm⁻¹. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded as indicated on either the Bruker Avance 300 spectrometer operating at 300 MHz for ¹H nuclei and 75 MHz for ¹³C nuclei or using the Bruker DRX-400 spectrometer operating at 400 MHz for ¹H nuclei and 100 MHz for ¹³C nuclei. Unless indicated otherwise, all NMR spectra were recorded at 300 K. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (δ 0 for ¹H NMR), CDCl₃ (δ 7.26 for ¹H NMR, δ 77.0 for ¹³C NMR). ¹H NMR data is reported as chemical shift, relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, , dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet, br = broad), coupling constant where applicable (J in Hz) and assignment. Assignments were made with the aid of DEPT 135, COSY, HSQC and NOESY experiments where required. High resolution mass spectra were recorded using a VG70-SE spectrometer at a nominal accelerating voltage of 70 eV or on a Bruker micrOTOF-Q II mass spectrometer.
5.2 Experimental procedures for chapter two

5.2.1 Synthesis of aldehyde 162

(S)-Dimethyl malate 181

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{CH}_3
\end{align*}
\]

Acetyl chloride (8.21 mL, 116 mmol) was added to methanol (150 mL) at rt followed after 10 min by (S)-malic acid 91 (25 g, 186 mmol). The solution was stirred at rt for 18 h before the volatile components were evaporated under reduced pressure. The resultant residue was purified by flash chromatography using CH₂Cl₂/MeOH (95:5) as eluent to afford the title compound (22.67 g, 139 mmol, 80 %) as a yellow oil.

\[R_f: 0.51 \text{ (95:5 CH}_2\text{Cl}_2/\text{MeOH)};\]

\[\alpha_{D}^0 +3.12 \text{ (c 0.80 in CHCl}_3); \text{ lit. } \alpha_{D}^0 +3.1 \text{ (c 0.80 in CHCl}_3);\]

\[\delta_H \text{ (300 MHz, CDCl}_3): 4.42 (1H, dd, } J = 6.3, 4.4 \text{ Hz, H-2), 3.67 (3H, s, C-1OMe), 3.61 (3H, s, C-4OMe), 3.35 (1H, br s, OH), 2.70 (2H, dd, } J = 16.4, 4.4 \text{ Hz, H-3);}\]

\[\delta_C \text{ (75 MHz, CDCl}_3): 173.7 \text{ (C=O, C-1), 171.0 (C=O, C-4), 67.2 (CH, C-2), 52.8 (CH}_3, \text{ C-1OMe), 52.0 (CH}_3, \text{ C-4OMe), 38.4 (CH}_2, \text{ C-3).}\]

The spectroscopic data was in agreement with that reported in the literature\(^9\)

(S)-Dimethyl 2-(benzyloxy)succinate 180

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

Benzyl 2,2,2-trichloroacetimidate 182 (16.3 g, 65.0 mmol) was added to a solution of (S)-dimethyl malate 181 (7.00 g, 43.0 mmol) in CH₂Cl₂ (35 mL) and cyclohexane (60 mL). Triflic acid (0.97 mL, 6.48 mmol) was then added dropwise. The mixture was stirred at rt for 24 h. The mixture was filtered and the filtrate was washed with aq. NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The resultant crude yellow residue was purified by flash chromatography using hexane/EtOAc (4:1) as eluent to afford the title compound (8.05 g, 31.9 mmol, 74 %) as a yellow oil.

\[R_f: 0.33 \text{ (4:1 hexanes/EtOAc)};\]
Experimental: Part 1

$\alpha_D$ -43.5 (c 1.60 in CHCl$_3$); lit. $\alpha_D$ -63.0 (c 1.60 in CHCl$_3$);

$\delta_H$ (300 MHz, CDCl$_3$): 7.32-7.29 (5H, m, Ph), 4.76 (1H, d, $J = 11.5$ Hz, CH$_2$Ph), 4.53 (1H, d, $J = 11.5$ Hz, CH$_2$Ph), 4.41-4.38 (1H, m, H-2), 3.69 (3H, s, C-1OMe), 3.60 (3H, s, C-4OMe), 2.76-2.72 (2H, m, H-3);

$\delta_C$ (75 MHz, CDCl$_3$): 171.6 (C=O, C-1), 170.3 (C=O, C-4), 2 x 128.2 (CH, Ph-H), 127.9 (CH, Ph-H), 2 x 127.7 (CH, Ph-H), 74.3 (CH$_2$, CH$_2$Ph), 72.7 (CH, C-2), 51.8 (CH$_3$, C-1OMe), 51.6 (CH$_3$, C-4OMe), 37.4 (CH, C-3).

The spectroscopic data was in agreement with that reported in the literature.$^{226}$

(5)-Methyl 3-(benzyloxy)-4-hydroxybutanoate 185

![Image of the molecule]

To a solution of diester 180 (1.00 g, 3.96 mmol) in CH$_2$Cl$_2$ (50 mL) was added MgBr$_2$·OEt$_2$ (1.15 g, 4.48 mmol) and the resultant mixture was stirred at rt for 1 h. The solution was cooled to -78 °C and DIBAL-H (9.92 mL of 1.0 M in toluene, 9.92 mmol) was added dropwise over 90 mins via syringe pump. After complete addition followed by 30 min stirring at -78 °C the reaction was warmed to 0 °C, then stirred for another 2 h before methanol (5 mL) and saturated aq. Rochelle’s salt solution (30 mL) were added. The solution was warmed to rt and stirred for a further 20 min. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 x 50 mL), dried over Na$_2$SO$_4$, concentrated under reduced pressure and the residue purified by flash column chromatography using hexane/ EtOAc (3:2) as eluent to afford the title compound (0.45 g, 2.01 mmol, 53 %) as a yellow oil.

R$_f$: 0.28 (3:2 hexanes/EtOAc);

$\alpha_D$ -2.1 (c 1.20 in CHCl$_3$);

HRMS (ESI): MH$^+$ found 224.0937 requires C$_{13}$H$_{18}$O$_2$ requires 224.1000;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3436, 1730,1057, 824, 736, 697;

$\delta_H$ (300 MHz, CDCl$_3$): 7.32-7.25 (5H, m, Ph-H), 4.57 (1H, d, $J = 11.5$ Hz, CH$_2$Ph), 4.46 (1H, d, $J = 11.5$ Hz, CH$_2$Ph), 3.97-3.93 (1H, m, H-3), 3.70 (3H, s, OMe), 3.65-3.55 (2H, m, H-4), 2.70-2.55 (2H, m, H-2);

$\delta_C$ (75 MHz, CDCl$_3$): 171.7 (C=O, C-1), 139.9 (C, Ph), 2 x 128.3 (CH, Ph-H), 127.7 (CH, Ph-H), 2 x 127.5 (CH, Ph-H), 76.2 (CH$_2$, CH$_2$Ph), 71.9 (CH, C-3), 63.7 (CH$_2$, C-4), 51.6 (CH$_3$, C-1OMe), 36.4 (CH$_2$, C-2).
(S)-Methyl 3-(benzyloxy)-4-oxobutanoate 162

To a solution of alcohol 185 (0.20 g, 0.892 mmol) and TEMPO (1.30 g, 0.892 µmol) in EtOAc (3 mL) was added NaHCO$_3$ (0.225 g, 2.67 mmol). The mixture was cooled to -5 °C and a solution of trichloroisocyanuric acid (TCIA) (0.217 g, 0.938 mmol) in EtOAc (5 mL) was added dropwise over 1 h. After stirring for 1 h at -5 °C, NaI (5 mL of 1.0 M solution in H$_2$O) was added. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 10 % aq. Na$_2$SO$_3$ (10 mL) and the aqueous layers were further extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the title compound (0.14 g, 0.63 mmol, 70 %) as a colourless oil.

R$_f$: 0.30 (3:2 hexanes/EtOAc);

$[\alpha]_D$ -16.7 (c 0.70 in CHCl$_3$); lit. $[\alpha]_D$ -56.3 (c 0.70 in CHCl$_3$);

$\delta$$_H$ (300 MHz, CDCl$_3$): 9.64 (1H, s, H-4), 7.36-7.25 (5H, m, Ph-H), 4.60 (1H, d, $J = 11.4$ Hz, CH$_2$Ph), 4.51 (1H, d, $J = 11.4$ Hz, CH$_2$Ph), 4.17-4.09 (1H, m, H-3), 3.60 (3H, s, OMe), 2.74-2.55 (2H, m, H-2);

$\delta$$_C$ (75 MHz, CDCl$_3$): 201.8 (C=O, C-4), 170.4 (C=O, C-1), 136.8 (C, Ph), 2 x 128.4 (CH, Ph-H), 128.3 (CH, Ph-H), 127.7 (CH, Ph-H), 127.6 (CH, Ph-H), 79.5 (CH, C-3), 73.0 (CH$_2$, CH$_2$Ph), 51.9(CH$_3$, OMe), 35.6 (CH$_2$, C-2).

The spectroscopic data was in agreement with that reported in the literature.$^{97}$

5.2.2 Synthesis of methyl ketone 161

(R)-Propylene oxide 113

(R,R,N,N) Bis-(3,5-di-tert-butylsalicyclidene)-1,2-cyclohexanediaminocobalt (II) A (2.42 mg, 0.40 mmol) was dissolved in toluene (5 mL) and acetic acid (240 µl, 4.2 mmol) was added dropwise. The resultant solution was stirred at rt open to air for 30 min resulting in a colour change from orange-red to dark brown. The solution was concentrated to give a crude brown solid. The cobalt (III) complex B was dissolved in propylene oxide (11.6 g, 14 mL, 200 mmol), cooled to 0 °C then H$_2$O (1.98 mL, 110 mmol) was added dropwise over 5 min. The reaction is allowed to reach rt and stirred overnight. (R)-propylene oxide was isolated by distillation at 36 °C at atmospheric pressure (5.6 g, 96.5 mmol 48 %).$^{80}$
CuI (1.14 g, 6.00 mmol) was gently heated under nitrogen until it turned light yellow. THF (100 mL) was added and the solution cooled to -30 °C after which allylmagnesium bromide in Et₂O (60 mL, 60 mmol) was added dropwise. The reaction was stirred for 5 min after which (R)-propylene oxide 113 (2.5 g, 43 mmol) in THF (15 mL) was added and the mixture stirred for 4 h at -30 °C. Saturated aq. NH₄Cl was added and the mixture extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give (R)-hex-5-en-2-ol as a yellow oil, which was used without further purification.

To a solution of NaH (2.82 g, 70 mmol) in dry THF (180 mL) was added (R)-hex-5-en-2-ol in THF (25 mL) and the reaction mixture was stirred at rt for 30 min. Benzyl bromide (7.75 mL, 65 mmol) and tetra-n-butylammonium iodide (75 mg, 0.2 mmol) were then added and stirring continued at rt for 15 h. The reaction was quenched by addition of sat. aq. NH₄Cl (50 mL), extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/EtOAc (9.9:0.1) as eluent to afford the title compound (5.08 g, 26.7 mmol, 60%) as a yellow oil.

**Rf:** 0.84 (4:1 hexane/EtOAc);

|α|D| -15.7 (c 1.10 in CHCl₃); lit. |α|D| +17.0 (c 1.00 in CHCl₃) for enantiomer;

δH (300 MHz, CDCl₃): 7.35-7.25 (5H, m, Ph-H), 5.80-5.76 (1H, m, H-2), 5.01-4.91 (2H, m, H-1), 4.57 (1H, d, J = 11.7 Hz, CH₂Ph), 4.44 (1H, d, J = 11.7 Hz, CH₂Ph), 3.52-3.47 (1H, m, H-5), 2.16-2.09 (2H, m, H-3), 1.71-1.67 (1H, m, H-4), 1.53-1.49 (1H, m, H-4), 1.17 (3H, d, J = 6.1 Hz, H-6);

δC (75 MHz, CDCl₃): 139.1 (CH, C-2), 138.6 (C, Ph), 2 x 128.3 (CH, Ph-H), 127.7 (CH, Ph-H), 127.4 (CH, Ph-H), 127.4 (CH, Ph-H), 114.4 (CH₂, C-1), 74.2 (CH, C-5), 70.3 (CH₂, CH₂Ph), 35.8 (CH₂, C-4), 29.7 (CH₂, C-3), 19.5 (CH₃, C-6).

The spectroscopic data was in agreement with that reported in the literature.

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(R)-5-Benzoyloxyhex-1-ene 170

![Chemical Structure](image)
Experimental: Part 1

(R)-5-(Benzyloxy)hexan-2-one 161

A solution of alkene 170 (1.00 g, 5.26 mmol) in DMF (7.5 mL) was added to a mixture of PdCl$_2$ (1.00 g, 2.68 mmol) and CuCl (0.67 g, 6.73 mmol) in DMF (15 mL) and H$_2$O (5 mL). Oxygen gas was bubbled through the solution. The reaction was stirred for 4 h then filtered through a plug of silica that was washed with further EtOAc and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/EtOAc (4:1) as eluent to afford the title compound (0.76 g, 3.69 mmol, 71%) as a yellow oil.

$R_f$: 0.40 (4:1 hexanes/EtOAc);

$[\alpha]_D$ -26.3 (c 1.00 in CHCl$_3$);

HRMS (ESI): MNa$^+$ found 229.1190 requires C$_{13}$H$_{18}$NaO$_2$ 229.1199;

$\nu_{\text{max}}$ (film)/cm$^{-1}$ 2969, 1714, 1356, 1093, 1063, 743, 697;

$\delta_H$ (300 MHz, CDCl$_3$): 7.35-7.25 (5H, m, Ph-H), 4.54 (1H, d, $J = 11.7$ Hz, CH$_2$Ph), 4.37 (1H, d, $J = 11.7$ Hz, CH$_3$Ph), 3.55 -3.49 (1H, m, H-5), 2.54-2.48 (2H, m, H-4), 2.11 (3H, s ,H-1), 1.85-1.75 (2H, m, H-3),1.19 (3H, d, $J = 6.1$ Hz, H-6);

$\delta_C$ (75 MHz, CDCl$_3$): 208.1 (C=O, C-2), 138.5 (C, Ph), 128.5 (CH, Ph-H), 128.4 (CH, Ph-H), 127.7 (CH, Ph-H), 127.5 (CH, Ph-H), 127.1 (CH, Ph-H), 73.4 (CH, C-5), 69.9 (CH$_2$, CH$_3$Ph),39.0 (CH$_2$, C-3), 30.1 (CH$_2$, C-4), 29.5 (CH$_3$, C-1), 19.2 (CH$_3$, C-6).

(R)-5-(Benzyloxy)-2-trimethylsilyloxyhex-1-ene 234

Et$_3$N (1.11 mL, 8.01 mmol) and TMSOTf (0.73 mL, 4.00 mmol) were added to a solution of ketone 161 (0.55 mL, 2.67 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. After 30 min the reaction was quenched by the addition of sat. aq. NH$_4$Cl (5 mL) and the organic layer was extracted with Et$_2$O (3 x 10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the crude silyl enol ether as a yellow oil which was used in the next step without further purification.
5.2.3 Synthesis of cephalosporolides E 24 and F 25

\((3S,4S,9R)-\text{Methyl 3,9 bis(benzyloxy)-4-hydroxy-6-oxodecanoate } 160\)

To a solution of aldehyde 162 (0.25 g, 1.12 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added MgBr\(_2\)-OEt\(_2\) (1.74 g, 6.76 mmol) at -78 °C. Silyl enol ether 234 (0.64 g, 2.30 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added and the reaction was stirred at 0 °C for 2 h after which it was quenched with pH 7 phosphate buffer (5 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The organic phases were then washed with brine (10 mL), dried over MgSO\(_4\) and evaporated under reduced pressure. The residue was purified by flash column chromatography using hexane/EtOAc (4:1) as eluent to afford the title compound (0.15 g, 0.35 mmol, 30 %) as a colourless oil.

\(R_f: 0.11\) (4:1 hexanes/EtOAc);

\([\alpha]_{D}^\text{D} -19.0\) (c 1.00 in CHCl\(_3\));

HRMS (ESI): M\(^{+}\)Na\(^+\) found 451.2105 requires C\(_{25}\)H\(_{32}\)NaO\(_6\) 451.2091;

\(v_{\text{max}}\) (film)/cm\(^{-1}\): 3457, 2928, 1713, 1454, 1167, 1068, 736, 697;

\(\delta H\) (300 MHz, CDCl\(_3\)):

- 7.35-7.20 (10H, m, Ph-H),
- 4.52 (1H, d, \(J = 5.7\) Hz, OH),
- 4.43 (2H, m, CH\(_2\)Ph),
- 4.25(2H, m, C\(_2\)H\(_2\)Ph),
- 4.06-4.04 (1H, m, H-4),
- 3.85-3.81 (1H, m, H-3),
- 3.71 (3H, s, C-1OMe),
- 3.45-3.40 (1H, m, H-9),
- 2.58-2.54 (2H, m, H-2),
- 2.52-2.45 (2H, m, H-5),
- 2.44-2.38 (2H, m, H-7),
- 1.73-1.63 (2H, m, H-8),
- 1.10 (3H, d, \(J = 6.1\) Hz, H-10);

\(\delta C\) (75 MHz, CDCl\(_3\)):

- 210.8 (C=O, C-6),
- 172.0 (C=O, C-1),
- 137.8 (C, Ph),
- 128.4 (CH, Ph-H),
- 128.2 (CH, Ph-H),
- 128.1 (CH, Ph-H),
- 127.9 (CH, Ph-H),
- 127.7 (CH, Ph-H),
- 127.6 (CH, Ph-H),
- 2 x 127.5 (CH, Ph-H),
- 127.3 (CH, Ph-H),
- 127.2 (CH, Ph-H),
- 77.3 (CH, C-9),
- 73.7 (CH, C-3),
- 72.6 (CH\(_2\), CH\(_3\)Ph),
- 70.1 (CH\(_2\), CH\(_3\)Ph),
- 68.1 (CH, C-4),
- 51.6 (CH\(_3\), OMe),
- 44.5 (CH\(_2\), C-5),
- 34.7 (CH\(_2\), C-2),
- 39.3 (CH\(_2\), C-7),
- 30.1 (CH\(_2\), C-8),
- 19.3 (CH\(_3\), C-10).

Cephalosporolide E 24 and Cephalosporolide F 25

To a solution of β-hydroxyketone 160 (0.30 g, 0.70 mmol) in MeOH (5 mL) was added Pd/C (0.05 g, 0.05 mmol) and the mixture was placed overnight in a Parr hydrogenator at 60 psi. The solution was filtered through a
plug of celite, washed with EtOAc (3 x 5 mL) and concentrated under reduced pressure to give a crude yellow oil.

To a solution of the above oil in CH₂Cl₂ (5 mL) was added Amberlyst-15® (0.05 g) and the mixture stirred at rt overnight. The solution was filtered, washed with CH₂Cl₂ (3 x 10 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/EtOAc (3:2) as eluent to afford a 3:2 separable mixture of cephalosporolide E 24 and cephalosporolide F 25, respectively (44.0 mg, 0.22 mmol, 86 %) over 2 steps.35

Cephalosporolide E 24

Rᵣ: 0.30 (3:2 hexanes/EtOAc);

[α]₀ +27.3 (c 0.41 in CHCl₃), lit [α]₀ +49.2 (c 0.25 in CHCl₃);

HRMS (ESI): MNa⁺ found 221.0792 requires C₁₀H₁₄NaO₄ 221.0784;

v_max (film)/cm⁻¹: 3498, 2934, 1781, 1375, 1165, 1056, 925, 715;

δ_H (300 MHz, CDCl₃): 5.15 (1H, t, J = 5.8 Hz, H-4), 4.88 (1H, t, J = 5.7 Hz, H-3), 4.22-4.10 (1H, m, H-9), 2.74 (1H, dd, J = 18.7, 7.5 Hz, H-2), 2.63 (1H, d, J = 18.7 Hz, H-2), 2.44 (1H, d, J = 14.2 Hz, H-5), 2.18-2.01 (4H, m, H-5, H-7, H-8), 1.49-1.41 (1H, m, H-8), 1.18 (3H, d, J = 6.2 Hz, H-10);

δ_C (75 MHz, CDCl₃): 175.9 (C=O, C-1), 115.0 (C, C-6), 83.3 (CH, C-4), 77.3 (CH, C-3), 75.0 (CH, C-9), 41.5 (CH₂, C-5), 37.5 (CH₂, C-2), 34.1 (CH₂, C-7), 31.3 (CH₂, C-8), 20.9 (CH₃, C-10).

Cephalosporolide F 25

Rᵣ: 0.15 (3:2 hexanes/EtOAc);

[α]₀ -33.9 (c 0.79 in CHCl₃), lit [α]₀ -33.9 (c 0.79 in CHCl₃);

HRMS (ESI): MNa⁺ found 221.0790 requires C₁₀H₁₄NaO₄ 221.0784;

v_max (film)/cm⁻¹: 3529, 2969, 1774, 1347, 1152, 1054, 917, 700;

δ_H (300 MHz, CDCl₃): 5.08 (1H, ddd, J = 2.1, 4.4, 6.6 Hz, H-4), 4.79 (1H, t, J = 5.3 Hz, H-3), 4.25-4.15 (1H, m, H-9), 2.74 (1H, dd, J = 18.4, 5.0 Hz, H-2), 2.68 (1H, d, J = 18.5 Hz, H-2), 2.51 (1H, dd, J = 14.7, 6.6 Hz, H-5), 2.33 (1H, dd, J = 14.9, 2.2 Hz, H-5), 2.18-1.95 (3H, m, H-7, H-8), 1.80-1.70 (1H, m, H-8), 1.28 (3H, d, J = 6.1 Hz, H-10);

δ_C (75 MHz, CDCl₃): 175.5 (C=O, C-1), 115.5 (C, C-6), 83.8 (CH, C-4), 79.9 (CH, C-3), 76.5 (CH, C-9), 42.1 (CH₂, C-2), 36.9 (CH₂, C-5), 36.0 (CH₂, C-7), 32.4 (CH₂, C-8), 22.7 (CH₃, C-10).
Experimental: Part 2
5.3 Experimental procedures for chapter three

5.3.1 Synthesis of oxime 306

1,2,5,6-Di-O-isopropylidene-D-mannitol 268

ZnCl₂ (34.0 g, 0.25 mol) in acetone (185 mL, 2.5 mol) was stirred until dissolved. The resultant solution was cooled to 0 °C and D-mannitol (18.3 g, 0.10 mol) was added. The reaction was warmed to rt and stirred for 24 h. A solution of K₂CO₃ (27.6 g, 0.19 mol) in H₂O (27 mL) was added at 0 °C and the mixture stirred for a further 1 h. The acetone was then decanted and the precipitate extracted with EtOAc (3 x 50 mL). The pH of the acetone layer was adjusted to 8 by the addition of conc. NH₄ solution (1-2 mL) and the combined organic extracts were concentrated in vacuo. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were washed with H₂O (50 mL), dried over MgSO₄ and concentrated in vacuo. The resultant solid was dried under vacuum overnight to give the title compound (21.0 g, 0.08 mol, 80%) as a white solid.

Rf: 0.66 (4:1 hexanes/EtOAc);
[α]D²⁰ +4.2 (c 1.00 in CH₂Cl₂); lit.[α]D²⁰ +2 (c 2.38 in CHCl₃);¹²²

δH (400 MHz, CDCl₃): 4.19-4.09 (4H, m, 2 × CH₂), 4.01-3.95 (2H, m, 2 × CH), 3.75 (2H, t, J = 6.2 Hz, 2 × CH), 2.59 (2H, d, J = 6.6 Hz, 2 × OH), 1.42 (6H, s, 2 × CH₃), 1.36 (6H, s, 2 × CH₃);

δC (100 MHz, CDCl₃): 109.3 (2 × C), 76.1 (2 × CH), 71.1 (2 × CH), 66.7 (2 × CH₂), 26.7 (2 × CH₃), 25.2 (2 × CH₃).

The spectroscopic data was in agreement with that reported in the literature.¹³¹

(R)-Glyceraldehyde acetonide 269

Alcohol 268 (10.0 g, 38.2 mmol) was dissolved in CH₂Cl₂ (100 mL) in a two-necked flask and sat. NaHCO₃ (4 mL) was added. NaIO₄ (16.37 g, 76.5 mmol) was added over 5 min keeping the temperature below 25 °C using a
water bath. The reaction was dried over MgSO₄ and the resultant suspension filtered. CH₂Cl₂ was removed at 40 °C keeping pressure above 150 mbar. The residue was purified by vacuum distillation at 60 °C/30 mbar to give the title compound (4.2 g, 32.3 mmol, 43%) as a colourless oil.

Rₛ: 0.42 (4:1 hexanes/EtOAc);

[α]₂₀° +38.7 (c 1.3 in CH₂Cl₂); lit. [α]₂₀° +61.6 (c 2.3 in CH₂Cl₂); ²²⁹

δₜ (400 MHz, CDCl₃): 9.72 (1H, s, H-1), 4.36-4.41 (1H, m, H-2), 4.08-4.12 (2H, m, H-3), 1.49 (3H, s, CH₃), 1.42 (3H, s, CH₃);

δₑ (100 MHz, CDCl₃): 201.7 (C=O, C-1), 111.2 (C, C-4), 79.8 (CH, C-2), 65.5 (CH₂, C-3), 26.2 (CH₃, C-5), 25.1 (CH₃, C-6).

The spectroscopic data was in agreement with that reported in the literature. ²²⁹

**Ethyl 4,5-O-isopropylidene-(S)-4,5-dihydroxy-2-pentenoate 271**

A stirring solution of aldehyde 269 (4.3 g, 33 mmol) in triethyl phosphonoacetate (13.4 mL, 67 mmol) was cooled to 0 °C and aqueous K₂CO₃ (6 M, 42 mL) was added. The reaction mixture was allowed to warm to rt and stirred for 22 h. The mixture was extracted with CH₂Cl₂ (3 × 40 mL), the combined organic fractions were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:2 hexanes/EtOAc) afforded the title compound as a colourless oil (5.3 g, 26.7 mmol, 80%).

Rₛ: 0.72 (3:2 hexanes/EtOAc);

[α]₂₀° +45.4 (c 0.50 in CHCl₃); lit. [α]₂₀° +43.3 (c 0.50 in CHCl₃); ²³⁰

δₜ (400 MHz, CDCl₃): 6.88 (1H, dd, J = 15.6, 5.7 Hz, H-3), 6.10 (1H, dd, J = 15.6, 1.4 Hz, H-2), 4.70-4.63 (1H, m, H-4), 4.16-4.24 (2H, m, H-5), 3.67 (2H, q, J = 7.1 Hz, CH₂CH₃), 1.45 (3H, s, CH₃), 1.41 (3H, s, CH₃), 1.29 (3H, t, J = 7.1 Hz, CH₂CH₃);

δₑ (100 MHz, CDCl₃): 166.0 (C=O, C-1), 144.6 (CH, C-3), 122.5 (CH, C-2), 110.2 (C, C-6), 74.9 (CH, C-4), 68.8 (CH₂, C-5), 60.5 (CH₂CH₃), 26.4 (CH₃), 25.7 (CH₃), 14.2 (CH₂CH₃).

The spectroscopic data was in agreement with that reported in the literature. ¹³¹
Ethyl (4S)-4,5-isopropylidene-dioxy pentanoate 272

Pd/C (0.1 g, 10% w/w) was added to a solution of ester 271 (4.0 g, 20 mmol) in EtOH (20 mL) and the solution was stirred under a H₂ atmosphere for 3 h. The reaction mixture was filtered through Celite and the filtrate concentrated in vacuo to give the title compound as a colourless oil (3.6 g, 17.8 mmol, 89%).

Rᵣ: 0.85 (3:2 hexanes/EtOAc);

$[\alpha]_D^{20} +4.9$ (c 2.2 in CHCl₃); lit. $[\alpha]_D^{20} +5.0$ (c 2.2 in CHCl₃);¹³⁵

$\delta$H (300 MHz, CDCl₃): 4.17-4.02 (4H, m, H-5, H-4, OCH₂CH₃), 3.55 (1H, dd, $J = 7.9$, 6.9 Hz, H-5), 2.52-2.33 (2H, m, H-2), 1.92-1.84 (2H, m, H-3), 1.40 (3H, s, CH₃), 1.34 (3H, s, CH₃), 1.26 (3H, t, $J = 7.1$ Hz, OCH₂CH₃);

$\delta$C (100 MHz, CDCl₃): 173.2 (C=O, C-1), 108.9 (C, C-6), 74.9 (CH, C-4), 69.0 (CH₂, C-5), 60.4 (CH₂, OCH₂CH₃), 30.4 (CH₂, C-2), 28.7 (CH₂, C-3), 26.9 (CH₃), 25.6 (CH₃), 14.2 (CH₃, OCH₂CH₃).

The spectroscopic data was in agreement with that reported in the literature.¹³⁵

(4S)-4,5-Isopropyliden-dioxy-pentanal 273

To a solution of ester 272 (0.5 g, 2.5 mmol) in CH₂Cl₂ (20 mL) at -78 °C was added DIBAL-H (1M in hexanes, 4 mL, 4 mmol) dropwise. The reaction mixture was stirred for 1 h. Acetone (5 mL) and a saturated solution of Rochelle salt (15 mL) were added. The reaction mixture was allowed to warm to rt, stirred for 1 h and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO₄ and concentrated in vacuo to afford the title compound as a colourless oil (0.37 g, 2.3 mmol, 94%).

Rᵣ: 0.43 (5:1 hexanes/EtOAc);

$[\alpha]_D^{20} -2.0$ (c 2.0 in CHCl₃); lit. $[\alpha]_D^{20} -2.2$ (c 2.0 in CHCl₃);²³¹

$\delta$H (400 MHz, CDCl₃): 9.80 (1H, t, $J = 1.3$ Hz, H-1), 4.15-4.09 (1H, m, H-4), 4.05 (1H, dd, $J = 7.9$, 6.1 Hz, H-5), 3.55 (1H, dd, $J = 7.9$, 6.7 Hz, H-5), 2.62-2.55 (2H, m, H-2), 1.97-1.78 (2H, m, H-3), 1.40 (3H, s, CH₃), 1.34 (3H, s, CH₃);
Experimental: Part 2

\[ \delta_C (100 \text{ MHz, CDCl}_3): 201.5 (\text{C}=\text{O}, \text{C}-1), 109.1 (\text{C}, \text{C}-6), 74.8 (\text{CH}, \text{C}-4), 69.0 (\text{CH}_2, \text{C}-5), 40.0 (\text{CH}_2, \text{C}-3), 26.8 (\text{CH}_3), 26.0 (\text{CH}_2, \text{C}-2), 25.5 (\text{CH}_3). \]

The spectroscopic data was in agreement with that reported in the literature. \(^{231}\)

**\((4S)-4,5-\text{Isopropyliden-dioxy-pentanal oxime 274}\)**

![Image of 274](image)

To a solution of aldehyde 273 (0.36 g, 2.29 mmol) in EtOH (10 mL) was added pyridine (0.15 mL) and NH\(_2\)OH-HCl (0.24 g, 3.45 mmol) and the reaction mixture stirred at rt for 2 h. The solvent was removed \textit{in vacuo} and the residue extracted with CH\(_2\)Cl\(_2\)/H\(_2\)O (5:2 mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated \textit{in vacuo} to give the \textit{title compound} as a yellow oil (1:1 mixture of \(E/Z\) isomers) (0.3 g, 1.9 mmol, 84%).

\( R_t: 0.43 \) (3:2 hexanes/EtOAc);

\([\alpha]_D +11.6 \) (c 1.0 in CHCl\(_3\));

**HRMS (ESI):** MH\(^+\) found 174.1125, requires C\(_8\)H\(_{16}\)NO\(_3\) 174.1125;

\( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3330, 2930, 1667, 1379, 1213, 1052, 847;

\[ \delta_H (400 \text{ MHz, CDCl}_3): 7.46 (1H, t, \text{J} = 5.8 \text{ Hz, H-1}), 6.77 (1H, t, \text{J} = 5.5 \text{ Hz, H-1'}), 4.12 (2H, t, \text{J} = 6.3 \text{ Hz, H-4, H-4'}), 4.09-4.03 (2H, m, H-5), 3.58-3.51 (2H, m, H-5'), 2.51-2.43 (2H, m, H-2), 2.38-2.24 (2H, m, H-2'), 1.85-1.72 (4H, m, H-3, H-3'), 1.41 (6H, s, H-7, H-7'), 1.35 (6H, s, H-8, H-8'); \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 151.2 (\text{C}=\text{N}, \text{C}-1), 109.0 (\text{C}, \text{C}-6), 75.4 (\text{CH}, \text{C}-4), 69.1 (\text{CH}_2, \text{C}-5), 29.9 (\text{CH}_2, \text{C}-3), 26.8 (2 \times \text{CH}_3), 26.0 (\text{CH}_2, \text{C}-2). \]

**\((4S)-4,5-\text{Isopropyliden-dioxy N-hydroxpentanimidoyl chloride 303}\)**

![Image of 303](image)

NCS (0.12 g, 0.87 mmol) was added to a solution of aldoxime 275 (0.10 g, 0.58 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 3 h, quenched by the addition of H\(_2\)O (5 mL) and extracted with Et\(_2\)O (3 \times 5
mL). The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. The organic extract was filtered and the filtrate concentrated in vacuo to give a yellow oil (0.12 g, 0.50 mmol, 95%).

R₆: 0.5 (3:2 hexanes/EtOAc);

δ_H (400 MHz, CDCl₃): 4.16-4.04 (2H, m, H-4, H-5), 3.60 (1H, dd, J = 7.9, 6.6 Hz, H-5), 2.72-2.56 (2H, m, H-2), 1.94-1.88 (2H, m, H-3), 1.42 (3H, s, H-7), 1.35 (3H, s, H-8);

δ_C (100 MHz, CDCl₃): 162.3 (C=N, C-1), 109.2 (C, C-6), 74.6 (CH, C-4), 69.0 (CH₂, C-5), 33.2 (CH₃, C-3), 30.3 (CH₂, C-2), 26.9 (CH₃), 25.6 (CH₃).

**Ethyl (S)-4,5-dihydroxypentanoate 275**

To a solution of 272 (1.0 g, 4.95 mmol) in EtOH (10 mL) was added 2M HCl (4 mL). The reaction mixture was stirred at rt for 2 h, cooled to 0 °C and NaHCO₃ (0.1 g) was added slowly. The solution was filtered and concentrated in vacuo to give the title compound as a colourless oil (0.37 g, 2.29 mmol, 46%).

R₆: 0.37 (3:2 hexanes/EtOAc);

[α]_D²₀ -4.0 (c 2.3 in MeOH); lit. [α]_D²₀ -4.63 (c 2.38 in MeOH);

δ_H (400 MHz, CDCl₃): 4.14 (2H, q, J = 7.1 Hz, OCH₂CH₃), 3.76-3.70 (1H, m, H-4), 3.64 (1H, dd, J = 11.1, 3.1 Hz, H-5), 3.46 (1H, dd, J = 11.1, 7.0 Hz, H-5), 2.48 (2H, dt, J = 7.1, 1.7 Hz, H-3), 1.84-1.72 (2H, m, H-2), 1.26 (3H, t, J = 7.1 Hz, OCH₂CH₃);

δ_C (100 MHz, CDCl₃): 174.2 (C=O, C-1), 71.4 (CH, C-4), 66.5 (CH₂, C-5), 60.7 (CH₂, OCH₂CH₃), 30.5 (CH₃, C-3), 27.9 (CH₂, C-2), 14.1 (CH₃, OCH₂CH₃).

The spectroscopic data was in agreement with that reported in the literature.

**Ethyl 5-(((tert-butyldimethylsilyl)oxy)-4-hydroxypentanoate 276**

Imidazole (0.4 g, 6.17 mmol), DMAP (0.02g, 0.12 mmol) and TBSCI (0.46 g, 3.08 mmol) were added to a solution of diol 275 (0.5 g, 3.08 mmol) in CH₂Cl₂ (6 mL) at 0 °C and stirred at this temperature overnight. The reaction mixture was quenched by the addition of sat. aq. NH₄Cl (2 mL), extracted with CH₂Cl₂ (3 x 5 mL) and
the combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography using 4:1 hexanes/EtOAc afforded the title compound (0.61 g, 2.21 mmol, 72%) as a colourless oil.

Rf: 0.5 (4:1 hexanes/EtOAc);

[α]₀D -15.6 (c 1.0 in CHCl₃);

HRMS (ESI): MH⁺ found 277.1747 requires C₁₃H₂₉O₄ 277.1757;

νmax (film)/cm⁻¹: 3500, 2930, 1734, 1253, 1081, 835;

δH (400 MHz, CDCl₃): 4.13 (2H, q, J = 7.1 Hz, OCH₂CH₃), 3.69-3.61 (2H, m, H-4, H-5), 3.43 (1H, dd, J = 9.7, 6.6 Hz, H-5), 2.54-2.40 (3H, m, OH, H-3), 1.82-1.66 (2H, m, H-2), 1.26 (3H, t, J = 7.1 Hz, OCH₂CH₃), 0.9 (9H, s, OSi₂BuMe₂), 0.07 (6H, s, OSi₂BuMe₂);

δC (100 MHz, CDCl₃): 173.8 (C=O, C-1), 71.0 (CH, C-4), 67.0 (CH₂, C-5), 60.4 (CH₂, OCH₂CH₃), 30.5 (CH₂, C-3), 27.9 (CH₂, C-2), 25.9 (3 x CH₃, OSi₂BuMe₂), 18.3 (C, OSi₂BuMe₂), 14.2 (CH₃, OCH₂CH₃), -5.4 (2 x CH₃, OSi₂BuMe₂).

(S)-5-(Benzylxoyxmethyl)tetrahydro-2-furanone 278

Bu₂SnO (0.31 g, 1.23 mmol) was added to a solution of diol 275 (0.2 g, 1.23 mmol) in toluene (20 mL) and heated to reflux under Dean Stark conditions overnight. The reaction mixture was cooled to rt and BnBr (0.29 mL, 2.47 mmol) and TBAI (0.46 g, 1.23 mmol) were added. The reaction was heated to reflux for a further 4 h, cooled to rt and sat. aq. NH₄Cl (5 mL) was added. The mixture was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic extracts washed with 1M HCl (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography using 4:1 hexanes/EtOAc as eluent afforded the title compound (0.23 g, 1.11 mmol, 92%) as a yellow oil.

Rf: 0.3 (3:2 hexanes/EtOAc);

[α]₀D +30.1 (c 1.12 in CHCl₃) lit. [α]₀D +32.98 (c 1.12 in CHCl₃);

δH (400 MHz, CDCl₃): 7.37-7.26 (5H, m, PhH), 4.68-4.63 (1H, m, H-4), 4.56 (2H, dd, J = 15.1, 12.0 Hz, CH₂Ph), 3.67 (1H, dd, J = 10.8, 3.3 Hz, H-5), 3.47 (1H, dd, J = 10.8, 4.2 Hz, H-5), 2.65-2.56 (1H, m, H-2), 2.51-2.42 (1H, m, H-2), 2.32-2.22 (1H, m, H-3), 2.16-2.06 (1H, m, H-3);
\[ \delta_C (100\text{ MHz, CDCl}_3): \begin{align*} 177.3 (\text{C=O, C-1}), & \quad 137.5 (\text{C, Ph}), \quad 128.4 (2 \times \text{CH, Ph}), \quad 127.7 (\text{C, Ph}), \quad 127.5 (2 \times \text{CH, Ph}), \quad 78.9 (\text{CH, C-4}), \quad 73.5 (\text{CH}_2, \text{CH}_2\text{Ph}), \quad 71.5 (\text{CH}_2, \text{C-5}), \quad 28.3 (\text{CH}_2, \text{C-2}), \quad 24.0 (\text{CH}_2, \text{C-3}). \end{align*} \]

The spectroscopic data was in agreement with that reported in the literature.\(^{233}\)

\((S)\)-\textit{Methyl 5-(benzylxy)-4-hydroxypentanoate 279}

\[
\text{BnO} \quad \text{O} \\
\text{\textbf{279}} \\
\text{\textbf{O}} \\
\text{Me}
\]

1M NaOH (1 mL) was added to a solution of lactone 278 (0.1 g, 0.48 mmol) in MeOH (1 mL) and stirred at rt for 1 h. The pH was adjusted to 4 by addition of 1M HCl and the reaction mixture was extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure to give a yellow oil and was used without further purification.

TMSCH\(_2\)N (2M in Et\(_2\)O, 0.23 mL, 0.44 mmol) was added to a solution of crude acid (0.1 g, 0.44 mmol) in MeOH/benzene (0.8/2.8 mL). The reaction mixture was stirred for 30 min then concentrated under reduced pressure to give the \textit{title compound} (0.106 g, 0.44 mmol, 100%) as a yellow oil.

\(R_\ell: 0.6 (3:2\text{ hexanes/EtOAc});\)

\([\alpha]_D^{20} +5.2 (c 2.40\text{ in CHCl}_3)\) lit. \([\alpha]_D^{20} -4.18 (c 2.40\text{ in CHCl}_3)\) for enantiomer;\(^{234}\)

\[\delta_H (400\text{ MHz, CDCl}_3): 7.37-7.26 (5\text{H, m, Ph}), 4.55 (2\text{H, s, CH}_2\text{Ph}), 3.87-3.80 (1\text{H, m, H-4}), 3.67 (3\text{H, s, OCH}_3), 3.50 (1\text{H, dd, } J = 9.4, 5.9\text{ Hz, H-5}), 3.35 (1\text{H, dd, } J = 9.4, 7.2\text{ Hz, H-5}), 2.25-2.42 (3\text{H, m, H-2, OH}), 1.85-1.70 (2\text{H, m, H-3});\]

\[\delta_C (100\text{ MHz, CDCl}_3): 174.2 (\text{C=O, C-1}), 137.8 (\text{C, Ph}), 128.5 (2 \times \text{CH, Ph}), 127.8 (\text{CH, Ph}), 127.7 (2 \times \text{CH, Ph}), 74.2 (\text{CH}_2, \text{C-5}), 73.4 (\text{CH}_2, \text{CH}_2\text{Ph}), 69.6 (\text{CH, C-4}), 51.6 (\text{CH}_3, \text{OCH}_3), 30.2 (\text{CH}_2, \text{C-2}), 28.2 (\text{CH}_2, \text{C-3}).\]

The spectroscopic data was in agreement with that reported in the literature.\(^{234}\)

\textit{Methyl (S)-5-O-benzyl-O-tert-butylidemethylsilyl-4,5-dihydroxypentanoate 280}

\[
\text{BnO} \quad \text{O} \\
\text{\textbf{280}} \\
\text{\textbf{O}} \\
\text{Me}
\]

Imidazole (0.12 g, 1.6 mmol), DMAP (6 mg, 0.04 mmol) and TBSCI (0.12g, 0.84 mmol) were added to a solution of alcohol 279 (0.1 g, 0.42 mmol) in CH\(_2\)Cl\(_2\) (6 mL). The reaction mixture was stirred at rt overnight, quenched by the addition of sat. aq. NH\(_4\)Cl (2 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic...
extracts were washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by column chromatography using 4:1 hexanes/EtOAc gave the title compound (0.07 g, 0.21 mmol, 49%) as a colourless oil.

R$_f$: 0.8 (9:1 hexanes/EtOAc);

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 7.36-7.26 (5H, m, Ph), 4.47 (2H, s, CH$_2$Ph), 3.90-3.84 (1H, m, H-4), 3.66 (3H, s, OCH$_3$), 3.41 (1H, dd, $J = 9.5$, 5.4 Hz, H-5), 3.34 (1H, dd, $J = 9.5$, 5.7 Hz, H-5), 2.46-2.32 (2H, m, H-2), 1.97-1.89 (1H, m, H-3), 1.82-1.72 (1H, m, H-3), 0.87 (9H, s, OSi$_2$BuMe$_2$), 0.04 (6H, d, $J = 2.75$ Hz, OSi$_2$BuMe$_2$);

$\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 174.2 (C=O, C-1), 138.2 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 74.3 (CH$_2$, C-5), 73.3 (CH$_2$, CH$_2$Ph), 70.2 (CH, C-4), 51.5 (CH$_3$, OCH$_3$), 29.6 (CH$_2$, C-2), 29.6 (CH$_2$, C-3), 25.9 (3 x CH$_3$, OSi$_2$BuMe$_2$), 18.1 (C, OSi$_2$BuMe$_2$), -4.4 (CH$_3$, OSi$_2$BuMe$_2$), -4.8 (CH$_3$, OSi$_2$BuMe$_2$).

The spectroscopic data was in agreement with that reported in the literature.

2-((Benzyloxy)methyl)oxirane 282

NaH (60% dispersion in oil, 5.40 g, 135 mmol) was added to a stirring solution of glycidol 281 (10 g, 135 mmol) and BnBr (10.5 mL, 176 mmol) in THF (300 mL) at 0°C. The reaction mixture was allowed to reach rt and stirred overnight. H$_2$O (200 mL) was added and the mixture extract with CH$_2$Cl$_2$ (3 x 100 mL), the combined organic extracts were washed with brine (100 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give a crude yellow oil. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent afford the title compound (18.8 g, 114 mmol, 84%) as a colourless oil.

R$_f$: 0.5 (4:1 hexanes/EtOAc);

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 7.35-7.25 (5H, m, PhH), 4.61 (1H, d, $J = 11.9$ Hz, CH$_2$Ph), 4.55 (1H, d, $J = 11.9$ Hz, CH$_2$Ph), 3.76 (1H, dd, $J = 3.1$, 11.4 Hz, H-1), 3.44 (1H, dd, $J = 5.8$, 11.4 Hz, H-1), 3.21-3.16 (1H, m, H-2), 2.81-2.78 (1H, m, H-3), 2.62-2.60 (1H, m, H-3);

$\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 137.8 (C, Ph), 128.4 (2 x CH, Ph), 127.7 (3 x CH, Ph), 73.3 (CH$_2$, CH$_2$Ph), 70.8 (CH$_2$, C-3), 50.8 (CH, C-2), 44.3 (CH$_2$, C-1).

The spectroscopic data was in agreement with that reported in the literature.
(R)-2-((benzyloxy)methyl)ozirane 283

(R,R,N,N) Bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanesanediaminocobalt (II) A (0.029 g, 0.05 mmol) was dissolved in 2-((benzyloxy)methyl)oxirane 282 (1.626 g, 9.91 mmol), AcOH (0.011 mL, 0.198 mmol) and THF (0.15 mL). The solution was cooled to 0°C and treated with H2O (0.098 mL, 5.45 mmol). The reaction was allowed to reach rt overnight. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent gave the title compound (0.795 g, 4.84 mmol, 48%) as a colourless oil.

Rf: 0.5 (4:1 hexanes/EtOAc); 
[α]D +6.03 (c 1.76 in CH2Cl2) lit. [α]D +5.4 (c 1.76 in CH2Cl2);80

δH (400 MHz, CDCl3): 7.35-7.25 (5H, m, PhH), 4.61 (1H, d, J = 11.9 Hz, CH2Ph), 4.55 (1H, d, J = 11.9 Hz, CH2Ph), 3.76 (1H, dd, J = 3.1, 11.4 Hz, H-1), 3.44 (1H, dd, J = 5.8, 11.4 Hz, H-1), 3.21-3.16 (1H, m, H-2), 2.81-2.78 (1H, m, H-3), 2.62-2.60 (1H, m, H-3);

δC (100 MHz, CDCl3): 137.8 (C, Ph), 128.4 (2 × CH, Ph), 127.7 (3 × CH, Ph), 73.3 (CH2, CH2Ph), 70.8 (CH2, C-3), 50.8 (CH, C-2), 44.3 (CH2, C-1).

The spectroscopic data was in agreement with that reported in the literature.80

(2S)-1-(benzyloxy)hex-5-en-2-ol 284

Allylmagnesium bromide (4.57 mL, 1M in Et2O) was added to a stirring solution of (R)-benzyl glycidyl ether 283 (0.5 g, 3.05 mmol) and CuI (0.058 g, 0.305 mmol) in THF (20 mL) at -40°C. The black solution was allowed to warm to rt over 3 h and quenched with sat. aq. NH4Cl (20 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL), the combined organic extracts were washed with brine (40 mL), dried over Na2SO4 and concentrated to give a yellow oil. Purification by flash chromatography using 4:1 hexanes/EtOAc as eluent gave the title compound (0.44 g, 2.13 mmol, 70%) as a yellow oil.

Rf: 0.38 (4:1 hexanes/EtOAc);

[α]D + 7.36 (c 1.00 in CHCl3); lit. [α]D -7.28 (c 1.00 in CHCl3)(for enantiomer);236
The spectroscopic data was in agreement with that reported in the literature.\textsuperscript{138}

\textbf{(2S)-\((1\text{-}(benzyloxy)hexanes-5-en-2-yl)oxy)(tert-butyldimethylsilyl)ene 285}

Imidazole (0.317 g, 4.66 mmol), DMAP (0.012 g, 0.097 mmol) and TBSCI (0.349 g, 2.33 mmol) were added to a solution of alcohol 284 (0.4 g, 1.94 mmol) in CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred at rt overnight and quenched by addition of sat. aq. NH$_4$Cl (10 mL). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL), the combined organic extracts were washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated to give a crude yellow oil. Purification by flash chromatography using 4:1 hexanes/EtOAc as eluent gave the \textit{title compound} (0.432 g, 1.35 mmol, 70\%) as a colourless oil.

R$_f$: 0.9 (4:1 hexanes/EtOAc);

$[\alpha]_{D}^{20}$ -12.9 (c 1.00 in CHCl$_3$);

HRMS (ESI): MH$^+$ 321.2250, requires C$_{19}$H$_{33}$O$_2$Si requires 321.2244;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 2952, 2856, 1252, 1090, 833;

$\delta$$_H$ (400 MHz, CDCl$_3$): 7.36-7.25 (5H, m, PhH), 5.82 (1H, ddd, $J$ = 2.9, 6.6, 6.8 Hz, H-5), 5.03-4.92 (2H, m, H-6), 4.52 (2H, s, CH$_2$Ph), 3.87-3.81 (1H, m, H-2), 3.38 (2H, m, H-1), 2.12-2.01 (2H, m, H-3), 1.70-1.61 (1H, m, H-4), 1.59-1.49 (1H, m, H-4), 0.88 (9H, s, OSi$^t$BuMe$_2$), 0.06 (3H, s, OSi$^t$BuMe$_2$), 0.04 (3H, s, OSi$^t$BuMe$_2$);

$\delta$$_C$ (100 MHz, CDCl$_3$): 138.8 (CH, C-5), 138.5 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 114.3 (CH$_2$, C-6), 74.7 (CH$_2$, CH$_2$Ph), 73.3 (CH$_2$, C-1), 71.0 (CH, C-2), 33.7 (CH$_2$, C-3), 29.4 (CH$_2$, C-4), 25.9 (3 x CH$_3$, OSi$^t$BuMe$_2$), 18.2 (C, OSi$^t$BuMe$_2$), -4.32 (CH$_3$, OSi$^t$BuMe$_2$), -4.75 (CH$_3$, OSi$^t$BuMe$_2$).
Ozone was bubbled through a solution of alkene 285 (2.0 g, 6.25 mmol) in CH₂Cl₂ (30 mL) at -78 °C until the blue colour persisted. Oxygen was bubbled through the solution for 20 min. Triphenylphosphine (3.28 g, 12.5 mmol) was added and the solution was allowed to warm to rt overnight. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a crude yellow oil. This was purified by column chromatography using 9:1 hexanes/EtOAc as eluent to give the title compound (1.625 g, 5.04 mmol, 81%) as a yellow oil.

Rᶠ: 0.69 (4:1 hexanes/EtOAc);

[α]Dᵣ-14.1 (c 1.01 in CHCl₃); lit. [α]Dᵣ-16.1 (c 1.01 in CHCl₃);

δ_H (400 MHz, CDCl₃): 9.76 (1H, t, J = 1.70 Hz, H-1), 7.36 -7.28 (5H, m, PhH), 4.53 (2H, d, J = 12.0 Hz, CH₂Ph), 4.49 (1H, d, J=12.0 Hz, CH₂Ph), 3.92-3.86 (1H, m, H-5), 3.41 (1H, dd, J = 9.5, 5.3 Hz, H-4), 2.51-2.47 (2H, m, H-2), 2.00-1.91 (1H, m, H-3), 1.84-1.75 (1H, m, H-3), 0.87 (9H, s, OSi'BuMe₂), 0.044 (3H, s, OSi'BuMe₂), 0.039 (3H, s, OSi'BuMe₂);

δ_C (100 MHz, CDCl₃): 202.5 (C=O, C-1), 138.1 (C, Ph), 128.4 (CH x 2, Ph), 127.6 (CH x 2, Ph), 127.1 (CH, Ph), 74.0 (CH₂, C-5), 73.4 (CH₂, CH₂Ph), 70.2 (CH₂, C-4), 39.5 (CH₂, C-3), 26.9 (CH₂, C-2), 25.8 (3 x CH₃, OSi'BuMe₂), 18.0 (C, OSi'BuMe₂), -4.4 (CH₃, OSi'BuMe₂), -4.8 (CH₃, OSi'BuMe₂).

The spectroscopic data was in agreement with that reported in the literature.237

(S)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)pentanal oxime 248

Pyridine (0.43 mL, 5.30 mmol) and hydroxylamine-hydrochloride (0.276 g, 3.98 mmol) were added to a solution of aldehyde 255 (0.854 g, 2.65 mmol) in CH₂Cl₂ (8 mL). The solution was stirred at rt overnight and quenched by the addition of H₂O (10 mL). The reaction mixture was extracted with CH₂Cl₂ (3 x10 mL), the combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, and concentrated to give the title compound (1:1 mixture of E/Z isomers) as a yellow oil (0.811 g, 2.40 mmol, 90%).
Experimental: Part 2

R_f: 0.52 (4:1 hexanes/EtOAc), 0.24 (4:1 hexanes/EtOAc);

[α]_D -12.5 (c 2.0 in CHCl);

HRMS (ESI): MH⁺ 338.2147, C_{18}H_{32}NO_3Si requires 338.2146;

ν_max (film)/cm⁻¹: 3270, 2928, 1454, 1094, 832;

δ_H (400 MHz, CDCl₃): 7.44 (1H, t, J = 5.8 Hz, H-1), 7.36-7.26 (10H, m, PhH), 6.73 (1H, t, J = 5.4 Hz, H-1'), 4.52 (4H, d, J = 3.7 Hz, 2 x CH₂Ph), 3.90-3.84 (2H, m, H-4, H-4'), 3.45-3.33 (4H, m, H-5, H-5'), 2.47-2.40 (2H, m, H-2, H-2'), 2.34-2.18 (2H, m, H-2, H-2'), 1.83-1.73 (2H, m, H-3, H-3'), 1.70-1.61 (2H, m, H-3, H-3'), 0.88 (9H, s, OSi'Bus₂), 0.87 (9H, s, OSi'Bus₂), 0.06 (3H, d, J = 2.2 Hz, OSi'Bus₂), 0.04 (6H, d, J = 1.1 Hz, OSi'Bus₂);

δ_C (100 MHz, CDCl₃): 152.0 (C=N, C-1), 138.2 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.6 (CH, Ph), 74.2 (CH₂, C-5), 73.3 (CH₂, CH₂Ph), 70.5 (CH, C-4), 31.3 (CH₂, C-3), 30.8 (C, OSi'Bus₂), 25.8 (3 x CH₃, OSi'Bus₂), 25.3 (CH₂, C-2), -4.4 (CH₃, OSi'Bus₂), -4.8 (CH₃, OSi'Bus₂).

(S)-5-(benzyloxy)-4-(tert-butylidimethylsilyloxy)-N-hydroxypentanimidoyl chloride 306

To a solution of oxime 248 (0.07 g, 0.21 mmol) in DMF (1 mL) was added N-chlorosuccinimide (0.04 g, 0.31 mmol). The reaction mixture was stirred for 2 h at rt and quenched by the addition of H₂O (0.5 mL). The mixture was extracted with Et₂O (3 x 1 mL), the combined organic extracts were washed with brine (1 mL), dried over Na₂SO₄ and concentrated to give the title compound (0.064 g, 0.17 mmol, 83%) as a crude yellow oil.

R_f: 0.6 (4:1 hexanes/EtOAc);

δ_H (400 MHz, CDCl₃): 7.36-7.26 (5H, m, PhH), 4.50 (2H, d, J = 2.2 Hz, CH₂Ph), 3.89-3.84 (1H, m, H-4), 3.40 (1H, dd, J = 9.6, 5.4 Hz, H-5), 3.35 (1H, dd, J = 9.6, 5.7 Hz, H-5), 2.51-2.47 (2H, m, H-3), 1.92-1.83 (1H, m, H-2), 1.75-1.66 (1H, m, H-2), 0.88 (9H, s, OSi'Bus₂), 0.04 (6H, d, J = 1.6 Hz, OSi'Bus₂);

δ_C (100 MHz, CDCl₃): 162.6 (C=N, C-1), 138.2 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.6 (CH, Ph), 74.1 (CH₂, C-5), 73.3 (CH, C-4), 70.1 (CH₂, CH₂Ph), 31.2 (CH₂, C-2), 27.8 (CH₂, C-3), 25.8 (3 x CH₃, OSi'Bus₂), 18.1 (C, OSi'Bus₂), -4.4 (CH₃, OSi'Bus₂), -4.8 (CH₃, OSi'Bus₂).
5.3.2 Synthesis of alkenes 286, 310 and 311

3-Hydroxy-2,2-dimethylpropionate 251

A solution of DMSO (7.2 mL, 84.5 mmol) in CH₂Cl₂ (20 mL) was added to a solution of oxalyl chloride (5.3 g, 41.4 mmol) in CH₂Cl₂ (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 10 min and then a solution of methyl 3-hydroxy-2,2-dimethylpropionate 169 (5.0 g, 37.8 mmol) in CH₂Cl₂ (20 mL) was added. After 1 h, NEt₃ (26.4 mL, 189 mmol) was added. The reaction mixture was warmed to rt and H₂O (20 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic extracts were washed with brine (3 × 50 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was used without further purification (4.60 g, 35.4 mmol, 89%).

Rᵣ: 0.45 (4:1 hexanes/EtOAc);

δₜ (400 MHz, CDCl₃): 9.56 (1H, s, H-3), 3.66 (3H, s, OCH₃), 1.26 (6H, s, 2 × CH₃);

δₜ (100 MHz, CDCl₃): 199.0 (C=O, C-3), 173.1 (C=O, C-1), 53.8 (C, C-2), 52.5 (OCH₃), 19.6 (2 × CH₃).

The spectroscopic data was in agreement with that reported in the literature.¹³⁹

Methyl 3-hydroxy-2,2-dimethylpent-4-enoate 286

Vinylmagnesium bromide (1.2 mL, 1M solution in THF) was added to a solution of aldehyde 251 (0.2 g, 1.2 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by the addition of sat. aq. NH₄Cl (5 mL) and the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (0.138 g, 0.8 mmol, 73%) as a yellow oil.

Rᵣ: 0.37 (4:1 hexanes/EtOAc);

δₜ (400 MHz, CDCl₃): 5.85 (1H, ddd, J=17.1, 10.5, 6.7 Hz, H-4), 5.30 (1H, ddd, J=17.1, 1.5, 1.4 Hz, H-5), 5.23 (1H, ddd, J=10.4, 1.4, 1.3 Hz, H-5), 4.17 (1H, d, J = 6.3 Hz, H-3), 3.70 (3H, s, OCH₃), 2.66 (1H, br s, OH), 1.19 (3H, s, CH₃), 1.17 (3H, s, CH₃).
δ₁ (100 MHz, CDCl₃): 177.6 (C=O, C-1), 136.2 (CH, C-4), 117.6 (CH₂, C-5), 77.9 (CH, C-3), 51.9 (OCH₃), 46.7 (C, C-2), 22.5 (CH₃), 19.8 (CH₃).

The spectroscopic data was in agreement with that reported in the literature.

(4S)-N-propionyl-4-benzyl-2-oxazolidinone 292

To a solution of (S)-4-benzylazolidin-2-one 295 (1.0 g, 5.65 mmol) in THF (25 mL) was added n-BuLi (1.6 M in hexanes, 3.70 mL, 5.93 mmol) at -78 °C. Propanoyl chloride (0.54 mL, 6.21 mmol) was added dropwise after 20 min and the reaction mixture was warmed to rt after 2 h, quenched by the addition of sat. aq. NH₄Cl and concentrated to remove THF. The residue was redissolved in CH₂Cl₂ (20 mL) and 1M NaOH (5 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 20 mL), the combined organic extracts were washed with brine (40 mL), dried over MgSO₄ and concentrated to give the title compound (1.21 g, 5.19 mmol, 92%) as a white solid.

Rₛ: 0.7 (7:3 hexanes/EtOAc);

[α]ᵢ₀ + 67 (c 1.00 in CHCl₃); lit. [α]ᵢ₀ + 55.6 (c 1.27 in CHCl₃);¹⁴⁴

δ₂ (400 MHz, CDCl₃): 7.35-7.20 (5H, m, PhH), 4.67 (1H, ddd, J = 10.5, 7.3, 3.8 Hz, H-4), 4.22-4.15 (2H, m, H-5), 3.30 (1H, dd, J = 13.4, 3.3 Hz, PhCH₂), 3.04-2.87 (2H, m, H-2’), 2.77 (1H, dd, J = 13.4, 9.6 Hz, PhCH₂), 1.21 (3H, t, J = 7.4 Hz, H-3’);

δ₃ (100 MHz, CDCl₃): 174.2 (C=O, C-1’), 153.6 (C=O, C-1), 135.5 (C, Ph), 129.5 (CH, Ph) 129.1 (CH x 2, Ph), 127.5 (CH x 2, Ph), 66.3 (CH₂, C-5), 55.3 (CH, C-4), 38.1 (CH₂, CH₂Ph), 29.3 (CH₂, C-2’), 8.4 (CH₃, C-3’).

The spectroscopic data was in agreement with that reported in the literature.¹⁴⁴
Experimental: Part 2

(4S)-N-[(2S,3R)-2-methyl-3-hydroxy-4-pentenoyl]-4-benzyl-2-oxazolidinone 296

To a dried round bottom flask under N₂ was added a solution of (S)-4-benzyl-3-propionyloxazolidin2-one 292 (0.233 g, 1.00 mmol) in CH₂Cl₂ (6 mL). The solution was cooled to 0°C and TiCl₄ (1 mL of 1M solution in CH₂Cl₂) was added. The reaction mixture was stirred for 5 min, then DIPEA (0.57 mL, 2.5 mmol) was added and the reaction mixture was stirred for 1 h. The resultant solution was cooled to -78 °C, acrolein (0.073 mL, 1.1 mmol) was added and the solution was stirred for 1 h. The reaction mixture was warmed to 0 °C, sat. aq. NH₄Cl (3 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic fractions were washed with brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography using 4:1 hexanes/EtOAc as eluent gave the title compound (0.195 g, 0.67 mmol, 67%) as a white solid.

Rᵣ: 0.47 (3:2 hexanes/EtOAc);

[α]ₐ + 56.4 (c 1.00 in CHCl₃); lit. [α]ₐ+ 59.2 (c 1.00 in CHCl₃);[145]

δₜ (400 MHz, CDCl₃): 7.36-7.18 (5H, m, PhH), 5.86 (1H, ddd, J = 15.9, 10.7, 6.5 Hz, H-5’), 5.36 (1H, d, J = 17.1 Hz, H-4’), 5.23 (1H, d, J = 10.5 Hz, H-4’), 4.74-4.68 (1H, m, H-4), 4.52-4.50 (1H, m, H-3’), 4.26-4.17 (2H, m, H-5), 3.88 (1H, dq, J = 7.1, 3.5 Hz, H-2’), 3.26 (1H, dd, J = 13.4, 3.3 Hz, PhCH₂), 2.84 (1H, d, J = 3.1 Hz, OH), 2.80 (1H, dd, J = 13.4, 9.4 Hz, PhCH₂), 1.25 (3H, d, J = 7.1 Hz, CH₃);

δₙ (100 MHz, CDCl₃): 176.6 (C=O, C-1’), 153.1 (C=O, C-2), 137.2 (CH, C-5’), 134.9 (C, Ph), 129.4 (2 x CH, Ph), 128.9 (2 x CH, Ph), 127.4 (CH, Ph), 116.3 (CH₂, C-4’), 72.6 (CH, C-3’), 66.2 (CH₂, C-5), 55.1 (CH, C-4), 42.4 (CH, C-2’), 37.8 (CH₂, CH₂Ph), 10.9 (CH₃).

The spectroscopic data was in agreement with that reported in the literature.[145]

(2S,3R)-Methyl-3-hydroxy-2-methylpent-4-enoate 297

To a solution of MeOH (10 mL) was added sodium metal (0.06 g, 2.49 mmol) in small portions until all the metal had dissolved. The resultant solution was cooled to 0 °C and oxazolidinone 296 (0.5 g, 1.73 mmol) was added. The reaction mixture was stirred for 45 min, quenched by the addition of sat. aq. NH₄Cl and concentrated
Experimental: Part 2

To remove MeOH. The residue was extracted with EtOAc (3 x 10 mL), the combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash column chromatography using 4:1 hexanes/EtOAc as eluent gave the title compound (0.109 g, 0.76 mmol, 44%) as a colourless oil.

Rf: 0.7 (1:1 hexanes/EtOAc);

[α]D + 10.4 (c 1.0 in CHCl₃); lit. [α]D + 30 (c 0.94 in MeOH);

δH (400 MHz, CDCl₃): 5.84 (1H, ddd, J = 16.2, 10.6, 5.7 Hz, H-4), 5.32 (1H, dt, J = 17.1, 1.4 Hz, H-5), 5.21 (1H, dt, J = 10.5, 1.4 Hz, H-5), 4.40-4.42 (1H, m, H-3), 3.71 (3H, s, OCH₃), 2.62-2.67 (2H, m, H-2), 1.82 (3H, d, J = 7.2 Hz, CH₃);

δC (100 MHz, CDCl₃): 175.7 (C=O, C-1), 137.3 (CH₂, C-5), 116.3 (CH, C-4), 73.1 (CH, C-3), 51.8 (OCH₃), 44.6 (CH, C-2), 11.2 (CH₃).

The spectroscopic data was in agreement with that reported in the literature.

(S)-4-Benzyl-3-isobutyloxazolidin-2-one 299

To a solution of (S)-4-benzoxazolidin-2-one 295 (1.20 g, 6.77 mmol) in THF (20 mL) was added n-BuLi (1.6 M in hexanes, 4.45 mL, 7.12 mmol) at -78 °C. The reaction mixture was stirred for 20 min and isobutyryl chloride (0.75 mL, 7.11 mmol) was added dropwise. The reaction solution was stirred for 2 h and then warmed to rt. The reaction was quenched with sat. aq. NH₄Cl (15 mL) and the THF was removed in vacuo. The residue was redisolved in CH₂Cl₂ (15 mL), washed with 1M NaOH (10 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic fractions were washed with brine (40 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a white solid. Purification by flash chromatography using 4:1 hexanes/EtOAc as eluent gave the title compound (1.64 g, 6.63 mmol, 98%) as a white solid.

Rf: 0.5 (4:1 hexanes/EtOAc);

m.p : 65-67 °C;

[α]D +61.4 (c 1.12 in CHCl₃); lit. [α] +61.7 (c 1.12 in CHCl₃);

δH (400 MHz, CDCl₃): 7.35-7.20 (5H, m, PhH), 4.67 (1H, ddd, 10.6, 7.4, 3.8 Hz, H-2), 4.20 (1H, dd, J = 9.0, 7.5 Hz, H-3), 4.16 (1H, dd, J = 9.0, 3.0 Hz, H-3), 3.76 (1H, sept, J = 6.8 Hz, H-2'), 3.26 (1H, dd, J = 13.4, 3.3
Hz, CH₂Ph), 2.77 (1H, dd, J = 13.4, 9.5 Hz, CH₂Ph), 1.24 (3H, d, J = 6.8 Hz, H-3'), 1.19 (3H, d, J = 6.8 Hz, H-4').

δc (100 MHz, CDCl₃): 177.6 (C=O, C-1'), 153.0 (C=O, C-1), 135.3 (C, Ph), 129.4 (2 x CH, Ph), 128.9 (2 x CH, Ph), 127.3 (CH, Ph), 66.0 (CH₂, C-3), 55.3 (CH, C₂Ph), 32.6 (CH, C-2'), 19.2 (CH₃, C-3'), 18.6 (CH₃, C-4').

The spectroscopic data was in agreement with that reported in the literature.¹⁴⁴

(S)-4-Benzyl-3-(2-bromo-2-methylpropanoyl) oxazolidin-2-one 300

To a solution of (S)-4-benzoxazolidin-2-one 295 (0.20 g, 1.13 mmol) in THF (8 mL) was added nBuLi (1.6 M in hexanes, 0.80 mL, 1.18 mmol) at -78 °C. The reaction mixture was stirred for 20 min and a sol. of 2-bromo-2-methylpropanoyl chloride 301 (0.42 g, 2.26 mmol) in THF (2 mL) was added dropwise. The resultant solution was stirred for 2 h at -78 °C, the reaction mixture was warmed to rt and sat. aq. NH₄Cl (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL), the combined organic fractions were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash column chromatography using 9:1 hexanes/EtOAc as eluent gave the title compound (0.18 g, 0.55 mmol, 49%) as an off white solid.

Rf: 0.6 (4:1 hexanes/EtOAc);

m.p: 60-62 °C;

[α]D + 56.6 (c 1.0 in CHCl₃);

HRMS (ESI): MH⁺, 348.0193, C₁₄H₁₄BrNNaO₃ requires 348.0206;

δH (400 MHz, CDCl₃): 7.36-7.22 (5H, m, PhH), 4.76-4.70 (1H, m, H-2), 4.26 (1H, t, J = 8.2 Hz, H-3), 4.19 (1H, dd, J = 9.0, 2.6 Hz, H-3), 3.26 (1 H, dd, J = 13.4, 3.4 Hz, CH₂Ph), 2.28 (1H, dd, J = 13.4, 9.5 Hz, CH₂Ph), 2.14 (3H, s, CH₃Br), 2.09 (3H, s, CH₃Br);

δc (100 MHz, CDCl₃): 171.2 (C=O, C-1'), 151.1 (C=O, C-1), 135.2 (C, Ph), 129.4 (2xCH, Ph), 128.9 (2xCH, Ph), 127.4 (CH, Ph), 66.2 (CH₂, C-3), 57.7 (CH, C-2), 56.8 (C, CBr), 37.6 (CH₂, CH₂Ph), 31.4 (CH₃), 30.4 (CH₃).
Ethyl 3-hydroxypent-4-enoate 310

To a solution of distilled EtOAc (1.23 mL, 12.5 mmol) in THF (1.23 mL) was added a solution of LiHMDS (14 mL, 1 M in hexanes) in THF (10 mL) at -78 °C. The reaction solution was stirred for 15 min and freshly distilled acrolein 291 (1.0 g, 1.19 mL, 17.9 mmol) was added dropwise. The reaction mixture was stirred for 2 h and quenched by the addition of sat. aq. NH₄Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), the combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography using 9:1 hexanes/EtOAc as eluent to give the title compound (1.15g, 7.95 mmol, 45%) as a yellow oil.

R_f: 0.5 (4:1 hexanes/EtOAc);

δ_H (400 MHz, CDCl₃): 5.89 (1H, ddd, J = 16.2, 10.7, 5.6 Hz, H-4), 5.24 (2H, dd, J = 16.6, 10.5 Hz, H-5), 4.58-4.51 (1H, m, H-3), 4.18 (2H, q, J = 7.2 Hz, CH₂CH₃), 3.0 (1H, s, OH), 2.61-2.48 (2H, m, H-2), 1.28 (3H, t, J = 7.2 Hz, CH₂CH₃);

δ_C (100 MHz, CDCl₃): 172.2 (C=O, C-1), 138.8 (CH, C-4), 115.4 (CH₂, C-5), 68.9 (CH, C-3), 60.8 (CH₂, C-2), 41.1 (CH₂), 14.1 (CH₃).

The spectroscopic data was in agreement with that reported in the literature. 242-243

3-((Tert-butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol 314

Imidazole (2.94 g, 13.3 mmol), DMAP (0.02 g, 0.14 mmol) and TBSCl (4.76 g, 31.7 mmol) were added to a solution of neopentyl glycol 313 (3.0 g, 28.8 mmol) in CH₂Cl₂ (60 mL). The reaction was stirred for 12 h at rt and quenched by the addition of sat. aq. NH₄Cl (50 mL) and the mixture was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude oil was purified by flash chromatography using 10:1 hexanes/EtOAc as eluent to give the title compound (5.0 g, 22.9 mmol, 80%) as a colourless oil.

R_f: 0.37 (9:1 hexanes/EtOAc);

δ_H (400 MHz, CDCl₃): 3.47 (2H, d, J = 5.6 Hz, H-1), 3.46 (2H, s, H-3), 2.82 (1H, t, J = 5.6 Hz, OH), 0.9 (9H, s, OSi'BuMe₂), 0.88 (6H, s, OSi'BuMe₂), 0.06 (6H, s, OSi'BuMe₂);
δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 72.7 (CH<sub>2</sub>, C-3), 72.2 (CH<sub>2</sub>, C-1), 36.4 (C, C-2), 25.8 (3 x CH<sub>3</sub>, OSi'BuMe<sub>2</sub>), 21.4 (2 x CH<sub>3</sub>), 18.1 (C, OSi'BuMe<sub>2</sub>), -5.6 (2 x CH<sub>3</sub>, OSi'BuMe<sub>2</sub>).

The spectroscopic data was in agreement with that reported in the literature.\textsuperscript{151}

3-((tert-butydimethylsilyl)oxy)-2,2-dimethylpropanal 315

\[
\begin{array}{c}
\text{TBSO} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array}
\]

Oxalyl chloride (0.24 mL, 2.75 mmol) was added to a solution of DMSO (0.47 mL, 5.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at -78 °C. The reaction was stirred for 1 h and a solution of alcohol 314 (0.5 g, 2.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added. The reaction was stirred for another 1 h before NEt<sub>3</sub> (1.27 mL, 9.17 mmol) was added and the mixture stirred for 1 h. The mixture was warmed to rt and sat. aq. NaHCO<sub>3</sub> (10 mL) was added and the mixture was extracted with hexanes (3 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.44 g, 2.03 mmol, 88%) as a yellow oil.

R<sub>f</sub>: 0.81 (9:1 hexanes/EtOAc);

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 9.55 (1H, s, H-1), 3.58 (2H, s, H-3), 1.02 (6H, s, (CH<sub>3</sub>)<sub>2</sub>), 0.85 (9H, s, OSi'BuMe<sub>2</sub>), 0.02 (6H, s, OSi'BuMe<sub>2</sub>);

δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 206 (C=O, C-1), 68.4 (CH<sub>2</sub>, C-3), 48.0 (C, C-2), 25.8 (3 x CH<sub>3</sub>, OSi'BuMe<sub>2</sub>), 21.3 (2 x CH<sub>3</sub>), 18.5 (C, OSi'BuMe<sub>2</sub>), -5.6 (2 x CH<sub>3</sub>, OSi'BuMe<sub>2</sub>).

The spectroscopic data was in agreement with that reported in the literature.\textsuperscript{151}

5-((tert-butydimethylsilyl)oxy)-4,4-dimethylpent-1-en-3-ol 311

\[
\begin{array}{c}
\text{TBSO} \\
\text{Me} \\
\text{Me} \\
\text{C} \\
\end{array}
\]

Vinylmagnesium bromide (1.2 mL, 1M in THF, 1.2 mmol) was added to a stirring solution of aldehyde 315 (0.2 g, 0.93 mmol) in THF (4.5 mL) at 0 °C. The solution was stirred for 1 h and quenched by the addition of sat. aq. NH<sub>4</sub>Cl (5mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), the combined organic fraction were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.21 g, 0.86 mmol, 91%) as a colourless oil.
Experimental: Part 2

R_f: 0.81 (9:1 hexanes/EtOAc);

δ_H (400 MHz, CDCl₃): 5.88 (1H, ddd, J = 17.0, 10.7, 6.5 Hz, H-2), 5.20 (2H, dd, J = 17.0, 10.5 Hz, H-1), 3.94 (1H, d, J = 6.3 Hz, H-3), 3.52 (1H, d, J = 9.7 Hz, H-5), 3.41 (1H, d, J = 9.7 Hz, H-5), 3.28 (1H, s, OH), 0.89 (9H, s, OSi’BuMe₂), 0.87 (3H, s, CH₃), 0.85 (3H, s, CH₃), 0.06 (6H, s, OSi’BuMe₂);

δ_C (100 MHz, CDCl₃): 137.6 (CH, C-2), 116.1 (CH₂, C-1), 80.4 (CH, C-3), 72.5 (CH₂, C-5), 38.2 (C, C-4), 25.8 (3 × CH₃, OSi’BuMe₂), 22.2 (2 × CH₃), 19.4 (C, OSi’BuMe₂), -5.6 (2 × CH₃, OSi’BuMe₂).

The spectroscopic data was in agreement with that reported in the literature.

5.3.3 Synthesis of isoxazolines 304-309

Methyl 3-((2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-4,5-dihydroisoxazol-5-yl)-3-hydroxy-2,2-dimethylpropanoate 304

A solution of chloride 303 (0.11 g, 0.55 mmol) and alkene 286 (0.17 g, 1.1 mmol) in CH₂Cl₂ (9 mL) was cooled to -40 °C. A solution of NEt₃ (0.07 mL, 0.55 mmol) in CH₂Cl₂ (1 mL) was added dropwise. The reaction was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH₄Cl (5 mL). The mixture was extracted with CH₂Cl₂ (3 × 10 mL), the combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude oil was purified by flash chromatography using 4:1 to 1:1 hexanes/EtOAc as eluent to give the title compound (0.09 g, 0.27 mmol, 50%) as a yellow oil.

R_f: 0.18 (3:2 hexanes/EtOAc);

HRMS (ESI): MH⁺, 352.1727, C₁₆H₂₇NNaO₆Si requires 352.1731;

ν_max (film)/cm⁻¹: 3478, 2930, 1725, 1056, 854;

δ_H (400 MHz, CDCl₃): 4.70 (1H, t, J = 9.4 Hz, H-4), 4.17-4.10 (1H, m, H-9), 4.06 (1H, dd, J = 7.8, 6.1 Hz, H-10), 3.74 (3H, s, OCH₃), 3.55 (1H, dd, J = 7.8, 6.9 Hz, H-10), 3.48 (1H, d, J = 10.5, H-3), 3.12 (1H, dd, J = 10.5, 5.3 Hz, OH), 3.03 (2H, d, J = 9.5 Hz, H-5), 2.52-2.33 (2H, m, H-7), 1.87-1.80 (2H, m, H-8), 1.41 (3H, s, CH₃), 1.35 (3H, s, CH₃), 1.30 (3H, s, H-12), 1.27 (3H, s, H-13);

δ_C (100 MHz, CDCl₃): 177.2 (C=O, C-1), 159.0 (C=N, C-6), 109.0 (C, C-11), 78.7 (CH, C-4), 78.4 (CH, C-3), 75.0 (CH, C-9), 69.0 (CH₂, C-10), 52.2 (CH₃, OCH₃), 45.4 (C, C-2), 41.1 (CH₂, C-5), 30.2 (CH₂, C-8), 26.9 (CH₃), 25.6 (CH₃), 24.1 (CH₂, C-7), 23.2 (CH₃, C-12), 21.7 (CH₃, C-13).
Methyl 3-((R)-4-(benzylxy)-3-(tert-butylidemethylsilyloxy)butyl-4,5-dihydroisoxazol-5-yl)-3-hydroxy-2,2-dimethyldimethylpropanoate 305

A solution of chloride 306 (0.05 g, 0.14 mmol) and alkene 286 (0.03 g, 0.19 mmol) in CH₂Cl₂ (1 mL) was cooled to -40 °C. A solution of NEt₃ (0.04 mL, 0.29 mmol) in CH₂Cl₂ (1 mL) was added dropwise. The reaction was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH₄Cl (0.5 mL). The reaction mixture was extracted with CH₂Cl₂ (3 × 1 mL), the combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude oil was purified by column chromatography using 9:1 hexanes/EtOAc as eluent to give the title compound (0.023 g, 0.05 mmol, 35%) as a yellow oil.

Rᵣ: 0.23 (4:1 hexanes/EtOAc);

HRMS (ESI): M⁺, 494.2903, C₂₆H₄₄NO₆Si requires 494.2923;

νₘₐₓ (film)/cm⁻¹: 3436, 2952, 1730, 1057, 824, 736, 697;

δH (400 MHz, CDCl₃): 7.35-7.25 (5H, m, PhH), 4.66 (1H, t, J = 9.5 Hz, H-4), 4.50 (2H, s, CH₂Ph), 3.90-3.81 (1H, m, H-9), 3.68 (3H, s, OCH₃), 3.48 (1H, br s, H-3), 3.41 (1H, dd, J = 5.4, 2.0 Hz, H-10), 3.36 (1H, dd, J = 9.5, 5.9 Hz, H-10), 3.08 (1H, br s, OH), 2.99 (2H, d, J = 9.56 Hz, H-5), 2.43-2.31 (2H, m, H-7), 1.89-1.80 (1H, m, H-8), 1.76-1.66 (1H, m, H-8), 1.29 (3H, s, CH₃), 1.26 (3H, s, CH₃), 0.88 (9H, s, OSiBuMe₂), 0.06 (3H, s, OSiBuMe₂); 0.04 (3H, s, OSiBuMe₂);

δC (100 MHz, CDCl₃): 177.1 (C=O, C-1), 159.6 (C=N, C-6), 138.1 (C, Ph), 128.2 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 78.5 (CH, C-4), 78.2 (CH, C-3), 74.0 (CH₂, C-10), 73.2 (CH₂, CH₂Ph), 70.4 (CH, C-9), 52.1 (CH₃, OCH₃), 45.5 (C, C-2), 41.0 (CH₂, C-5), 31.1 (CH₂, C-8), 25.8 (3 x CH₃, OSiBuMe₂), 23.3 (CH₃, C-7), 23.0 (CH₃), 21.6 (CH₃), 18.0 (C, OSiBuMe₂), -4.5 (CH₃, OSiBuMe₂), -4.9 (CH₃, OSiBuMe₂).
(2S,3S)-Methyl 3-(3-((R)-4-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-4,5-
dihydroisoxazol-5-yl)-3-hydroxy-2-methylpropanoate 307

A solution of chloride 306 (0.077 g, 0.21 mmol) and alkene 297 (0.03 g, 0.21 mmol) in CH₂Cl₂ (1 mL) was cooled to -40 °C. A solution of NEt₃ (0.043 mL, 0.31 mmol) in CH₂Cl₂ (1 mL) was added dropwise. The reaction was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH₄Cl (0.5 mL). The mixture was extracted with CH₂Cl₂ (3 × 2 mL), the combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude oil was purified by column chromatography using 9:1 hexanes/EtOAc as eluent to give the title compound (0.03 g, 0.06 mmol, 32%) as a yellow oil.

Rₛ: 0.2 (4:1 hexanes/EtOAc);

HRMS (ESI): MH⁺, 480.2763, C₂₂H₄₂NO₅Si requires 480.2776;

νₘₐₓ (film)/cm⁻¹: 3450, 2928, 2856, 1731, 1254, 1103, 836;

δ_H (400 MHz, CDCl₃): 7.26 (5H, m, PhH), 4.07-4.52 (1H, m, H-4), 4.51 (2H, s, CH₂Ph), 3.89-3.86 (1H, m, H-3), 3.71 (3H, s, OCH₃), 3.70 (1H, bs, OH), 3.44-3.40 (1H, m, H-10), 3.37-3.32 (1H, m, H-10), 3.02-2.86 (2H, m, H-5), 2.69 (1H, t, J = 7.1 Hz, H-2), 2.45-2.26 (2H, m, H-7), 1.89-1.80 (1H, m, H-8), 1.76-1.67 (1H, m, H-8), 1.27 (3H, dd, J = 7.1, 2.4 Hz, CH₃), 0.88 (9H, s, OSi′BuMe₂), 0.05 (3H, s, OSi′BuMe₂), 0.04 (3H, s, OSi′BuMe₂);

δ_C (100 MHz, CDCl₃): 174.9 (C=O, C-1), 159.7 (C=N, C-6), 138.2 (C, Ph), 128.3 (2x CH, Ph), 127.6 (2x CH, Ph), 127.5 (CH, Ph), 79.8 (CH, C-4), 74.1 (CH,C-3), 74.0 (CH₂, C-10), 73.2 (CH₂, CH₂Ph), 70.5 (CH, C-9), 51.9 (CH₃, OCH₃), 42.9 (C, C-2), 40.1 (CH₂, C-5). 31.1 (CH₂, C-8), 25.8 (3x CH₃, OSi′BuMe₂), 23.3 (CH₂, C-7), 18.1 (C, OSi′BuMe₂), 12.9 (CH₃), -4.4 (CH₃, OSi′BuMe₂), -4.8 (CH₃, OSi′BuMe₂).

Ethyl 3-(3-((R)-4-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-
hydroxypropanoate 308

A solution of chloride 306 (0.13 g, 0.35 mmol) and alkene 310 (0.05 g, 0.35 mmol) in CH₂Cl₂ (2 mL) was cooled to -40 °C. A solution of NEt₃ (0.072 mL, 0.52 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise. The reaction was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH₄Cl (5 mL). The
mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL), the combined organic extracts were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography using 9:1 hexanes/EtOAc as eluent to give the title compound (0.02 g, 0.04 mmol, 12%) as a yellow oil.

R$_f$: 0.13 (4:1 hexanes/EtOAc);

**HRMS (ESI):** MH$^+$, 480.2780, C$_{25}$H$_{42}$NO$_6$Si requires 480.2776;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3443, 2929, 1729, 1253, 1094, 836;

$\delta_H$ (400 MHz, CDCl$_3$): 7.35-7.26 (5H, m, PhH), 4.59-4.40 (1H, m, H-4), 4.51 (2H, s, CH$_2$Ph), 4.18 (2H, q, $J$ = 7.1 Hz, OCH$_2$CH$_3$), 4.04-3.96 (1H, m, H-3), 3.91-3.84 (1H, m, H-9), 4.42 (1H, dd, $J$ = 9.5, 5.2 Hz, H-10), 3.35 (1H, dd, $J$ = 9.5, 6.0 Hz, H-10), 3.03-2.86 (2H, m, H-5), 2.69-2.35 (4H, m, H-2, H-7), 1.90-1.81 (1H, m, H-8), 1.77-1.68 (1H, m, H-8), 1.27 (3H, t, $J$ = 7.1 Hz, OCH$_2$CH$_3$), 0.87 (9H, s, OSi$_{tBu}$Me$_2$), 0.047 (6H, d, $J$ = 4.18 Hz, OSi$_{tBu}$Me$_2$);

$\delta_C$ (100 MHz, CDCl$_3$): 171.8 (C=O, C-1), 159.2 (C=N, C-6), 138.2 (C, Ph), 128.3 (2 x CH, Ph), 127.7 (2 x CH, Ph), 127.6 (CH, Ph), 81.2, 80.9 (CH, C-4), 74.1 (CH$_2$, C-10), 73.3 (CH$_2$, CH$_2$Ph), 70.5 (CH, C-9), 69.3, 68.6 (CH, C-3), 61.0, 60.9 (CH$_2$, OCH$_2$CH$_3$), 39., 38.8 (CH$_2$, C-5), 38.1, 37.5 (CH$_2$, C-2), 31.1 (CH$_2$, C-8), 25.8 (3 x CH$_3$, OSi$_{BuMe_2}$), 23.4 (CH$_2$, C-7), 14.1 (CH$_3$, OCH$_2$CH$_3$), -4.3 (CH$_3$, OSi$_{BuMe_2}$), -4.7 (CH$_3$, OSi$_{BuMe_2}$).

1-(3-(((R)-4-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol 309

A solution of alkene 311 (0.05 g, 0.21 mmol) and oxime 306 (0.07 g, 0.21 mmol) in CH$_2$Cl$_2$ (3 mL) was cooled to -40 °C. A solution of NEt$_3$ (0.04 mL, 0.31 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise. The solution was allowed to warm to rt overnight and quenched by the addition of sat. aq. NaHCO$_3$ (0.5 mL). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 x 2 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography using 10:1 hexanes/EtOAc as eluent gave the title compound (0.01 g, 0.02 mmol, 8.4%) as a yellow oil.

R$_f$: 0.63 (4:1 hexanes/EtOAc);

**HRMS (ESI):** MH$^+$, 580.3779, C$_{39}$H$_{58}$NO$_5$Si$_2$ requires 580.3775;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3452, 2928, 1726, 1603, 1463, 1253, 1093, 833;

$\delta_H$ (400 MHz, CDCl$_3$): 7.35-7.27 (5H, m, PhH), 4.72 (1H, t, $J$ = 10.7 Hz, H-4), 4.51 (2H, s, CH$_2$Ph), 3.92-3.85 (1H, m, H-9), 3.70 (1H, d, $J$ = 9.5 Hz, H-1), 3.44-3.39 (1H, m, H-3), 3.38-3.29 (3H, m, H-1, H-10), 3.11 (1H, dd,
$J = 8.3, 1.6, \text{OH}$, $3.05-2.90 (2H, m, H-5), 2.45-2.29 (2H, m, H-7), 1.90-1.81 (1H, m, H-8), 1.77-1.67 (1H, m, H-8), 0.99 (3H, s, CH$_3$), 0.94 (3H, s, CH$_3$), 0.88 (18H, d, $J = 6.5 \text{ Hz}$, OSi'BuMe$_2$), 0.06 (6H, d, $J = 5.2 \text{ Hz}$, OSi'BuMe$_2$), 0.04 (6H, d, $J = 5.6 \text{ Hz}$, OSi'BuMe$_2$);

$\delta$C ($100 \text{ MHz, CDCl}_3$): 159.3 (C=N, C-6), 138.3 (C, Ph), 1283 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 79.0 (CH, C-4), 78.3 (CH, C-3), 74.2(CH$_2$, C-10), 73.3 (CH$_2$, CH$_2$Ph), 71.5 (CH$_2$, C-1), 70.6 (CH, C-9), 41.4 (CH$_3$, C-5), 39.8 (C, C-2), 31.1 (CH$_2$, C-8), 25.8 (6 x CH$_3$, OSi'BuMe$_2$), 23.5 (CH$_2$, C-7), 22.4 (CH$_3$), 21.0 (CH$_3$), 18.1 (C, OSi'BuMe$_2$), -4.3 (CH$_3$, OSi'BuMe$_2$), -4.7 (CH$_3$, OSi'BuMe$_2$), -5.6 (CH$_3$, OSi'BuMe$_2$), -5.7 (CH$_3$, OSi'BuMe$_2$).

5.3.4 Synthesis of methyl ketone 166

(S)-6-(benzyl oxy)-5-(tert-butyldimethylsilyloxy)hexanone 166

A solution of alkene 285 (2.00 g, 6.25mmol) in DMF (7.5 mL) was added to a mixture of PdCl$_2$ (0.553 g, 3.13 mmol) and CuCl (0.804 g, 8.13mmol) in DMF (15 mL) and H$_2$O (5 mL). Oxygen gas was bubbled through the solution and the reaction was stirred for 4 h. The reaction mixture was filtered through a plug of silica and washed with further EtOAc (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography using 4:1 hexanes/EtOAc as eluent to afford the title compound (0.96 g, 2.85 mmol, 46%) as a yellow oil.

R$_f$: 0.71 (4:1 hexanes/EtOAc);

$[\alpha]_D$ -11.3 (c 1.0, CHCl$_3$);

HRMS (ESI): MH$^+$, 337.2197, C$_{18}$H$_{33}$O$_3$Si requires 337.2193;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 2929, 1717, 1091;

$\delta$H ($400 \text{ MHz, CDCl}_3$): 9.36-9.26 (5H, m, PhH), 4.51 (2H, d, $J = 2.2 \text{ Hz}$, CH$_2$Ph), 3.90-3.83 (1H, m, H-5), 3.40 (1H, dd, $J = 5.3$, 9.7 Hz, H-6), 3.34 (1H, dd, $J = 5.7$, 9.7 Hz, H-6), 2.51-2.47 (2H, m, H-4), 2.12 (3H, s, H-1), 1.92-1.83 (1H, m, H-3), 1.75-1.66 (1H, m, H-3), 0.88 (9H, s, OSi'BuMe$_2$), 0.04 (6H, d, $J = 1.76 \text{ Hz}$, OSi'BuMe$_2$);

$\delta$C ($100 \text{ MHz, CDCl}_3$): 208.8 (C=O, C-1), 138.3 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 74.3 (CH$_2$, C-6), 73.3 (CH$_2$, CH$_2$Ph), 70.3 (C, C-4), 39.0 (CH$_2$, C-3), 29.9 (CH$_3$), 28.5 (CH$_2$, C-2), 25.8 (3 x CH$_3$, OSi'BuMe$_2$), 18.1 (C, OSi'BuMe$_2$), -4.4 (CH$_3$, OSi'BuMe$_2$), -4.9 (CH$_3$, OSi'BuMe$_2$).

5.3.5 Synthesis of aldehydes 320 and 322
**Methyl 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpent-4-enoate 321**

![Diagram 321]

Imidazole (0.32 g, 4.74 mmol), DMAP (0.03 g, 0.16 mmol) and TBSCl (0.57 g, 3.79 mmol) were added to a solution of alkene 286 (0.5 g, 3.16 mmol) in DMF (1 mL) at 0 °C. The solution was allowed to warm to rt and stirred overnight. The reaction was quenched by the addition of sat. aq. NH₄Cl (3 mL) and the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash chromatography using hexanes/ EtOAc (15:1) as eluent to afford the title compound (0.524 g, 1.92 mmol, 61%) as a yellow oil.

Rᶠ: 0.67 (9:1 hexanes/EtOAc);

**HRMS (ESI):** MNa⁺ 295.1699, C₁₄H₂₈NaO₃Si requires 295.1700;

ν_{max} (film)/cm⁻¹: 2989, 1739, 1373, 1237, 1045, 604;

δ_H (400 MHz, CDCl₃): 5.77-5.68 (1H, m, H-4), 5.18-5.13 (2H, m, H-5), 4.28 (1H, d, J = 7.5 Hz, H-3), 3.65 (3H, s, OCH₃), 1.14 (3H, s, CH₃), 1.05 (3H, s, CH₃), 0.86 (9H, s, OSi'BuMe₂), 0.013 (3H, s, OSi'BuMe₂), -0.013 (3H, s, OSi'BuMe₂);

δ_C (100 MHz, CDCl₃): 177.2 (C=O, C-1), 137.5 (CH, C-4), 117.2 (CH₂, C-5), 78.9 (CH, C-3), 51.6 (OCH₃), 48.1 (C, C-2), 25.6 (3 x CH₃, OSi'BuMe₂), 21.2 (CH₃), 19.7 (CH₃), 18.0 (C, OSi'BuMe₂), -4.0 (CH₃), OSi'BuMe₂), -5.2 (CH₃, OSi'BuMe₂).

**Methyl 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethyl-4-oxobutanoate 320**

![Diagram 320]

Ozone was bubbled through a solution of alkene 321 (0.05 g, 0.18 mmol) in MeOH/CH₂Cl₂ (1:1, 1 mL) at -78 °C until a blue colour persisted. Oxygen was bubbled through the solution for 20 min and DMS (0.02 mL, 0.27 mmol) was added under a nitrogen atmosphere. The reaction mixture was allowed to warm to rt, stirred overnight and concentrated under reduced pressure to give the title compound (0.046 g, 0.16 mmol, 91%) as a colourless oil.

Rᶠ: 0.5 (9:1 hexanes/EtOAc);
Methyl 3-(ethoxymethoxy)-2,2-dimethylpent-4-enoate 323

\[
\text{Methyl 3-(ethoxymethoxy)-2,2-dimethylpent-4-enoate 323}
\]

DIPEA (0.22 mL, 1.27 mmol) and EMCl (0.23 mL, 2.53 mmol) were added to a solution of alkene 286 (0.1 g, 0.633 mmol) in CH₂Cl₂ (10 mL). The solution was stirred at rt for 12 h and quenched with sat. aq. NH₄Cl (10 mL) and the reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent gave the title compound (0.094 g, 0.44 mmol, 69%) as a yellow oil.

Rₚ: 0.73 (4:1 hexanes/EtOAc);

HRMS (ESI): M⁺Na⁺ 239.1257, C₁₁H₂₀NaO₄ requires 239.1254;

νₘₐₓ (film)/cm⁻¹: 2977, 1731, 1261, 1115, 1029, 928;

δ_H (400 MHz, CDCl₃): 5.72-5.63 (1H, m, H-4), 5.34-5.25 (2H, m, H-5), 4.67 (1H, d, J = 6.9 Hz, H-1’), 4.58 (1H, d, J = 6.9 Hz, H-1’), 4.23 (1H, d, J = 8.2 Hz, H-3), 3.68 (3H, s, OCH₃), 3.65-3.61 (1H, m, H-2’), 3.50-3.44 (1H, m, H-2’), 1.19 (6H, t, J = 7.0 Hz, H-3’, CH₃), 1.12 (3H, s, CH₃);

δ_C (100 MHz, CDCl₃): 176.8 (C=O, C-1), 133.9 (CH, C-4), 120.4 (CH₂, C-5), 92.4 (CH₂, C-1’), 82.1 (CH, C-3), 63.4 (CH₂, C-2’), 51.7 (OCH₃), 46.6 (C, C-2), 22.0 (CH₃), 19.8 (CH₃), 14.9 (CH₃, C-3’).
Ozone was bubbled through a solution of alkene 323 (0.1 g, 0.46 mmol) in CH$_2$Cl$_2$ (5 mL) at -78 °C until a blue colour persisted (10 min). Oxygen was bubbled through the reaction mixture to remove excess ozone. Under a nitrogen atmosphere DMS (0.1 mL, 1.4 mmol) was added, the reaction was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated under reduced pressure to give the *title compound* (0.09 g, 0.41 mmol, 90%) as a yellow oil.

R$_f$: 0.3 (9:1 hexanes/EtOAc);

**HRMS (ESI):** MH$^+$, 218.1152, C$_{11}$H$_{21}$O$_4$ requires 218.1154;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 2977, 1727, 1471, 1115, 1017, 928;

$\delta$$_H$ (400 MHz, CDCl$_3$): 9.68 (1H, d, $J = 2.3$ Hz, H-4), 4.78 (1H, d, $J = 6.9$ Hz, H-1’), 4.70 (1H, d, $J = 6.9$ Hz, H-1’), 3.90 (1H, d, $J = 2.2$ Hz, H-3), 3.71 (3H, s, OCH$_3$), 3.70-3.66 (2H, m, H-2’), 1.27 (3H, s, CH$_3$), 1.25 (3H, s, CH$_3$), 1.17 (3H, t, $J = 1.2$ Hz, H-3’);

$\delta$$_C$ (100 MHz, CDCl$_3$): 202.2 (C=O, C-4), 175.4 (C=O, C-1), 96.1 (CH, C-3), 86.3 (CH$_2$, C-1’), 64.1 (CH$_2$, C-2’), 52.2 (CH$_3$, OCH$_3$), 46.6 (C, C-2), 21.7 (CH$_3$), 21.5 (CH$_3$), 14.8 (CH$_3$, C-3’).

### 5.3.6 *Synthesis of alcohol 328*

(E)-*Ethyl 5-((tert-butyldimethylsilyl)oxy)-4,4-dimethylpent-2-enoate 330*

To a solution of NaH (60% in oil, 0.28 g, 6.94 mmol) in THF (40 mL) was added triethylphosphonoacetate 270 (2.3 mL, 11.6 mmol) at 0 °C. The reaction mixture was stirred for 10 min and a solution of aldehyde 315 (1.0 g, 4.63 mmol) in THF (40 mL) was added dropwise. The solution was allowed to warm to rt and stirred overnight. The reaction was quenched by the addition of H$_2$O (20 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave the *title compound* (0.842 g, 2.94 mmol, 63%) as a colourless oil.
\( R_f: 0.75 \) (9:1 hexanes/EtOAc);

\( \delta_H (400 \text{ MHz, CDCl}_3): 6.95 \) (1H, d, \( J = 16.0 \text{ Hz, } H-2 \)), \( 5.75 \) (1H, d, \( J = 16.0 \text{ Hz, } H-3 \)), \( 4.16 \) (2H, q, \( J = 7.0 \text{ Hz, } CH_2CH_3 \)), \( 3.34 \) (2H, s, H-5), \( 1.26 \) (3H, t, \( J = 7.0 \text{ Hz, } CH_3 \)), \( 1.01 \) (6H, s, 2 x CH_3), \( 0.87 \) (9H, s, OSiBuMe_2);

\( \delta_C (100 \text{ MHz, CDCl}_3): 167.1 \) (C=O, C-1), 155.9 (CH, C-3), 118.7 (CH, C-2), 70.9 (CH_2, C-5), 60.1 (CH_2, CH_2CH_3), 39.1 (C, C-4), \( 25.8 \) (3 x CH_3, OSiBuMe_2), 23.2 (2 x CH_3), 18.2 (C, OSiBuMe_2), 14.2 (CH_3, CH_2CH_3), \( -5.6 \) (2 x CH_3, OSiBuMe_2).

The spectroscopic data was in agreement with that reported in the literature. \(^{245}\)

**\((E)\-5\-((\text{tert-butyldimethylsilyl})\text{oxy})\-4,4\-\text{dimethylpent-2-en-ol 331}**

\[
\text{To a stirring solution of ester 330 (1.0 g, 3.49 mmol) in CH}_2\text{Cl}_2 (32 \text{ mL}) was added DIBAl-H (8.04 mL, 1M in toluene, 8.04 mmol) dropwise at -78 °C. The solution was stirred for 3 h and then quenched by the addition of MeOH (2 mL) and Rochelle Salts (20 mL). The reaction mixture was warmed to rt and stirred for 1 h and the reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the **title compound** (0.8 g, 3.27 mmol, 94%) as a colourless oil.**

\( R_f: 0.15 \) (9:1 hexanes/EtOAc);

\( \delta_H (400 \text{ MHz, CDCl}_3): 5.68 \) (1H, d, \( J = 16.0 \text{ Hz, } H-3 \)), \( 5.58 \) (1H, dt, \( J = 15.4,5.6 \text{ Hz, } H-2 \)), \( 4.08 \) (1H, t, \( J = 5.4 \text{ Hz, } H-1 \)), \( 3.28 \) (2H, s, H-5), \( 0.96 \) (6H, s, 2 x CH_3), \( 0.87 \) (9H, s, OSiBuMe_2), 0.00 (6H, s, OSiBuMe_2);

\( \delta_C (100 \text{ MHz, CDCl}_3): 140.4 \) (CH, C-3), 126.0 (CH, C-2), 71.7 (CH_2, C-5), 64.2 (CH_2, C-1), 38.0 (C, C-4), 25.9 (3 x CH_3, OSiBuMe_2), 23.8 (2 x CH_3, 4-CH_3), 18.3 (C, OSiBuMe_2), \( -5.6 \) (2 x CH_3, OSiBuMe_2).

The spectroscopic data was in agreement with that reported in the literature. \(^{245}\)
(E)-((5-bromo-2,2-dimethylpent-3-en-1-yl)oxy)(tert-butyl)dimethylsilane 327

\[ \text{Br} \quad \text{Me} \quad \text{Me} \quad \text{OTBS} \]

327

Triphenylphosphine (0.11 g, 0.43 mmol) and CBr₄ (0.16 g, 0.49 mmol) were added to a solution of alcohol 331 (0.1 g, 0.41 mmol) in CH₂Cl₂ (3 mL) at 0 °C. The reaction mixture was stirred for 20 min, sat. aq. NaHCO₃ (3 mL) was added and the solution was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The crude oil was purified by flash chromatography using 20:1 hexanes/EtOAc as eluent to give the title compound (0.78 g, 0.25 mmol, 62%) as a colourless oil.

R°: 0.93 (9:1 hexanes/EtOAc);

HRMS (ESI): MNa⁺ 329.0920, C₁₃H₂₇BrNaOSi requires 329.0907;

vₘₐₓ (film)/cm⁻¹: 2929, 1469, 1096, 837, 503;

δH (400 MHz, CDCl₃): 5.77 (1H, d, J = 15.5 Hz, H-3), 5.65 (1H, dt, J = 15.2, 7.7 Hz, H-4), 3.98 (2H, d, J = 7.3 Hz, H-5), 3.29 (2H, s, H-1), 0.98 (6H, s, 2 x CH₃), 0.89 (9H, s, OSi′BuMe₂), 0.02 (6H, s, OSi′BuMe₂);

δC (100 MHz, CDCl₃): 143.4 (CH, C-3), 123.6 (CH, C-4), 71.5 (CH₂, C-1), 38.3 (C, C-2), 33.9 (CH₂, C-5), 25.9 (3 x CH₃, OSi′BuMe₂), 23.7 (2 x CH₃), 18.3 (C, OSi′BuMe₂), -5.5 (2 x CH₃, OSi′BuMe₂).

(2S,E)-1-(benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-10-(((tert-butyldimethylsilyl)oxy)-9,9-dimethyldec-7-en-5-ol 328

\[ \text{BnO} \quad \text{OH} \quad \text{Me} \quad \text{Me} \quad \text{OTBS} \]

328

A solution of bromide 327 (95 mg, 0.31 mmol) in THF (0.4 mL) was added to activated Zn (0.02 g, 0.31 mmol) [stirred with a crystal of iodine till the solution turned colourless] in THF (0.1 mL). The suspension was stirred for 10-15 min, a solution of aldehyde 255 (0.05 g, 0.16 mmol) in THF (0.5 mL) was added and the solution was stirred at rt overnight. NH₄Cl (aq, 0.2 mL) was added, the mixture was extracted with Et₂O (3 x 1 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography using 20:1 hexanes/EtOAc to give a yellow oil (0.017 g, 0.03 mmol, 20%).

R°: 0.31 (9:1 hexanes/EtOAc);

HRMS (ESI): MH⁺ 554.3925, C₃₁H₅₀O₄Si₂ requires 551.3946;

vₘₐₓ (film)/cm⁻¹: 3433, 2927, 1728, 1464, 1094, 836;
[α]₀^20 = -8.4 (c 1.0, CHCl₃);

δ_(H) (400 MHz, CDCl₃): 7.36-7.26 (10H, m, Ph), 5.52 (1H, d, J = 15.9 Hz, H-8), 5.40-5.32 (1H, m, H-7), 4.52 (4H, s, CH₂Ph), 3.94-3.84 (2H, m, H-2, H-2’), 3.58-3.50 (1H, m, H-5), 3.44-3.33 (4H, m, H-1, H-1’), 3.27 (2H, s, H-10), 2.26-2.19 (1H, m, H-6), 2.11-2.03 (1H, m, H-6), 1.66-1.49 (4H, m, H-3, H-4), 0.96 (6H, d, J = 2.6 Hz, 2 x CH₃), 0.88 (9H, s, OSi’BuMe₂), 0.87 (9H, d, J = 2.0 Hz, OSi’BuMe₂), 0.07-0.04 (12H, m, 2 x OSi’BuMe₂);

δ_(C) (100 MHz, CDCl₃): 142.1 (CH, C-8), 141.9 (CH, C-8’), 138.4 (C, Ph), 128.3 (2 x CH, Ph), 128.3 (CH, Ph), 127.6 (CH, Ph), 123.0 (CH, C-7), 122.9 (CH, C-7’), 74.6 (CH₂C-1), 74.4 (CH₂C-1’), 73.3 (CH₂, CH₂Ph), 71.9 (CH₂, C-10), 71.5 (CH, C-2), 71.3 (CH, C-2’), 71.0 (CH, C-5), 70.6 (CH, C-5’), 40.9 (CH₂, C-6), 38.4 (C, C-9), 32.2 (CH₂, C-4), 31.9 (CH₂, C-4’), 31.1 (CH₂, C-3), 30.6 (CH₂, C-3’), 25.9 (6 x CH₃, OSi’BuMe₂), 24.1 (CH₃), 23.9 (CH₃), 18.4 (C, OSi’BuMe₂), 18.3 (C, OSi’BuMe₂), -4.41 (CH₃, OSi’BuMe₂), -4.71 (CH₃, OSi’BuMe₂), -4.88 (CH₃, OSi’BuMe₂), -5.48 (CH₃, OSi’BuMe₂).

5.3.7 Synthesis of dithiane 252

(S)-((1-(benzyloxy))-4-(1,3-dithian-2-yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane 252

1,3-Propanedithiol (0.18 mL, 1.86 mmol) and CoCl₂·6H₂O (19 mg, 0.08 mmol) were added to a solution of aldehyde 255 (0.50 g, 1.55 mmol) in MeCN (5 mL). The solution was stirred for 2 h at rt and then concentrated under reduced pressure to give a crude oil. The compound was purified by flash chromatography using 20:1 hexanes/EtOAc as eluent to give the title compound (0.36 g, 0.87 mmol, 57%) as a colourless oil.

Rf: 0.69 (4:1 hexanes/EtOAc);

[α]₀D = -6.5 (c 1.0 in CHCl₃);

HRMS (ESI): MNa⁺ 435.1818, C₂₃H₃₆NaO₂S₂Si requires 435.1821;

ν (film)/cm⁻¹: 2928, 1738, 1248, 1095, 834, 735;

δ_(H) (400 MHz, CDCl₃): 7.34-7.27 (5H, m, Ph), 4.51 (2H, s, CH₂Ph), 4.02 (1H, t, J = 6.5 Hz, H-1), 3.88-3.82 (1H, m, H-4), 3.43-3.32 (2H, m, H-5), 2.90-2.77 (4H, m, CH(SCH₂)₂CH₃), 2.14-2.06 (1H, m, CH(SCH₂)₂CH₂H₈), 1.92-1.74 (4H, m, CH(SCH₂)₂CH₂H₂O, H-2, H-3a), 1.70-1.63 (1H, m, H-3b), 0.88 (9H, s, OSi’BuMe₂), 0.05 (6H, d, J = 7.7 Hz, OSi’BuMe₂);
Experimental: Part 2

δC (100 MHz, CDCl3): 138.3 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 74.4 (CH2 - C-5), 73.3 (CH2, OCH3Ph), 70.8 (CH, C-4), 47.7 (CH, C-1), 31.6 (CH2, C-3), 31.1 (CH2, CH(SCH2)2CH2), 30.4 (2 x CH2, C-2, CH(SCH2)2CH2), 26.0 (CH2, CH(SCH2)2CH2), 25.8 (3 x CH3, OSi'BuMe2), 18.1 (C, OSi'BuMe2), -4.4 (CH3, OSi'BuMe2), -4.8 (CH3, OSi'BuMe2).

5.3.8 Synthesis of alkene 347

(2S)-Tetrahydro-5-hydroxy-2-(benzyloxymethyl)furan 353

![Formula](image)

To a solution of alkene 284 (0.2 g, 0.97 mmol) in dioxane/H2O (3:1, 4 mL) was added 2,6-lutidine (0.11 mL, 0.97 mmol), OsO4 (0.25 mL, 2.5% solution in t-BuOH, 2 μmol) and NaIO4 (0.42 g, 1.94 mmol) respectively. The suspension was stirred for 2 h and sat. aq. Na2S2O3 (2 mL) was added. The reaction mixture was extracted with EtOAc (3 x 5 mL), the combined organic extracts were washed with brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent gave the title compound (0.14 g, 0.694 mmol, 71%) as a colourless oil (1:1 mixture of diastereomers).

Rf: 0.23 (9:1 hexanes/EtOAc);

δH (400 MHz, CDCl3): 7.37-7.27 (10H, m, PhH), 5.60-5.58 (1H, m, H-4), 5.45-5.42 (1H, m, H-4'), 4.60-4.56 (4H, m, CH2Ph), 4.47-4.40 (1H, m, H-1), 4.33-4.27 (1H, m, H-1'), 3.70-3.56 (2H, m, H-5), 3.51-3.42 (2H, m, H-5'), 2.66-1.66 (8H, m, H-2, H-2', H-3, H-3'), 1.95 (2H, br s, 2 x OH);

δC (100 MHz, CDCl3): 138.2 (C, Ph), 137.6 (C’, Ph), 128.5 (2 x CH, Ph), 128.3 (CH, Ph), 127.9 (2 x CH, Ph), 127.8 (2 x CH, Ph), 127.7 (CH, Ph), 127.6 (CH, Ph), 127.6 (CH, Ph), 98.9 (CH, C-4), 98.8 (CH, C-4’), 78.9 (CH, C-1), 78.7 (CH, C-1’), 73.5 (CH2, CH2Ph), 72.5 (CH2, CH2Ph), 34.6 (CH2, C-3), 32.7 (CH2, C-3’), 25.8 (CH2, C-2), 24.5 (CH2, C-2’).

The spectroscopic data was in agreement with that reported in the literature.246

(2S)-Benzyloxymethyl-5-allyltetrahydrofuran 347

![Formula](image)

To a solution of alcohol 353 (5.34 g, 25.9 mmol) in CH2Cl2 (125 mL) at -78 °C was added allyl TMS (12.4 mL, 77.7 mmol) followed by dropwise addition of BF3·OEt2 (3.49 mL, 28.5 mmol). The reaction mixture was stirred for 3 h and sat. aq. NH4Cl (20 mL) was added and the mixture was extracted with CH2Cl2 (3 x 20 mL). The
combined organic extracts were washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a 1:1 mixture of diastereoisomers of the title compound (5.0 g, 21.5 mmol, 83%) as a yellow oil.

$R_f$: 0.38 (9:1 hexanes/EtOAc);

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 7.36-7.25 (5H, m, PhH), 5.81 (1H, ddt, $J$ = 17.2, 10.2, 7.0 Hz, H-7), 5.10-5.02 (2H, m, H-8), 4.57 (2H, dd, $J$ = 5.6, 12.3 Hz, CH$_2$Ph), 4.23-4.17 (0.3H, m, H-4), 4.11-4.00 (1H, m, H-4'), 3.97-3.90 (0.7H, m, H-1), 3.51-3.42 (2H, m, H-5), 2.42-2.35 (1H, m, H-6), 2.27-2.19 (1H, m, H-6'), 2.03-1.87 (2H, m, H-2, H-3), 1.71-1.64 (1H, m, H-3'), 1.59-1.51 (1H, m, H-2');

$\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 138.4 (C, Ph), 135.0 (2 x CH, C-7, C-7'), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 116.8 (CH$_2$, C-8), 116.8 (CH$_2$, C-8'), 79.2 (CH, C-4), 78.7 (CH, C-4'), 78.1 (CH, C-1), 77.7 (CH, C-1'), 73.3 (CH$_2$, CH$_2$Ph), 73.0 (CH$_3$, H-5), 72.9 (CH$_2$, H-5'), 40.2 (CH$_2$, C-6), 40.1 (CH$_2$, C-6'), 31.1 (CH$_2$, C-2), 30.2 (CH$_2$, C-2'), 28.5 (CH$_2$, C-3), 28.1 (CH$_2$, C-3').

The spectroscopic data was in agreement with that reported in the literature.$^{247}$

5.3.9 Synthesis of alkenes 354 and 358

Benzyl 3-hydroxy-2,2-dimethylpropanoate 356

LiOH (15.9 g, 37.9 mmol) in THF/MeOH/H$_2$O (1:1:0.5, 62.5 mL) was added to a solution of 3-hydroxy-2,2-dimethylpropionate 169 (5 g, 37.9 mmol) in THF/MeOH (1:1, 25 mL) at 0 °C. The solution was warmed to rt and stirred for 1.5 h. The reaction mixture was adjusted to pH 2 by addition of H$_2$SO$_4$. The solution was then concentrated under reduced pressure to remove THF and the residue was washed with H$_2$O (10 mL), extracted with EtOAc (3 x 12 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the acid (3.3 g, 27.9 mmol, 73%) as a white solid.

Benzyl bromide (1.9 mL, 16.1 mmol) was added to a solution of crude acid (2.0 g, 16.9 mmol) and K$_2$CO$_3$ (2.57 g, 18.6 mmol) in DMF (20 mL). The reaction mixture was stirred for 5 h and then quenched by the addition of H$_2$O (5 mL). The reaction mixture was extracted with Et$_2$O (3 x 10 mL), the combined organic extracts were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography using 9:1 to 3:2 hexanes/EtOAc as eluent gave the title compound (3.04 g, 14.6 mmol, 86%) as a yellow oil.

$R_f$: 0.48 (3:2 hexanes/EtOAc);
Experimental: Part 2

δH (400 MHz, CDCl3): 7.39-7.29 (5H, m, Ph), 5.14 (2H, s, CH3Ph), 3.57 (2H, d, J = 6.4 Hz, H-3), 2.54 (1H, br s, OH), 1.21 (6H, s, 2 x CH3);

δc (100 MHz, CDCl3): 176.9 (C=O, C-1), 135.8 (C, Ph), 128.3 (2 x CH, Ph), 127.9 (CH, Ph) 127.5 (2 x CH, Ph), 69.3 (CH2, C-3), 66.1 (CH2, CH2Ph), 44.2 (C, C-2), 21.8 (2 x CH3).

The spectroscopic data was in agreement with those reported in literature.166

**Benzyl 2,2-dimethyl-3-oxopropanoate 357**

![357]

Oxalyl chloride (2.5 mL, 29.2 mmol) was added dropwise to a solution of DMSO (4.14 mL, 58.4 mmol) in CH2Cl2 (100 mL) at -78 °C. The reaction mixture was stirred for 10 min and a solution of alcohol 356 (5.0 g, 24.3 mmol) in CH2Cl2 (20 mL) was added. The solution was stirred for 1 h, NEt3 (13.5 mL, 97.3 mmol) was added and the solution was allowed to warm to rt. H2O (25 mL) was added and the mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na2SO4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave the **title compound** (4.13 g, 20.0 mmol, 82%) as a yellow oil.

Rf: 0.58 (4:1 hexanes/EtOAc);

δH (400 MHz, CDCl3): 9.68 (1H, s, H-3), 7.39-7.31 (5H, m, Ph), 5.19 (2H, s, CH3Ph), 1.37 (6H, s, 2 x CH3);

δc (100 MHz, CDCl3): 198.9 (C=O, C-3), 172.5 (C=O, C-1), 135.3 (C, Ph), 128.6 (2 x CH, Ph) 128.3 (CH, Ph), 127.9 (2 x CH, Ph), 67.1 (CH2, CH2Ph), 45.9 (C, C-2), 19.6 (2 x CH3).

The spectroscopic data was in agreement with that reported in the literature.167

**Benzyl 2,2-dimethylbut-3-enoate 354**

![354]

To a solution of methyl triphenylphosphonium bromide (5.2 g, 14.5 mmol) in THF (40 mL) was added LiHMDS (17.1 mL, 0.85 M in THF, 14.5 mmol) at 0 °C. The reaction mixture was stirred for 30 min and a solution of aldehyde 357 (2 g, 9.71 mmol) was added. The solution was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH4Cl (15 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL), the combined organic extracts were washed with brine (20 mL), dried over Na2SO4 and concentrated under reduced
pressure. Purification by column chromatography using 20:1 hexanes/EtOAc as eluent gave the *title compound* (0.75 g, 3.67 mmol, 38%) as a yellow oil.

\[ R_f : 0.77 \text{ (9:1 hexanes/EtOAc);} \]

**HRMS (ESI):** MNa⁺, 227.1040, C₁₃H₁₆NaO₂ requires 227.1043;

\[ v_{\text{max}} \text{ (film)/cm}^{-1} : 2977, 1728, 1259, 1132, 695; \]

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{):} 7.37-7.29 \text{ (5H, m, Ph), 6.05 \text{ (1H, dd, } J = 17.4, 10.5 \text{ Hz, H-3), 5.11 \text{ (3H, s, CH}_3\text{Ph, H-4),} 5.06 \text{ (1H, d, } J = 10.5 \text{ Hz, H-4),} 1.33 \text{ (6H, s, 2 x CH}_3\text{);} \]

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{):} 176.1 \text{ (C=O, C-1), 142.4 \text{ (CH, C-3), 136.3 \text{ (C, Ph), 128.5 \text{ (2 x CH, Ph),} 127.9 \text{ (CH, Ph),} 127.7 \text{ (2 x CH, Ph),} 113.0 \text{ (CH}_2\text{, C-4), 66.3 \text{ (CH}_2\text{, CH}_3\text{Ph),} 44.9 \text{ (C, C-2),} 24.6 \text{ (2x CH}_3\text{).} \]

**Tert-butyl((2,2-dimethylbut-3-en-1-yl)oxy)dimethylsilane 358**

To a solution of methyltriphenylphosphonium bromide (4.96 g, 13.9 mmol) in THF (20 mL) was added LiHMDS (16.3 mL, 0.85M in THF, 13.9 mmol) at 0 °C. A solution of aldehyde 315 (2 g, 9.25 mmol) in THF (10 mL) was added after 30 min and the solution was allowed to warm to rt. The reaction mixture was stirred overnight and quenched by the addition of sat. aq. NH₄Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography using 20:1 hexanes/EtOAc as eluent afforded the *title compound* (1.3 g, 6.07 mmol, 65%) as a yellow oil.

\[ R_f : 0.9 \text{ (12:1 hexanes/EtOAc);} \]

**HRMS (ESI):** MH⁺, 215.1751, C₁₂H₂₇OSi requires 215.1753;

\[ v_{\text{max}} \text{ (film)/cm}^{-1} : 2929, 2857, 1467, 1253, 1096, 847; \]

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{):} 5.84 \text{ (1H, dd, } J = 17.6, 10.7 \text{ Hz, H-3), 5.00-4.93 \text{ (2H, m, H-4),} 3.29 \text{ (2H, s, H-1),} 0.97 \text{ (6H, s, 2 x CH}_3\text{),} 0.89 \text{ (9H, s, OSi}^\text{BuMe}_2\text{),} 0.02 \text{ (6H, s, OSi}^\text{BuMe}_2\text{);} \]

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{):} 146.1 \text{ (CH, C-3), 111.3 \text{ (CH}_2\text{, C-4),} 71.7 \text{ (CH}_2\text{, C-1),} 38.9 \text{ (C, C-2),} 25.9 \text{ (3 x CH}_3\text{, OSi}^\text{BuMe}_2\text{),} 23.5 \text{ (2 x CH}_3\text{),} 18.3 \text{ (C, OSi}^\text{BuMe}_2\text{),} -5.4 \text{ (2 x CH}_3\text{, OSi}^\text{BuMe}_2\text{).} \]
5.3.10 Synthesis of alkene 360

\(((5-(5S)-5-((benzylxy)methyl)tetrahydrofuran-2-yl)-2,2-dimethylpent-3-en-1-yl)oxy)(tert-butyl)dimethylsilane 359\)

A solution of alkene 358 (0.05 g, 0.22 mmol) and alkene 347 (0.18 g, 0.86 mmol) in DCE (0.5 mL) in a screw-capped vial was degassed by freeze-pump-thaw method. A solution of Grubbs’II (0.01 g, 0.01 mmol) in DCE (0.2 mL) (freeze-pump-thaw) under Argon was added. The solution was heated at 80 °C for 15 h. A further portion of Grubbs’ II (0.01 g, 0.01 mmol) in DCE (0.2 mL) was added and the solution was stirred for 20 h. Purification by column chromatography using 20:1 hexanes/EtOAc as eluent afforded the title compound (0.01 g, 0.03 mmol, 12%) as a yellow oil.

\(R_f: 0.4 (12:1 \text{ hexanes/EtOAc});\)

HRMS (ESI): M\(^{+}\)Na, 441.2796, C\(_{25}\)H\(_{42}\)NaO\(_3\)Si requires 441.2795;

\(v_{\text{max}}\) (film)/cm\(^{-1}\): 2929, 2856, 1466, 1256, 1095, 843;

\(\delta\)H (\(400\) MHz, CDCl\(_3\)): 7.35-7.27 (5H, m, PhH), 5.48 (1H, dd, \(J = 15.8, 3.6\) Hz, H-3), 5.40-5.32 (1H, m, H-4), 4.58 (2H, q, \(J = 12.1\) Hz, \(2 \times \text{CH}_2\)Ph), 3.76 (1H, dd, \(J = 15.8, 3.6\) Hz, H-3), 3.51-3.41 (2H, m, H-10), 3.25 (2H, s, H-1), 1.98-1.60 (4H, m, H-7, H-8), 0.94 (6 H, d, \(J = 1.2\) Hz, \(2 \times \text{CH}_3\)), 0.88 (9H, s, OSi\(^t\)BuMe\(_2\)), 0.08 (6H, s, OSi\(^t\)BuMe\(_2\));

\(\delta\)C (\(100\) MHz, CDCl\(_3\)): 140.4 (CH, C-3), 140.3 (CH, C-3’), 138.4 (C, Ph), 128.3 (2 x CH, Ph) 127.7 (CH, Ph), 127.5 (2 x CH, Ph), 122.9 (2 x CH, C-4, C-4’), 79.7 (CH, C-6), 79.3 (CH, C-6’), 78.1 (CH, C-9), 77.7 (CH, C-9’), 73.3 (CH\(_2\), CH\(_3\)Ph), 73.1 (CH\(_2\), C-10), 72.9 (CH\(_2\), C-10’), 72.0 (CH\(_2\), C-1), 39.2 (CH\(_2\), C-5), 39.1 (CH\(_2\), C-5’), 38.2 (C, C-2), 30.9 (CH\(_2\), C-7), 29.9 (CH\(_2\), C-7’), 28.5 (CH\(_2\), C-8), 28.1 (CH\(_2\), C-8’), 25.9 (3 x CH\(_3\), OSi\(^t\)BuMe\(_2\)), 24.0 (2 x CH\(_3\)), 18.3 (C, OSi\(^t\)BuMe\(_2\)), -5.4 (2 x CH\(_3\), OSi\(^t\)BuMe\(_2\)).

**Benzyl 5-((5S)-5-((benzylxy)methyl)tetrahydrofuran-2-yl)-2,2-dimethylpent-3-enoate 360**

A solution of alkene 347 (0.1 g, 0.43 mmol) and alkene 354 (0.35 g, 1.7 mmol) in toluene (3 mL) in a microwave vessel was degassed by freeze-pump-thaw method. A solution of Grubbs’II (0.04 g, 0.04 mmol) in
toluene (1 mL) under Argon was added. Chlorodicyclohexyl borane (0.04 mL, 1 M in hexane, 0.04 mmol) was added and the solution heated in the microwave at 90 °C for 9h. Purification by column chromatography afforded the title compound (0.04 g, 0.09 mmol, 22%) as a yellow oil.

R_f: 0.51 (4:1 hexanes/EtOAc);

HRMS (ESI): MNa^+, 431.2194, C_{26}H_{32}NaO_4 requires 431.2193;

ν_{max} (film)/cm⁻¹: 2930, 1726, 1455, 1130, 697;

δ_H (400 MHz, CDCl₃): 7.36-7.25 (10H, m, PhH), 5.69 (1H, dt, J = 15.6, 1.4 Hz, H-3), 5.53-5.45 (1H, m, H-4), 5.09 (2H, s, CH₂Ph), 4.61-4.52 (2H, m, CH₂Ph), 4.20-4.14 (0.4 H, m, H-9), 4.10-4.03 (0.6 H, m, H-6), 3.48-3.40 (2H, m, H-10), 2.40-2.32 (1H, m, H-5), 2.24-2.13 (1H, m, H-5), 1.98-1.78 (2H, m, H-8), 1.67-1.58 (2H, m, H-7), 1.30 (6 H, d, J = 3.45 Hz, 2 x CH₃);

δ_C (100 MHz, CDCl₃): 176.3 (C=O, C-1), 138.4 (C, Ph), 136.7 (2 x CH, 2 x C-3), 136.3 (C, Ph), 128.4 (2 x CH, Ph) 128.3 (2 x CH, Ph), 127.9 (CH, Ph),127.7 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 124.9 (2 x CH, 2 x C-4), 79.3 (CH, C-9), 78.8 (CH, C-9), 78.1 (CH, C-6), 77.8 (CH, C-6), 73.3 (CH₂, CH₃Ph), 73.0 (CH₂, C-10), 72.9 (CH₂, C-10), 66.2 (CH₂, CH₃Ph), 44.2 (C, C-2), 38.8 (CH₂, C-5), 38.7 (CH₂, C-5), 30.8 (CH₂, C-7), 29.9 (CH₂, C-7), 28.5 (CH₂, C-8), 28.1 (CH₂, C-8), 25.1 (2 x CH₃).

5.3.11 Synthesis of lactones 345-383

2-(((S)-5-((benzylOxy)methyl)tetrahydrofuran-2-yl)acetaldehyde 363

Ozone was bubbled through a solution of alkene 347 (0.1 g, 0.43 mmol) in MeOH/CH₂Cl₂ (1:1, 1 mL) at -78 °C until a blue colour persisted (10 min). Oxygen was bubbled through the reaction mixture to remove excess ozone. Under a nitrogen atmosphere DMS (0.1 mL, 1.4 mmol) was added, the reaction was allowed to warm to rt and stirred overnight. The reaction mixture was then concentrated under reduced pressure to give the title compound (0.09 g, 0.38 mmol, 89%) as a colourless oil.

R_f: 0.4 (3:2 hexanes/EtOAc);

HRMS (ESI): MH^+, 235.1329, C_{14}H_{19}O₃ requires 235.1320;

δ_H (400 MHz, CDCl₃): 9.81-9.79 (1H, m, H-7), 7.34-7.27 (5H, m, Ph), 4.61-4.52 (2H, m, CH₂Ph), 4.47-4.40 (0.34 H, m, H-1), 4.37-4.30 (0.58H, m, H-1), 4.26-4.20 (0.42H, m, H-4), 4.14-4.08 (0.86H, m, H-4), 3.50-3.44 (2H, m, H-5), 2.75-2.67 (1H, m, H-6), 2.62-2.54 (1H, m, H-6'), 2.14-1.94 (2H, m, H-2, H-3), 1.79-1.69 (1H, m, H-3), 1.63-1.52 (1H, m, H-2);
δ_C (100 MHz, CDCl₃): 201.25 (C=O, C-7), 138.3 (C, Ph), 128.4 (2 x CH, Ph), 127.7 (2 x CH, Ph), 127.6 (CH, Ph), 78.5(CH, C-4), 78.0 (CH, C-4’), 74.6 (CH, C-1), 74.1 (CH, C-1’), 73.3 (CH₂, CH₂Ph), 72.7 (CH₂, C-5), 49.6 (CH₂, C-6), 49.5 (CH₂, C-6’), 31.9 (CH₂, C-2), 31.1 (CH₂, C-2’), 28.3 (CH₂, C-3), 27.9 (CH₂, C-3).

A solution of (DHQD)₂PHAL (0.009 g, 0.01 mmol), methanesulfonamide (0.023 g, 0.02 mmol), OsO₄ (0.02 mL, 2.5% solution in t-BuOH, 2.4 μmol), K₂Fe(CN)₆ (0.23 g, 0.73 mmol) and K₂CO₃ (0.09 g, 0.73 mmol) in t-BuOH/H₂O (1 mL) was stirred for 30 min. A solution of alkene 360 (0.10 g, 0.24 mmol) in t-BuOH/H₂O (0.3 mL) was added and the reaction mixture was stirred at rt overnight before Na₂SO₃ (0.02 g) was added. The suspension was stirred for 30 min and the mixture was extracted with EtOAc (3 x 1 mL), the combined organic extracts were washed with 2 N KOH (0.01 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a separable 1:1 mixture of diastereomers as yellow oils (0.06 g, 0.18 mmol, 73%).

Rᵣ: 0.36 (3:2 hexanes/EtOAc);

[α]₀ +12.1 (c 1.0 in CHCl₃);

HRMS (ESI): MNa⁺ 357.1677 , C₁₉H₂₆NaO₅ requires 357.1672;

ν_max (film)/cm⁻¹: 3438, 2926, 1765, 1456, 1095;

δ_H (400 MHz, CDCl₃): 7.37-7.27 (5H, m, PhH), 4.55 (2H, s, CH₂Ph), 4.54-4.50 (1H, m, H-4), 4.27-4.21 (1H, m, H-9), 4.07-4.00 (2H, m, H-6, H-3), 3.73 (1H, d, J = 2.6 Hz, OH), 3.48 (1H, dt, J = 12.5, 10.2, 4.8 Hz, H-10), 2.21-2.13 (2H, m, H-5), 2.08-1.97 (1H, m, H-8), 1.18-1.59 (3H, m, H-8, H-7), 1.26 (6H, d, J = 1.98 Hz, 2 x CH₃);

δ_C (100 MHz, CDCl₃): 181.0 (C=O, C-1), 138.1 (C, Ph), 128.4 (2 x CH, Ph), 127.6 (CH, Ph), 127.5 (2 x CH, Ph), 80.1 (CH, C-4), 78.6 (CH, C-9), 76.4 (CH, C-6), 75.7 (CH, C-3), 73.2 (CH₂, CH₂Ph), 72.4 (CH, C-10), 45.0 (C, C-2), 34.5 (CH₂, C-5), 32.9 (CH₂, C-7), 28.2 (CH₂, C-8), 23.2 (CH₃), 17.8 (CH₃).

(4R,5R)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 345b
**Experimental: Part 2**

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R<sub>f</sub>: 0.25 (3:2 hexanes/EtOAc);

[α]<sub>D</sub> +7.0 (c 0.3 in CHCl<sub>3</sub>);

**HRMS (ESI):** MNa<sup>+</sup> 357.1682, C<sub>19</sub>H<sub>26</sub>NaO<sub>5</sub> requires 357.1672;

ν<sub>max</sub> (film)/cm<sup>-1</sup>: 3439, 2920, 1759, 1458, 1088;

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 7.37-7.27 (5H, m, PhH), 4.67-4.62 (1H, m, H-4), 4.54 (2H, s, CH<sub>2</sub>Ph), 4.14-4.09 (2H, m, H-9, H-6), 3.95 (1H, d, J = 3.4 Hz, H-3), 3.58 (1H, dd, J = 10.1, 3.4 Hz, H-10), 3.46 (1H, dd, J = 10.2, 4.7 Hz, H-10), 2.37-2.29 (1H, m, H-5), 2.15-2.09 (1H, m, H-5), 2.03-1.92 (2H, m, H-8), 1.90-1.83 (1H, m, H-7), 1.76-1.65 (1H, m, H-7), 1.21 (3H, s, CH<sub>3</sub>), 1.09 (3H, s, CH<sub>3</sub>);

δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 181.0 (C=O, C-1), 138.1 (C, Ph), 128.4 (2 x CH, Ph), 127.7 (CH, Ph), 127.6 (2 x CH, Ph), 78.1 (CH, C-9), 77.8 (CH, C-4), 76.3 (CH, C-3), 76.1 (CH, C-6), 73.4 (CH<sub>2</sub>, CH<sub>2</sub>Ph), 72.2 (CH, C-10), 45.0 (C, C-2), 31.3 (CH<sub>2</sub>, C-5), 29.1 (CH<sub>2</sub>, C-7), 27.7 (CH<sub>2</sub>, C-8), 23.2 (CH<sub>3</sub>), 17.9 (CH<sub>3</sub>)

*(4S,5S)-5-(((2R,5R)-5-((benzyl)oxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 380*

A solution of (DHQ)<sub>2</sub>PHAL (0.016 g, 0.02 mmol), methanesulfonamide (0.04 g, 0.04 mmol), OsO<sub>4</sub> (0.4 mL, 2.5% solution in t-BuOH, 0.04 mmol), K<sub>3</sub>Fe(CN)<sub>6</sub> (0.4 g, 1.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.18 g, 1.3 mmol) in t-BuOH/H<sub>2</sub>O (1 mL) was stirred for 30 min. A solution of alkene 359 (0.18 g, 0.43 mmol) in t-BuOH/H<sub>2</sub>O (0.3 mL) was added and the reaction mixture was stirred at rt overnight before Na<sub>2</sub>SO<sub>3</sub> (0.02 g) was added. The suspension was stirred for 30 min and the mixture was extracted with EtOAc (3 x 3 mL), the combined organic extracts were washed with 2 N KOH (0.01 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a separable 1:1 mixture of diastereomers (0.11 g, 0.33 mmol, 76%) as white solids.

R<sub>f</sub>: 0.36 (3:2 hexanes/EtOAc);

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[Image of chemical structure of 345b and 380]
Experimental: Part 2

$[\alpha]_D$ -37.5 (c 1.0 in CHCl$_3$);

**Mp:** 60-64 °C;

**HRMS (ESI):** MK$^+$ 373.1207, C$_{19}$H$_{26}$KO$_5$ requires 373.1412;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3430, 2930, 1762, 1457, 1068;

$\delta$H (400 MHz, CDCl$_3$): 7.36-7.26 (5H, PhH), 4.54 (2H, s, CH$_2$Ph), 4.54-4.50 (1H, m, H-4), 4.18-4.12 (1H, m, H-9), 4.04-4.02 (2H, m, H-6, H-3), 3.99 (1H, d, $J = 2.9$ Hz, OH), 3.52 (1H, dd, $J = 10.0$, 3.6 Hz, H-10), 3.38 (1H, dd, $J = 10.1$, 5.7 Hz, H-10), 2.17-2.04 (3H, m, H-5, H-7), 1.98-1.89 (1H, m, H-8), 1.87-1.78 (1H, m, H-8), 1.74-1.64 (1H, m, H-7), 1.28 (3H, s, CH$_3$), 1.26 (3H, s, CH$_3$);

$\delta$C (100 MHz, CDCl$_3$): 181.1 (C=O, C-1), 137.5 (C, Ph), 128.4 (2 x CH, Ph), 128.1 (2 x CH, Ph), 127.8 (CH, Ph), 80.4 (CH, C-4), 78.8 (CH, C-9), 76.5 (CH, C-6), 76.5 (CH, C-3), 73.5 (CH$_2$, CH$_2$Ph), 71.8 (CH, C-10), 45.0 (C, C-2), 34.9 (CH$_2$, C-5), 32.1 (CH$_2$, C-7), 27.4 (CH$_2$, C-8), 23.2 (CH$_3$), 17.9 (CH$_3$).

(4S,5S)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethylidihydrofuran-2(3H)-one 383

\[ \text{Rf: 0.25 (3:2 hexanes: EtOAc)} \]

$[\alpha]_D$ -18 (c 0.3 in CHCl$_3$);

**Mp:** 59-65 °C;

**HRMS (ESI):** MNa$^+$,357.1675, C$_{19}$H$_{26}$NaO$_5$ requires 357.1672;

$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3441, 2929, 1763, 1466, 1095;

$\delta$H (400 MHz, CDCl$_3$): 7.36-7.26 (5H, m, PhH), 4.71-4.66 (1H, H-4), 4.55 (2H, s, CH$_2$Ph), 4.26-4.19 (2H, m, H-6, H-9), 3.92 (1H, t, $J = 3.6$ Hz, H-3), 3.61 (1H, d, $J = 3.6$ Hz, OH), 3.46 (2H, d, $J = 4.9$, H-10), 2.31-2.24 (1H, m, H-5), 2.14-2.02 (3H, m, H-5, H-8), 1.79-1.63 (2H, m, H-7), 1.26 (6H, d, $J = 3.5$ Hz, 2 x CH$_3$);

$\delta$C (100 MHz, CDCl$_3$): 180.8 (C=O, C-1), 138.1(C, Ph), 128.4 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.6 (CH, Ph), 78.3 (CH, C-9), 77.8 (CH, C-4), 76.5 (CH, C-3), 75.4 (CH, C-6), 73.4 (CH$_2$, CH$_2$Ph), 72.6 (CH$_2$, C-10), 45.2 (C, C-2), 31.8 (CH$_2$, C-5), 30.4 (CH$_2$, C-7), 28.5 (CH$_2$, C-8), 23.3 (CH$_3$), 17.9 (CH$_3$).
5.3.12 Synthesis of spiroacetals 164-393

\((2S,3a'R,5S,6a'R)-5'-((benzyloxy)methyl)-6',6'-\text{dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 164a}\)

A solution of lactone 345a (0.02 g, 0.06 mmol) in CH\(_2\)Cl\(_2\) (0.1 mL) was added to a stirring solution of PhI(OAc)\(_2\) (0.04 g, 0.12 mmol) and I\(_2\) (0.04 g, 0.14 mmol) in hexane (0.2 mL). N\(_2\) gas was bubbled through the solution for 5 min and the reaction was then irradiated with a 75 W desk lamp for 1 h. The solution was diluted with Et\(_2\)O (0.2 mL) and saturated aq. Na\(_2\)S\(_2\)O\(_3\) (0.1 mL) was added, the mixture was extracted with Et\(_2\)O (3 x 1 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification on deactivated silica using 9:1 to 3:2 hexanes: EtOAc gave a colourless oil (0.01 g, 0.03 mmol, 51%).

R\(_f\): 0.69 (1:1 hexanes: EtOAc);

\([\alpha]_D +42.0\) (c 0.26 in CHCl\(_3\));

HRMS (ESI): MNa\(^+\),355.1528, C\(_{19}\)H\(_{24}\)NaO\(_5\) requires 355.1516;

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2930, 1776, 1050,754;

\(\delta_H\) (400 MHz, CDCl\(_3\)): 7.36-7.7 (5H, m, PhH), 5.02 (1H, ddd, \(J = 6.4, 3.7, 1.6\) Hz, H-4), 4.56 (2H, dd, \(J = 12.2, 9.0\) Hz, CH\(_2\)Ph), 4.32 (1H, d, \(J = 3.8\) Hz, H-3), 4.30-4.26 (1H, m, H-9), 3.48-3.41 (2H, m, H-10), 2.58 (1H, dd, \(J = 15.0, 6.5\) Hz, H-5), 2.36 (1H, dd, \(J = 15.1, 1.5\) Hz, H-5), 2.17-1.96 (4H, m, H-7, H-8), 1.74-1.66 (1H, m, H-8), 1.26 (3H, s, CH\(_3\)), 1.22 (3H, s, CH\(_3\));

\(\delta_C\) (100 MHz, CDCl\(_3\)): 175.0 (C=O, C-1), 138.2 (C, Ph), 128.4 (3 x CH, Ph), 127.6 (2 x CH, Ph), 116.0 (C, C-6), 85.3(CH, C-9), 80.5 (CH, C-4), 77.7 (CH, C-3), 73.4 (CH\(_2\), C-10), 72.4 (CH\(_2\), CH\(_2\)Ph), 44.4 (C, C-2), 41.9 (CH\(_2\), C-5), 35.2 (CH\(_2\), C-7), 26.8 (CH\(_2\), C-8), 23.0 (CH\(_3\)), 18.0 (CH\(_3\)).
(2R,3a'R,5S,6a'R)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 164b

\[
\begin{align*}
R_f: & \quad 0.56 \text{ (1:1 hexanes: EtOAc)}; \\
[a]_D & -2.9 \text{ (c 0.17 in CHCl}_3); \\
HRMS \text{ (ESI)}: & \quad M\text{Na}^+, 333.1694, \text{ C}_{19}\text{H}_{25}\text{O}_5 \text{ requires 333.1697}; \\
\nu_{\text{max}} \text{ (film)/cm}^{-1}: & \quad 2926, 1773, 1214, 746; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3): & \quad 7.35-7.27 \text{ (5H, m, PhH)}, 5.06 \text{ (1H, t, } J = 4.8 \text{ Hz, H-4)}, 4.53 \text{ (2H, dd, } J = 29.3, 12.1 \text{ Hz, CH}_2\text{Ph)}, 4.28 \text{ (1H, d, } J = 4.5 \text{ Hz, H-3)}, 4.25-4.19 \text{ (1H, m, H-9)}, 3.56 \text{ (1H, dd, } J = 9.9, 5.4 \text{ Hz, H-10)}, 3.48 \text{ (1H, dd, } J = 9.8, 5.8 \text{ Hz, H-10)}, 2.51 \text{ (1H, d, } J = 14.2 \text{ Hz, H-5)}, 2.18-1.99 \text{ (5H, m, H-5, H-7, H-8)}, 1.92-1.84 \text{ (1H, m, H-7), 1.27 (3H, s, CH}_3), 1.21 \text{ (3H, s, CH}_3);
\]

(2S,3a'S,5S,6a'S)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 389

\[
\begin{align*}
R_f: & \quad 0.69 \text{ (1:1 hexanes: EtOAc)}; \\
[a]_D & -41.5 \text{ (c 0.4 in CHCl}_3); \\
\end{align*}
\]

A solution of lactone 380 (0.03 g, 0.09 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.1 mL) was added to a stirring solution of Ph\textsubscript{I}(OAc)\textsubscript{2} (0.06 g, 0.18 mmol) and I\textsubscript{2} (0.05 g, 0.21 mmol) in hexane (0.2 mL). N\textsubscript{2} gas was bubbled through the solution for 5 min and the reaction was then irradiated with a 75 W desk lamp for 1 h. The solution was diluted with Et\textsubscript{2}O (0.2 mL) and saturated aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (0.1 mL) was added, the mixture was extracted with Et\textsubscript{2}O (3 x 1 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Purification on deactivated silica using 9:1 to 3:2 hexanes: EtOAc gave a colourless oil (0.015 g, 0.04 mmol, 51%).
HRMS (ESI): MNa+, 355.1516, C_{19}H_{24}NaO_{5} requires 355.1516;

v_{\text{max}} (\text{film})/\text{cm}^{-1}: 2933, 1776, 1138, 1089, 1052;

δ_{H} (400 MHz, CDCl_{3}): 7.36-7.26 (5H, m, PhH), 5.00 (1H, ddd, J = 6.3, 3.9, 1.5 Hz, H-4), 4.58 (2H, s, CH_{2}Ph), 4.34-4.27 (1H, m, H-9), 4.24 (1H, d, J = 3.7 Hz, H-3), 3.49 (1H, dd, J = 9.9, 7.7 Hz, H-10), 3.42 (1H, d, J = 9.9, 4.0 Hz, H-10), 2.57 (1H, dd, J = 15.0, 6.4 Hz, H-5), 2.34 (1H, dd, J = 15.0, 1.4 Hz, H-5), 2.10-1.90 (3H, m, H-7, H-8), 1.81-1.70 (1H, m, H-8), 1.19 (6H, d, J = 5.1 Hz, CH_{3});

δ_{C} (100 MHz, CDCl_{3}): 180.8 (C=O, C-1), 138.2 (C, Ph), 128.4 (2 x CH, Ph), 127.8 (2 x CH, Ph), 127.6 (CH, Ph), 115.7 (C, C-6), 85.1 (CH, C-9), 80.3 (CH, C-4), 79.0 (CH, C-3), 74.2 (CH_{2}, C-10), 73.2 (CH_{2}, CH_{2}Ph), 44.3 (C, C-2), 41.5 (CH_{2}, C-5), 36.1 (CH_{2}, C-7), 27.3 (CH_{2}, C-8), 23.0 (CH_{3}), 17.9 (CH_{3}).


R_{f}: 0.57 (1:1 hexanes: EtOAc);

[α]_{D} -20.4 (c 0.25 in CHCl_{3});

HRMS (ESI): MK+, 371.1268, C_{19}H_{24}KO_{5} requires 371.1255;

v_{\text{max}} (\text{film})/\text{cm}^{-1}: 2936, 1774, 1120, 1105;

δ_{H} (400 MHz, CDCl_{3}): 7.36-7.26 (5H, m, PhH), 5.10 (1H, t, J = 5.2 Hz, H-4), 4.53 (2H, s, CH_{2}Ph), 4.35 (1H, d, J = 5.0 Hz, H-3), 4.29-4.25 (1H, m, H-9), 3.52-3.42 (2H, m, H-10), 2.47 (1H, d, J = 14.1 Hz, H-5), 2.15-2.01 (4H, m, H-5, H-7, H-8), 1.84-1.80 (1H, m, H-8), 1.24 (6H, d, J = 15.0 Hz, 2 x CH_{3});

δ_{C} (100 MHz, CDCl_{3}): 180.8 (C=O, C-1), 138.5 (C, Ph), 128.3 (2 x CH, Ph), 127.6 (2 x CH, Ph), 127.5 (CH, Ph), 115.7 (C, C-6), 86.9 (CH, C-3), 79.9 (CH, C-4), 78.6 (CH, C-9), 73.3 (CH_{2}, CH_{2}Ph), 72.1 (CH_{2}, C-10), 44.3 (C, C-2), 41.4 (CH_{2}, C-5), 34.2 (CH_{2}, C-7), 26.7 (CH_{2}, C-8), 25.2 (CH_{3}), 18.4 (CH_{3}).
(2R,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 392

A solution of spiroacetal 388 (6.0 mg, 0.018 mmol) was stirred in EtOAc (0.5 mL) with 10% Pd/C (0.01 g) under H₂ atmosphere overnight. The mixture was filtered through a plug of celite and concentrated under reduced pressure to give the title compound as a colourless oil (3 mg, 0.012 mmol, 68%).

Rᵣ: 0.13 (1:1 hexanes: EtOAc);

[α]₀ -1.4 (c 0.13 in CHCl₃);

HRMS (ESI): MK⁺, 281.0790, C₁₂H₁₈KO₅ requires 281.0786;

νₘₐₓ (film)/cm⁻¹: 3432, 2923, 1772, 1460, 1125, 828;

δ_H (400 MHz, CDCl₃): 5.14 (1H, t, J = 5.1 Hz, H-4), 4.39 (1H, d, J = 4.9 Hz, H-3), 4.24-4.18 (1H, m, H-9), 3.68 (1H, dd, J = 11.8, 2.9 Hz, H-10), 3.47 (1H, q, J = 5.8 Hz, H-10), 2.48 (1H, d, J = 14.1 Hz, H-5), 2.17 (1H, dd, J = 14.2, 5.5 Hz, H-5), 2.14-2.02 (4H, m, H-5, H-7, H-8), 1.27 (6H, d, J = 11.7 Hz, 2 x CH₃);

δ_C (100 MHz, CDCl₃): 180.9 (C=O, C-1), 115.4 (C, C-6), 86.8 (CH, C-3), 79.8 (CH, C-3), 79.8 (CH, C-4), 64.7 (CH₂, C-10), 44.4 (C, C-2), 41.5 (CH₂, C-5), 34.5 (CH₂, C-7), 25.5 (CH₂, C-8), 25.5 (CH₃), 18.2 (CH₃).

(2S,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 393

A solution of spiroacetal 389 (0.011 g, 0.03 mmol) was stirred in EtOAc (1 mL) with 10% Pd/C (0.02 g) under H₂ atmosphere overnight. The mixture was filtered through a plug of celite and concentrated under reduced pressure to give the title compound as a colourless oil (7.0 mg, 0.029 mmol, 87%).

Rᵣ: 0.13 (1:1 hexanes: EtOAc);

[α]₀ +0.91 (c 0.22 in CHCl₃);

HRMS (ESI): MK⁺, 281.0790, C₁₂H₁₈KO₅ requires 281.0786;
$v_{\text{max}}$ \text{ (film)/cm}^{-1}: 3432, 2923, 1772, 1460, 1125, 828;

$\delta_{\text{H}}$ \text{ (400 MHz, CDCl})$: 5.05 (1H, ddd, $J = 6.0, 3.7, 1.4$ Hz, H-4), 4.39-4.31 (2H, m, H-3, H-9), 3.75 (1H, dd, $J = 9.9$ Hz, H-12), 3.51-3.48 (1H, m, H-10), 2.58 (1H, dd, $J = 15.2, 6.1$ Hz, H-5), 2.50 (1H, dd, $J = 15.2, 0.9$ Hz, H-5), 2.20-1.96 (4H, m, H-7, H-8), 1.26 (6H, d, $J= 12.8$ Hz, 2 x CH$_3$);

$\delta_{\text{C}}$ \text{ (100 MHz, CDCl})$: 180.4 (C=O, C-1), 115.7 (C, C-6), 85.4 (CH, C-9), 80.9 (CH, C-3), 80.1 (CH, C-4), 64.7 (CH$_2$, C-10), 44.5 (C, C-2), 41.1 (CH$_2$, C-5), 37.2 (CH$_2$, C-7), 24.8 (CH$_2$, C-8), 22.8 (CH$_3$), 17.9 (CH$_3$).
EXPERIMENTAL: BIOLOGICAL EVALUATION
5.4 Method for biological evaluation of anti-Helicobacter pylori compounds

The *H. pylori* type strain NCTC11637 was used to determine the MIC and MBC of each of the eight analogues and the results are displayed in Table 19. *H. pylori* was cultured in Brucella broth (Difco 211088) supplemented with 2.5% foetal calf serum (FCS); or on agar plates containing Brucella broth, 2.5% FCS and 15 g/L Bacto™ agar (Difco 214010). Cultures were placed in large volumes (10 mL) in standard petri dishes (LabServ LBS60001) or small volumes (2–3 mL) in small petri dishes (Falcon 35-3001). Cultures were incubated in 2.5 L gas jars containing a CampyPak (Oxoid CN0025A) to generate a microaerophilic atmosphere. Gas jars were placed in a 37°C incubator with shaking (70 rpm). *H. pylori* cultures typically took 48–72h to become visibly turbid, which indicated good culture growth. All manipulations were undertaken in a class II biohazard cabinet. The biological testing was carried out by the following procedure:

1. A 48 h *H. pylori* culture was diluted 1/100 in fresh broth and cultured overnight. The test compounds were weighed out on day of testing and dissolved in dimethyl sulfoxide (DMSO) at 10 mg/mL. Compounds were diluted in Brucella broth. The highest concentration used for testing was 100 μg/mL.
2. The baseline absorbance of the *H. pylori* culture was measured at A570 and bacterial numbers enumerated by plating serial 10-fold dilutions of the culture onto quarter sections of Brucella agar and cultured face-up at 37°C for 5 days.
3. *H. pylori* was transferred into small petri dishes (2 mL/dish) and 0.5 mL compound added. Equivalent amounts of DMSO or Brucella broth alone were included as controls. Cultures were incubated for 24h.
4. A570 was measured for each condition tested. The MIC value is defined as the lowest concentration of compound at which there is no visible growth of the bacteria.
5. The *H. pylori* was plated in serial 10-fold dilutions of the culture onto quarter sections of Brucella agar and cultured face-up for 5 days at 37°C.
6. The colony forming units (CFU/ml) were calculated to determine the MBC after the five day culture time by screening the plates to identify the highest dilution factor with visible single colonies and enumerate the colonies (Table x). The MBC value was defined as the lowest concentration able to kill 99% of the bacteria.

The analogues were tested in two independent experiments and the same MIC and MBC values were obtained in both experiments.
Table 19: Biological results of new spirolaxine analogues. \(^{223}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>MIC (µg/mL)</th>
<th>MBC</th>
<th>Entry</th>
<th>Structure</th>
<th>MIC (µg/mL)</th>
<th>MBC</th>
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<td>1.0</td>
<td>6</td>
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<td>12.5</td>
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<tr>
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<td>3.0</td>
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<tr>
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<td>3.0</td>
<td>8</td>
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<td>16</td>
</tr>
<tr>
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<td>8.3</td>
<td>9</td>
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<td>&gt;100</td>
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<tr>
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<td>12.5</td>
<td>12.5</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(4S)-4,5-Isopropyliden-dioxy-pentanal oxime 274

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(4S)-4,5-Isopropyliden-dioxy N-hydroxypentanimidoyl chloride 303

$^1$H NMR (400 MHz, CHCl$_3$):

![NMR spectrum of 303](image)

$^{13}$C NMR (100 MHz, CHCl$_3$):

![NMR spectrum of 303](image)
(S)-Ethyl 5-((tert-butyldimethylsilyl)oxy)-4-hydroxypentanoate 276

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

(2S)-((1-(benzyloxy)hexanes-5-en-2-yl)oxy)(tert-butyl)dimethysilane 285

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(S)-5-(Benzyloxy)-4-(tert-butyldimethylsilyloxy)pentanal oxime 248

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(S)-5-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-N-hydroxypentanimidoyl chloride 306

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

(S)-4-Benzyl-3-(2-bromo-2-methylpropanoyl) oxazolidin-2-one 300

$^1$H NMR (400 MHz, CHCl$_3$):

![NMR Spectrum](image1)

$^{13}$C NMR (100 MHz, CHCl$_3$):

![NMR Spectrum](image2)

Methyl 3-(3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-4,5-dihydroisoxazol-5-yl)-3-hydroxy-2,2-dimethylpropanoate 304

$^1$H NMR (400 MHz, CHCl$_3$):

Methyl 3-(3-((R)-4-(benzyloxy)-3-((tert-butyldimethylsilyloxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-hydroxy-2,2-dimethyldimethylpropanoate 305

$^{13}$C NMR (100 MHz, CHCl$_3$):
\(^1\)H NMR (400 MHz, CHCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CHCl\(_3\)):
(2S,3S)-Methyl 3-((3-((R)-4-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-hydroxy-2-methylpropanoate 307

^1^H NMR (400 MHz, CHCl\textsubscript{3}):
Ethyl 3-((R)-4-((benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-hydroxypropanoate 308

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
1-(3-((R)-4-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-4,5-dihydroisoxazol-5-yl)-3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol 309

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(S)-6-(benzyloxy)-5-(tert-butyldimethylsilyloxy)hexanone 166

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Methyl 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpent-4-enoate 321

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
**Methyl 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethyl-4-oxobutanoate 320**

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

Methyl 3-(ethoxymethoxy)-2,2-dimethylpent-4-enoate 323

$^1$H NMR (400 MHz, CHCl$_3$):

![H NMR spectrum](image)

$^{13}$C NMR (100 MHz, CHCl$_3$):

![C NMR spectrum](image)
Methyl 3-(ethoxymethoxy)-2,2-dimethyl-4-oxobutanoate 322

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(E)-((5-bromo-2,2-dimethylpent-3-en-1-yl)oxy)(tert-butyl)dimethylsilane 327

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(2S,E)-1-(benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-10-((tert-butyldimethylsilyl)oxy)-9,9-dimethyldec-7-en-5-ol 328

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

(S)-((1-(benzyloxy)-4-(1,3-dithian-2-yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane 252

\(^1\)H NMR (400 MHz, CHCl\(_3\)):

\(^{13}\)C NMR (100 MHz, CHCl\(_3\)):
Benzyl 2,2-dimethylbut-3-enoate 354

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Tert-butyl((2,2-dimethylbut-3-en-1-yl)oxy)dimethylsilane 358

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

((5-((5S)-5-(benzyloxy)methyl)tetrahydrofuran-2-yl)-2,2-dimethylpent-3-en-1-yl)oxy)(tert-butyl)dimethylsilane 359

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Benzyl 5-((5S)-5-((benzyl oxy)methyl)tetrahydrofuran-2-yl)-2,2-dimethylpent-3-enoate 360

$^1$H NMR (400 MHz, CHCl₃):

$^{13}$C NMR (100 MHz, CHCl₃):
2-((5S)-5-(((benzyloxy)methyl)tetrahydrofuran-2-yl)acetaldehyde 363

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(4R,5R)-5-(((2R,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 345a

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(4R,5R)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 345b

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(4S,5S)-5-(((2R,5R)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethylidihydrofuran-2(3H)-one 380

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(4S,5S)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 381

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(2S,3a'R,5S,6a'R)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b][furan]-5'(3a'H)-one 164a

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

(2R,3a'R,5S,6a'R)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 164b

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(2S,3a'S,5S,6a'S)-5-(((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b][furan]-5'(3a'H)-one 389

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(2R,3a'S,5S,6a'S)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one 388

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
Appendix

(2S,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b][furan]-5'(3a'H)-one 392

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
(2R,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-
furo[3,2-b][furan]-5'(3a'H)-one 393

$^1$H NMR (400 MHz, CHCl$_3$):

$^{13}$C NMR (100 MHz, CHCl$_3$):
References

References


References


References


