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Total Synthesis and Stereochemical Revision of Pestalospirane B

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

Doctor of Philosophy

By
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School of Chemical Sciences
University of Auckland
December 2016
A detective with his murder mystery, a chemist seeking the structure of a new compound, use little of the formal and logical modes of reasoning. Through a series of intuitions, surmises, fancies, they stumble upon the right explanation, and have a knack of seizing it when it once comes within reach.

~ Gilbert Lewis

Being defeated is often temporary, giving up makes it permanent

~Marilyn von Savant
Abstract

This thesis describes a synthetic journey that culminated in the first enantioselective total synthesis and structural revision of the natural product pestalospirane B (3). Pestalospiranes A (2) and B (3) are novel 1,9,11,18-tetraoxadispiro[6.2.6.2]octadecane spiroketal metabolites that were isolated from *Pestalotiopsis virgatula* inhabiting the plant *Terminalia chebula*. These compounds were discovered during investigations into the subculture and fermentation of *Pestalotiopsis virgatula* broth using a relatively new method of detection and isolation HPLC-PDA-MS-SPE-NMR.

![pestalospirane B (3)](image1)

![pestalospirane A (2)](image2)

The first part of this thesis describes the initial synthetic approach to pestalospiranes A (2) and B (3), which examined the use of a novel double oxidative radical cyclisation to construct the 7,6-membered spiroketal moiety of pestalospirane core 114. The first model study explored several synthetic approaches for the construction of the key substituted 1,4-dioxane intermediate 115 for application in the total synthesis of the natural products.

A second model study investigated the synthesis of mono-substituted 1,4-dioxane 212 using the oxidative radical cyclisation method and demonstrated that the oxidative radical cyclisation procedure could be used to construct 7,6-membered spiroketal ring systems.

Unable to access the desired intermediate 114, an alternative third model study towards the pestalospirane core 257 was devised that was based on our own proposed biosynthesis of the natural product. This strategy enabled successful construction of pestalospirane cores A (275a) and B (275b) via dimerisation of synthetic monomer 273. These investigations established a sound platform from which a total synthesis of the natural product pestalospirane B (3) could be achieved.
The second part of this thesis describes considerable effort focused on identifying a suitable protecting group for the phenol group during the synthesis of the natural product. Initial attempts at late stage deprotection of isopropyl dimer 314 were unsuccessful, thus a revision in protecting group strategy was enforced where access to the natural product was envisioned to allow deprotection prior to dimerisation of acetal 342.

Attention, therefore focused on an acid labile protecting group that would be readily cleaved after cyclisation thereby avoiding a sensitive late-stage deprotection step to furnish the natural product. Accordingly, an EOM protecting group was chosen and ketone 334 was assembled from alkyne 339 and Weinreb amide 364b. Global deprotection of 334 under mild acidic conditions resulted in unexpected formation of ketal 342, which underwent CBS reduction and dimerisation to furnish pestalospirane B ((+)-3) as the major isomer. Interestingly, the ECD data for the proposed structure of synthetic pestalospirane B ((+)-3) and reported data of the natural product did not match. Detailed ECD and X-ray crystal structure analysis unequivocally supported the stereochemical revision of pestalospirane B (3).
Acknowledgements

First and foremost I would like to thank my supervisor D. Prof. Margaret Brimble for the opportunity to work on this project and believing in me. Your passion, knowledge and commitment for organic chemistry over the years have been invaluable and provided a constant inspiration to me. I am very grateful for your ongoing guidance and support, both in research and in writing this thesis.

I would also like to thank Dr Jon Sperry for being an excellent mentor over the course my Hons and PhD. Thanks for the initial training in synthetic organic chemistry and for always being available to hear me out when I’ve lost all hope in my reaction working.

To Dr Dan Furket, thanks for checking on me and making sure I wasn’t going too off track and reminding that it’s ok to give up on a ‘bad’ reaction.

To Assoc. Prof. Brent Copp, for all the friendly banter as your ‘PA’ and help with processing the ECD data, would have been a great struggle without your guidance. To Zaid thank you for showing how to use and run the ECD machine.

A special thanks to Daniel, and Morgan, the middle lab would have been boring without our constant banter, complaining and the occasional gossip session over Friday breakfast. Your support and help over the years have been invaluable to me and I don’t think I would have survived my PhD without you guys!! I am forever indebted and grateful to you guys. To Louise, James and Darcy, you have always given me the time and patience when I needed it the most, especially during the final stages of PhD. Thanks for also the painstaking task of proofreading my thesis.

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Sandhya Badrinarayanan

December 2016
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<th>Name</th>
<th>Nature of Contribution</th>
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<td>Conducted experimental work. Prepared manuscript and supporting information</td>
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<td>Margaret A Brimble</td>
<td>Advisor on synthetic routes, revised manuscript</td>
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<td>Advisor on synthetic route, revised manuscript</td>
</tr>
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<td>X-ray Crystallographers</td>
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### Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

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<td>8th June 2017</td>
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<tr>
<td>Christopher Squire</td>
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<td>19/12/16</td>
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Abbreviations

δ  chemical shift
μ  micro
Å  Ångström
°C  degrees Celsius
2D  two-dimensional
AChE  acetylcholinesterase
AIBN  azobisisobutyronitrile
aq.  aqueous
Ar  aryl
b.p.  boiling point
Bn  benzyl
br  broad
Bz  benzoyl
c  concentration
cAMP  cyclic adenosine monophosphate
CD  circular dichroism
cod  cyclooctadienyl
COSY  correlated spectroscopy
CSA  camphorsulfonic acid
d  doublet
d.r.  diastereomeric ratio
dd  doublet of doublets
ddd  doublet of doublet of doublets
DBU  1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE  1,2-dichloroethane
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT  distortionless enhancement by polarisation transfer
DFA  Di-α-fructose dihydroxides
DHP  dihydropyran
DIAD  diisopropyl azodicarboxylate
DIB  (diacetoxyiodo)benzene
DIBAL  diisobutylaluminium hydride
DIPA  diisopropylamine
DIPEA  diisopropylethylamine
DMAP  N,N-dimethylanilino pyridine
DMF  N,N-dimethylformamide
3,5-DMP  3,5-dimethylpyrazole
DMP  Dess-Martin periodinane
DMPU  N,N′-dimethylpropyleneurea
DMSO  dimethylsulfoxide
E50  half-maximal effective concentration
ECD  electronic circular dichroism
e.e.  enantiomeric excess
EI  electron impact
EOM  ethoxymethyl
equiv.  equivalent(s)
ESI  electrospray ionisation
Et  ethyl
eq.  equivalent(s)
G1/2  growth inhibition of 50%
g  gram(s)
Et al.  et alia (and others)
GPCR  G-protein coupled receptor
GI50  growth inhibition of 50%
h  hour(s)
HKR  hydrolytic kinetic resolution
HMBC  heteronuclear multiple-bond correlation spectroscopy
HMDS  hexamethyldisilazide
HMPA  hexamethylphosphoramide
HPLC  high-performance liquid chromatography
HRMS  high resolution mass spectroscopy
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xii
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Chapter One: Introduction
1.1 Natural products from Endophytic Fungi

Natural products produced by living organisms such as plants, microorganisms, and marine invertebrates provide a rich source of biologically active secondary metabolites. For many centuries, natural products have been one of the most significant sources of inspiration for the design or development of novel pharmaceuticals. Since 1981, approximately 50% of all new small molecule drugs approved by the FDA were either natural products, compounds derived from natural products or synthetic compounds designed from the pharmacophore of a natural product. Plants and microorganisms are the main sources of inspiration and have been instrumental in discovery of a huge variety of novel chemotherapeutic, antibacterial, and agrochemical agents.

Up until the early 2000’s, there was a relatively untapped source of structurally diverse natural products found in microorganisms known as endophytes. Endophytes were first discovered in the 1940s and are defined as microorganisms (bacteria or fungi) that colonise the interior organs of a plant, without having pathogenic effects on the host. Endophytes and their hosts have a symbiotic relationship where the host plant protects and feeds the endophytes, and in return, the endophytes produce bioactive metabolites that enhance growth and colonisation of the host plant as well as protecting it from herbivores and plant pathogens. Surprisingly, it is only recently that endophytes have received attention as a potentially rich source of structurally interesting, novel secondary metabolites with a diverse range of biological activities.

Interest in endophytes began to grow in popularity following the discovery of the world’s first billion dollar anticancer drug, paclitaxel (taxol) (1), isolated from an endophyte fungus. Initially isolated from the bark of the Pacific Yew tree (Taxus brevifolia) in 1971 by Wani et al., taxol was subsequently isolated in 1993 by Stierle et al. from Taxomyces andreanae inhabiting the plant Taxus brevifolia. Since then, endophytes have become an alternative source of taxol via microorganism fermentation, making the process of taxol production more renewable and cost effective. In addition to T. andreanae, one of the most commonly found and widely distributed endophytes are the Pestalotiopsis (Amphisphaeriaceae) genus, which has also been shown to produce taxol and are isolated from the inner bark of the Himalayan yew tree Taxus wallachiana. Furthermore, several other isolates from the genus including P. microspora obtained from Bald cypress in South Carolina.
have also been shown to produce taxol; providing the first evidence that endophytes residing in plants other than the genus *Taxus* species are capable of producing taxol (1).\textsuperscript{11,16}

![Structure of taxol (1)](image)

**Figure 1.1: Structure of taxol (1)**

The growing interest in endophytic fungi has resulted in the isolation of over a 100 different endophytic microorganisms. These endophytes have been cultured and subjected to detailed investigations of their secondary metabolites, leading to the chemical elucidation and biological evaluation of a vast number of natural products over the past two decades.\textsuperscript{4,8,9,11,15} In particular, studies of the *Pestalotiopsis* genus have attracted much attention due to numerous discoveries of structurally diverse and biologically active natural products. In the next section, a selection of structurally unusual secondary metabolites, isolated from the *Pestalotiopsis* genus will be outlined and any biological activity present will be discussed.\textsuperscript{4,8,11,15,17}
1.2 Pestalospiranes A and B: isolation and structure elucidation

Pestalospiranes A (2) and B (3) contain an unprecedented 1,9,11,18-tetraoxadispiro[6.2.6.2]octadecane spiroketal core and were isolated and characterised in 2011 by Kesting et al.,18 (Figure 1.2). The compounds were discovered during investigations into the subculture and fermentation broth of Pestalotiopsis virgatula isolated from the plant Terminalia chebula using a relatively new method of detection/characterisation and isolation; high-performance liquid chromatography-photodiode array detection-mass spectrometry-solid phase extraction-nuclear magnetic resonance hyphenated system (HPLC-PDA-MS-SPE-NMR).19-21 Unfortunately, pestalospiranes A (2) and B (3) were inseparable and repeated preparative HPLC failed to yield a pure sample of the natural products. Furthermore, no biological testing was conducted, which is a frequent problem of natural product isolation as useful amounts cannot always be obtained from natural sources, thus requiring the need for efficient synthetic routes to natural products.

![Figure 1.2: Structure of pestalospiranes A (2) and B (3)](image)

The core structures of pestalospiranes A (2) and B (3) were elucidated by a combination of HPLC-SPE-MS-NMR along with electronic circular dichroism (ECD) spectroscopy supported by time-dependent density-functional theory calculations (TDDFT) of chiral electronic transitions.21 The use of nOe correlations allowed for relative configuration assignment (Figure 1.3).
The absolute stereochemistry of pestalospirane B (3) was then determined by comparison of its ECD spectrum to the B3LYP/TZVP ECD-calculated spectrum (Figure 1.4). NMR analysis of pestalospirane A (3) displayed similar resonances to pestalospirane B (3), except the resonances were doubled. Consequently, it was concluded that pestalospirane A (3) is, in fact, the epimer of pestalospirane B (3) where the anomic carbon at C-13’ differs, possessing a 3,13-\textit{anti},3',13'-\textit{syn}-relationship.

By utilising the HPLC-PDA-MS-SPE-NMR method, Kesting \textit{et al.}, discovered a series of structurally related benzo[\textit{c}]oxepine derivative natural products 4-11. These metabolites represent a small but growing family of natural benzo[\textit{c}]oxepine derivatives of fungal origin. Remarkably, this method highlights the advantages over traditional procedures, which can contribute to a loss of tautomeric and labile compounds such as triol 9 and hemiketal 10 that otherwise would not have been detected/isolated.
Pestalospiranes A (2) and B (3) both contain a spiroketal and a benzo[c]oxepine moiety and will be the main focus of this thesis. The two relevant structural motifs namely a spiroketal and benzo[c]oxepine will therefore be discussed.
1.3 Other examples of spiroketal natural products from *Pestalotiopsis* species

Many natural products have structurally similar motifs and can be organised into groups and sub-groups based on those similarities. One such group are the spiroketals, which will be the main focus of this section.

The spiroketal moiety is a structural element found in a broad range of biologically active natural products. The interesting structural diversity and biological activity of these molecules have motivated our research group to investigate the synthesis of spiroketal-containing natural products. Spiroketal (spiroacetals) are generally characterised by a bicyclic acetal system where the base of the acetal is the only carbon common to both rings and through which they are linked (Figure 1.7). A high degree of structural diversity is observed in spiroketal containing natural products, including benzannulation and a varying degree of saturation and substitution around the spiroketals rings, making them both synthetically attractive and challenging.

![Figure 1.7: Selection of spiroketal motifs observed in natural products](image)

The interesting structural diversity and biological activity of spiroketal-containing molecules have motivated our group to conduct research into the synthesis of such natural products. Below, a selection of spiroketal natural products is described to illustrate the structural and biological diversity of this subclass of natural products isolated from endophyte fungi in the genus *Pestalotiopsis*.
1.3.1 Virgatolides A-C

Virgatolides A-C (20-22) are a family of three rare 6,6-benzannulated spiroketals with a characteristic 3,4,5,6-tetrahydrospiro[chroman-2,2-pyran] core, which were isolated by Che et al.,\textsuperscript{25} in 2011 (Figure 1.8). The compounds 20-22 were discovered during investigations into fungal metabolites produced by the endophytic fungus \textit{Pestalotiopsis vigatula}, inhabiting leaves of the traditional Chinese medicinal plant, \textit{Dracontomelon duperreanum}. All three metabolites share a common tetracyclic core that differs in their stereochemistry and substitution around the spiroketal rings. Virgatolides A-C (20-22) exhibited cytotoxicity towards HeLa cells with IC\textsubscript{50} values of 19.0, 22.5, and 20.6 µM, respectively.\textsuperscript{25,26} In 2013 the first total synthesis of virgatolide B (21) was accomplished by our research group.\textsuperscript{26}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{virgatolides.png}
\caption{Structure of virgatolides A-C (20-22)}
\end{figure}

1.3.2 Pestafolide A

Pestafolide A (23) is a reduced spiro-azaphilone derivative, with a rare tetrahydro-1\textit{H}-isochromen-8(5\textit{H}) moiety that was isolated by Ding et al., in 2008.\textsuperscript{9,27} Pestafolide A (23) was discovered during investigations for bioactive natural products from the endophyte fungi \textit{Pestalotiopsis foedan} isolated from solid substrate fermentation cultures obtained from branches and leaves of an unidentified tree. Pestafolide A (23) exhibited potent antifungal activity against \textit{Aspergillus fumigatus} (ATCC10894) and \textit{Candida albicans} (ATCC 10231) with an inhibition of 13 mM and 10 mM respectively.\textsuperscript{17,27}
1.3.3 Chloropupukeanolides A-E

Chloropupukeanolides A-E (24-28) are a class of sesquiterpenoids which are chlorinated pupukeanane derivatives. These natural products feature an unprecedented spiroketal peroxide derived from the chlorinated tricyclo[4.3.1.3,7]decane spirally joined to the 2,6-dihydroxy-4-methylbenzoic acid moieties based on the 1,3-dioxane-4-one moiety (Figure 1.10).\(^{4,28,29}\) Chloropupukeanolides (24-28) were discovered during a continued search by Liu et al.,\(^ {28,29}\) for new bioactive natural products from a subculture of Pestalotiopsis fici, inhabiting the plant, Camellia sinensis (Theaceae). Chloropupukeanolide A (24) exhibited inhibitory effects on HIV-1 replication in C8166 cells with an EC\(_{50}\) of 6.9 µM. Chloropupukeanolides A (24) and B (25) both exhibited cytotoxicity against HeLa, MCF-7 cells and MDA-MB-231 human tumour cell line with IC\(_{50}\) values of 16.9, 15.5 and 15.9 µM respectively. Chloropupukeanolides C and D (26 and 27) exhibited weak activity for a small panel of human tumour cell lines including HeLa and HT29 with IC\(_{50}\) values ranging from 1.2-7.9 µM for both cell lines. Chloropupukeanolides C-E (26-28) also exhibited weak activities against pathogens of tropical diseases such as malaria, Chagas disease, leishmaniosi, and African sleeping sickness with IC\(_{50}\) values ranging from 1.3-37.5 µM.\(^ {4,28,29}\)
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1.3.4 Chloropestolides A-G

Chloropestolide A (29) is a highly functionalised spiroketal with an unprecedented spiroketal skeleton derived from the chlorinated bicyclo[2.2.2]oct-2-en-5-one ring and a 2,6-dihydroxy-4-methylbenzoic acid unit (Figure 1.11). Chloropestolide A (29) was discovered in fermented subcultures of *P. fici* isolated from the branches of an unidentified tree in 2009 by Liu et al. Chloropestolide A (29) exhibited significant inhibitory effects on the growth of two human cancer cell lines, HeLa and HT29 with GI\textsubscript{50} values of 0.7 µM and 4.2 µM respectively, as well as inhibition of replication of HIV-1 in C8166 cells with an IC\textsubscript{50} value of 64.5 µM.

Later in 2013, Liu *et al.*, continued attempts to discover more structurally diverse and biologically active secondary metabolites and subsequently isolated six more novel metabolites, chloropestolide B-G (30-35) from subcultures of *P. fici*, inhabiting the plant *Camellia sinensis* (Theaceae) (Figure 1.11). Out of the six new metabolites, chloropestolide B-D (30-32) contain the chlorinated spiro[benzo[d][1,3]dioxine-2,7-bicyclo[2.2.2]oct-4,8-diones in which the bicyclo[2.2.2]oct-2-en-5-one is spirally joined to the benzo[d][1,3]dioxin-4-one.
moiety at C-10, whereas in E-G (33-35) the benzo[d][1,3]dioxin-4-one unit is spirally joined to the 4a,5,8,8a-tetrahydronapthalen-2(1H)-one moiety at C-10. All metabolites B-G (30-35) were tested for cytotoxicity and only chloropestolide B (30) showed cytotoxic activity against human tumour cell lines CNE1-LMP1, A375, and MCF-7 with IC₅₀ values of 16.4, 9.9 and 23.6 µM, respectively.

Figure 1.11: Structures of chloropestolides A-G (29-35)
1.4 Synthetic Methods to Access 7-Membered Spiroketalts

1.4.1 Chemistry of spiroketalts

The wealth of biological activity displayed by spiroketalts in nature has inspired the development of numerous strategies for the synthesis of spiroketalts. The synthesis of spiroketalts has been extensively reviewed; such methods include acid-catalysed spiroketalisation, transition metal catalysis, hetero-Diels-Alder reaction and intramolecular hydride abstraction (Figure 1.12). The methods employed in the current work will be outlined in more detail in the relevant sections. To the best of our knowledge, while no total synthesis of 7,6-spiroketal natural products have been reported, synthetic methodologies to access 7-membered spiroketalts have been studied. After a discussion of the stereochemistry of spiroketalts a selection of methods that have been used to construct 7-membered spiroketal model systems are presented.

Figure 1.12: Overview of methods for the synthesis of spiroketalts.34
1.4.2 Stereochemistry and the anomeric effect

When spiroketals are formed, both synthetically and naturally, the resulting conformation and configuration at the spirocentre is governed by a combination of both steric and electronic factors. The most stable conformation is when the two C-O bonds adopt the position that is axial relative to the ring to which they are attached. The preference for the axial arrangement compared to the generally less hindered and most stable equatorial position is most commonly explained using the anomeric effect (Figure 1.13).²²

The anomeric effect is a stereoelectronic effect where the net stabilisation of a system is attributed to the overlapping of the non-bonding oxygen orbital with the antibonding σ* orbital of the adjacent C-X bond (Figure 1.14, A). In a tetrahydropyranoid ring, this requires the nonbonding electrons of the oxygen and the anti-bonding σ* orbital of the heteroatom to be arranged in a periplanar fashion. Alternatively, the anomeric effect has also been described as an electrostatic effect arising from the interactions between the dipoles of the two heteroatoms attached to the anomeric centre (Figure 1.14, B). In the equatorial conformation these dipoles align in a parallel manner resulting in repulsion. The unfavourable dipole conformation is avoided in the axial arrangement where the dipoles align in an antiparallel arrangement. It is presumed that the repulsive effect observed in the equatorial arrangement is strong enough to overcome the inherent energetic cost in placing the heteroatom substituents in the more sterically demanding axial position.³⁵
The anomeric effect is most commonly used to predict the conformation of simple 6,6- or 5,6-spiroketal compounds. This argument, however, is less relevant in the case of pestalospiranes A (2) and B (3), which contains a 7,6-spiroketal unsaturated ring strain, resulting in an inability to adopt the chair-conformation. Consequently, the stereochemistry of this 7,6-spiroketal system is often more complicated and largely depends on the other stereocenters present in the molecule making the conformation difficult to predict.

1.4.3 Spirocyclisation via ring-opening of glycal epoxides

Tan et al., 36,37 reported the synthesis of a library of various spiroketal based on intramolecular stereoselective kinetic spirocyclisation starting from C1-substituted glycal epoxides 37 (Scheme 1.1). This approach uses the C3-substituent as a directing group for the stereoselective epoxidation of the adjacent olefin. Epoxide 37 could then be used to enable stereochemical control in two discrete kinetic spirocyclisation reactions, providing access to both spiroketal isomers from a common glycal intermediate 37. This approach enables access to a variety of spiroketal ring sizes by varying the length of the side-chains at the C1-position.

Starting from glycal 36, epoxidation of the double bond was achieved using dimethyldioxirane in dichloromethane/acetone (1:1) at -78 °C providing glycal epoxide 33, which was subsequently treated with acetic acid to afford a mixture of spiroketal 38 and 39 (1:1). Spiroketal 38 could be converted to spiroketal 39 with inversion of stereochemistry exclusively using
Introduction

*p*-toluenesulfonic acid. On the other hand, glycal epoxide 37 undergoes spiroketalisation upon treatment with titanium (IV) tetraisopropoxide to provide spiroketal 39 exclusively with complete retention of initial stereochemistry (Scheme 1.1).

\[
R\text{O}\left(\begin{array}{c} n+m = 0-3 \\
\text{OTIPS} \end{array}\right)
\]

Reagents and conditions: i. DMDO, CH\(_2\text{Cl}_2\), acetone, -78 or -63 °C; ii. AcOH, CH\(_2\text{Cl}_2\), -78 °C, 68-98%; iii. Ti(O\text{Pr})\(_4\), -78 → 0 °C, 81-98%.

Scheme 1.1: Overall approach to stereocontrolled synthesis of spiroketals 38 and 39 using glycal epoxide sprioketalisation.\(^{38-40}\)

An epoxide should be kinetically predisposed for spirocyclisation with inversion of configuration proceeding \textit{via} trans-diaxial epoxide opening. However, this can be over-ridden by Lewis acid coordination to promote oxonium intermediate 42; that delivers the sidechain hydroxyl to the β-face of the anomeric carbon to give 43. As a result, the desired epoxide opening proceeds with retention of configuration to furnish spirketal 44 (Scheme 1.2).\(^{40}\) 6,5-, 6,6-, 6-7 Monobenzannulated spiroketals have been synthesised using this procedure in which retention or inversion at C-1 takes place (Figure 1.15).
1.4.4 Spirocyclisation using an octacarbonyl dicobalt complex

In 2013, Mukai et al.,\textsuperscript{41} reported the synthesis of 7,5 and 8,5-spiroketalts 52 from the corresponding cyclopropane derivatives 51 by employing the Nicholas reaction. (Scheme 1.3)\textsuperscript{41,42} Mechanistically, the reaction was postulated to begin with complexation of the alkyne functionality of propargyl carbonyl 51 with octacarbonyl dicobalt Co\textsubscript{2}(CO)\textsubscript{8}. Followed by the formation of a stabilised cation complex 53 upon treatment with a protic or Lewis acid. Complex 53 was suspected to accelerate the ring opening of the cyclopropane to produce the thermodynamically more stable \textit{cis}-olefin species 54. Nucleophilic attack of the
Introduction

Oxygen affords carbocation intermediate 55 and subsequent cyclisation of the primary alcohol onto the dihydrofuran moiety leads to the desired spiroketal 52. 41,43,44

\[
\begin{align*}
\text{Reagents and conditions: } & \text{i. } \text{Co}_2(\text{CO})_8, \text{CH}_2\text{Cl}_2, \text{r.t.}, \text{then BF}_3\cdot\text{OEt}_2, \text{toluene, } -78 \, ^\circ\text{C} \rightarrow -20 \, ^\circ\text{C} \rightarrow 7 \, \text{h} \rightarrow 43-76\%. \\
\text{Scheme 1.3: Synthesis of spirokets using cyclopropane derivatives.}^{41}
\end{align*}
\]

The authors performed a reductive decomplexation/ hydrosilylation using triethylsilane in benzene at 65 °C for 2 hours to furnish the unsaturated ring 56 that was used for NMR studies. 41,45

\[
\begin{align*}
\text{Reagents and conditions: } & \text{i. } \text{Me}_3\text{SiH, benzene, } 65 \, ^\circ\text{C}, 2 \, \text{h}, 84\%. \\
\text{Scheme 1.4: Methods for decomplexation of dicobalt unit.}
\end{align*}
\]
1.4.5 Dehydrative / acid-catalysed spirocyclisation

A. Koutek et al., 2004

The synthesis of a library of various spiroketals via the addition of lactones to lithium alkynyltrifluoroborates 58 under non-acidic conditions was reported by Koutek and co-workers (Scheme 1.5). The key intermediate, lithium alkynyltrifluoroborate 58 was readily formed in situ by the addition of stoichiometric quantities of n-BuLi and BF$_3$·EtO$_2$ in THF to alkyne 57. Subsequent addition of lactone 59 to reaction mixture promoted regioselective acyl C-O ring cleavage to furnish α-alkynone 60, which in turn was subjected to hydrogenolysis/hydrogenation using Pd/C in either ethanol or ethyl acetate to provide the desired spiroketals 61 in excellent yields.

![Scheme 1.5: Synthesis of spiroketals from dihydroxy-α-alkynones precursor.](image)

**Reagents and conditions:** i. n-BuLi/THF, -78 °C then BF$_3$·EtO$_2$, 79-98%; ii. H$_2$, Pd/C, EtOH or EtOAc, r.t., 75-95%.

B. Cossy et al., 2012

In 2012, Cossy et al. reported the convergent synthesis of a variety of monobenzannulated spiroketals via a sequential Suzuki-Miyaura cross-coupling-acidic-catalysed spiroketalisation strategy (Scheme 1.6). The Suzuki cross-coupling of boronate 63 and aryl halide 62 was achieved using Pd(dpdpf)Cl$_2$ and NaOH in 1,4-dioxane/H$_2$O (3:1) under microwave irradiation at a 100 °C. Once cross-coupling was complete, the reaction mixture was treated with p-toluenesulfonic acid affording the desired spiroketals 64 in moderate to excellent yields.
Reagents and conditions: i. Pd(dpff)Cl₂, NaOH, 1,4-dioxane/H₂O (3:1), MW, 100 °C, 10 min; ii. p-TsOH·H₂O, r.t., 10 min 34-96%.

Scheme 1.6: A tandem Suzuki-Miyaura cross-coupling and acidic-catalysed spiroketalisation.⁴⁸

5,5-, 5,6-, 5,7- and 6,6-benzannualted spiroketals have been successfully prepared using this method.⁴⁸
1.5 Benzoxepine Natural Products

Pestalospiranes A (2) and B (3) also belong to a subgroup of natural products that contain a rare benzo[c]oxepin motif. These structurally interesting metabolites represent a small but growing group of natural benzo[c]oxepin derivatives of fungal origin, some of which have been shown to exhibit anti-inflammatory and analgesic activity. Isolation and biological studies of natural products displaying structural similarities to pestalospiranes A (2) and B (3), as well as synthetic endeavours towards their total syntheses will be discussed henceforth.

![Figure 1.16: Structure of pestalospirane B (3)](image)

1.5.1 Oxepine Nomenclature

Oxepines are classified as any seven-membered ring containing a single oxygen atom, with varying degrees of saturation (65-68). Herein, oxepine will be used as a general term for this class of heterocycles (Figure 1.17).  

![Figure 1.17: Structure of oxepines](image)

Where an aromatic group is fused to the heterocycle, the same definitions would apply, where the [b-d] denotes the bond (edge face) on which fusion occurs on the aromatic ring (Figure 1.18).
1.5.2 Benzo[c]oxepine containing natural products

Heptacyclosordariolone (73) was isolated by Bouillant and co-workers from the fungus *Sordaria macrospora* in 1989 (Figure 1.19).²⁴ Heptacyclosordariolone (73) is structurally related to hemiketal 10 (Figure 1.5).¹⁸ The authors reported that the characterisation of 73 was challenging because it decomposed relatively quickly during isolation and when recording the NMR spectra.²⁴ They were able to conclude that the metabolite existed as a racemic mixture and no biological testing was conducted.

Structurally related benzo[c]oxepines, xylarinols A (74) and B (75) were first isolated from fruiting bodies of *Xylaria polymorpha* in 2009 by Lee et al.,⁵⁵ (Figure 1.19). Xylarinols A (74) and B (75) showed moderate 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical scavenging activity, with 40-45% inhibition respectively at a 100 µM concentration. Kesting et al.,⁵⁶ also independently isolated xylarinol A (74) using the HPLC-SPE-NMR hyphenated method from *Pestalotiopsis virgatula* in 2009. No biological testing was conducted.

Ulocladol A (76a) was isolated in 1999 by Höllar et al.,⁵⁷ from the fungus *Ulocladium botrytis* discovered on the marine sponge *Callispongia vaginalis* (Figure 1.20). Ulocladol A (76a) was found to exhibit tyrosine kinase inhibitory activity against p56lk with a reduction in enzyme
activity to 7% at 0.02 µg/µL. The first total synthesis of ulocladol A (76a) was accomplished in 2006 by Abe et al.58 A second total synthesis was reported in 2009 by Altermöller et al.,59 which will be discussed in Section 1.6.3C.

Several years later, ulocladol diacetate (76b) and ulocladol triacetate (76c) were isolated in 2005 by Hormazabal and co-workers from the fungus Microsphaeropsis olivacea inhabiting the plant Pilgerodendron uviferum (Figure 1.20).60 Ulocladol triacetate (76b) was active against the fungus Alternaria alternata with a MIC value of 62.5 µg/mL. Ulocladol triacetate (76c) was active against the fungi Botrytis cinerea and A. alternata with a MIC value of 62.5 µg/mL and showed slight inhibition of acetylcholinesterase (AChE) with an IC₅₀ value of 37 µg/mL.

Alterlactone (77) was discovered during investigations into an endophytic fungal strain Alternaria sp., which was isolated from the leaves of plant Polygonum senegalense in 2008 by Aly and co-workers (Figure 1.20).61 Alterlactone (77) was also isolated from solid cultures of an endolithic fungus Ulocladium sp. in 2012 by Wang et al.62 Alterlactone (77) exhibited activity towards L5178Y mouse lymphoma cells, which caused inhibition of cell growth by 11.8% when assayed at a dose of 10 µg/mL. In 2011, the first total synthesis of alterlactone (77) was accomplished by Cudaj et al.,63 and will be discussed in Section 1.6.3D.

Graphislactones D (78a) were first isolated from the spore-derived lichen mycobionts, Graphis scripta, in 1997 by Tanahashi et al.,64 (Figure 1.20). In 2003, Tanahashi and co-workers65 re-isolated graphislactones D (78a) along with its acetylated derivatives (78b) from cultured mycobionts of G. prunicola. The first total synthesis of graphislactones D (78a) was

---

Figure 1.20: Structure of ulocladol A (76a), ulocladol diacetate (76b), ulocladol triacetate (76c), alterlactone (77), graphislactone D (78a) and graphislactone D acetate (78b)
accomplished in 2006 by Abe et al.,\textsuperscript{58} followed by a synthesis by Altermöller et al.,\textsuperscript{59} in 2009 and then will be discussed in Section 1.6.3C.
1.6 Previous Syntheses of Structural Motifs Related to Pestalospiranes

To the best of our knowledge, there have been no reports of synthetic routes towards pestalospirane A (2) and B (3). Furthermore, only a limited number of strategies have been reported for the synthesis of benzo[c]oxepine ring systems. In order to highlight the relevant literature examples that are available, the synthesis of benzo[c]oxepine functionalities and natural products containing them will be discussed in the section below.

1.6.1 Condensation method

Satyanarayanan and co-workers published two synthetic routes to access the benzo[c]oxepine core ring system (Scheme 1.7). In 2013, the authors successfully devised a key sequential one-pot intermolecular oxy-Michael addition, followed by intramolecular Heck coupling and base-promoted condensation reaction sequence to furnish benzoxepin-3-(1H)-one 82 (Scheme 1.7, route A). The reaction sequence commenced with treatment of 2-bromobenzyl alcohol with caesium carbonate and ethyl acrylate 80, followed by the addition of Pd(OAc)$_2$ and triphenylphosphine to promote the intramolecular Heck coupling providing key intermediate cinnamate diester 81. Cinnamate diester 81 was then subjected to base-promoted condensation to construct the desired benzoxepin-3-(1H)-one 82 in 48% yield.
Reagents and conditions: i. Cs$_2$CO$_3$, toluene, 50 °C, 48 h; ii. Pd(OAc)$_2$, PPh$_3$, 80°C, 24 h; iii. DMF, 120°C, 12 h, 48%; iv. Pd(OAc)$_2$, PPh$_3$, Et$_3$N, toluene, 110 °C, 24 h, 85%, v. NaBH$_4$, AcOH, r.t., 1.5 h, 77%; vi. Cs$_2$CO$_3$, DMF, 120 °C, 4 h, 71%.

Scheme 1.7: Synthesis of benzoxepin-3-(1H)-one 82

Building on their preliminary work, Satyanarayanan et al.,$^{49}$ found that route A did not require the formation of the cinnamate diester 81 and the base-promoted condensation actually proceeds via ester 84. Consequently, Satyanarayanan et al.,$^{49}$ reported a more efficient procedure for the synthesis of benzoxepin-3-(1H)-one 82 by directly synthesising ester 84 as the cyclisation precursor, improving the yield of the product 82 significantly (Scheme 1.7, route B).

The authors three-step procedure began with Heck coupling of o-bromobenzaldehyde 83 with ethyl acrylate 80, using Pd(OAc)$_2$, triphenylphosphine, caesium carbonate in acetonitrile followed by sodium borohydride to afford ester 84 in 93% yield. Ester 84 was then subjected to basic conditions to promote the key base-mediated intramolecular condensation via double bond isomerisation to give benzoxepin-3-(1H)-one 82. The proposed mechanism for the formation of the benzoxepin ring is outlined in Scheme 1.8. The base-mediated reaction is postulated to proceed through a novel intramolecular oxy-Michael addition to give cyclic enolate 85 which in turn exists in equilibrium with intermediate 86 via E-to-Z isomerisation of the ester bond. Subsequent, intramolecular condensation then provides the desired benzoxepin-3-(1H)-one 82.
1.6.2 Ring closing metathesis

The use of ring closing metathesis (RCM) is the most common method for construction of the benzo[\(c\)]oxepine moieties as detailed in a review.\textsuperscript{67} Otterlo and co-workers reported the synthesis of benzo[\(c\)]oxepine \(89\) using a combination of isomerisation and intramolecular RCM using Grubbs’ second-generation catalyst (Scheme 1.9).\textsuperscript{68} The C-allyl group of compound \(87\) was isomerised selectively by treatment of \(t\)-BuOK to provide RCM precursor \(88\) in excellent yields. Intermediate \(88\) was then treated with Grubbs’ second-generation catalyst in toluene and heated to 60 °C for 2 hours and then 80 °C for a further 2 hours to furnish the desired cyclised product \(89\) in 64% yield.
Reagents and conditions: i. t-BuOK, DMF, r.t., 18 h, quant.; ii. Grubbs II (5%), toluene, 2 h, 60 °C, then 2 h at 80 °C, 64%.

Scheme 1.9: Synthesis of the benzoepine core 89 using RCM as reported by van Otterlo et al.\textsuperscript{68}

1.6.3 Palladium mediated cyclisation

C. Total synthesis of graphislactone D (78a) and ulocladol A (76a)

Graphislactone D (78a) and ulocladol A (76a) both contain a rare 7H-dibenzo[c,e]oxepin-5-one core, and due to their structural similarities, the total syntheses reported of these two natural products have comparable strategies. In 2005, Abe et al.\textsuperscript{69} reported the first synthesis of graphislactone D (78a) using a palladium-mediated biaryl coupling followed by lactone reconstruction strategy in 12 steps. The following year Abe et al.\textsuperscript{58} published the first total synthesis of ulocladol A (76a) using three different routes, which utilised intermediates from their graphislactone D (78a) synthesis.

![Graphislactone D and Ulocladol A Structures](image)

Figure 1.21: Structures of ulocladol A (76a) and graphislactone D (78a)

Synthesis of graphislactone D (78a) involved the key palladium-mediated union of aryl iodide 91 and phenol 93 to provide the cyclisation precursor 94. Accordingly, aryl iodide 91 was prepared in 69% yield over 5 steps from commercially available 3,5-dimethoxyaniline (90). The phenol 93 coupling partner was synthesised from commercially available methyl-3,4-dihydroxy-5-methoxybenzoate (92) over 2 steps in 80% yield. Coupling of phenol
Introduction

93 and aryl halide 91 via esterification using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) in dichloromethane afforded ester 94 in 61% yield. Palladium-mediated intramolecular biaryl coupling of ester 94, yielded the six-membered lactone 95. Silyl deprotection of lactone 95 and subsequent treatment with potassium carbonate in methanol promoted the reconstruction of lactone 95 via ring opening and closing to furnish benzoxepine 97. Benzoxepine 97 was then subjected to hydrogenolysis using Pd/C in ethyl acetate to remove the benzyl ether protecting group furnishing graphislactone D (78a) in 58% yield.

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\text{OMe} & \quad \text{MeO} \\
\text{90} & \quad \text{MeO} \\
\text{O} & \quad \text{I} \\
\text{91} & \quad \text{MeO} \\
\text{H} & \quad \text{OBn} \\
\text{92} & \quad \text{O} \\
\text{O} & \quad \text{MeO} \\
\text{93} & \quad \text{MeO} \\
\text{O} & \quad \text{MeO} \\
\text{94} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{95} & \quad \text{MeO} \\
\text{Bn} & \quad \text{O} \\
\text{96} & \quad \text{MeO} \\
\text{MeO} & \quad \text{O} \\
\text{97} & \quad \text{MeO} \\
\end{align*}
\]

\text{over 5 steps} 69% \hspace{2cm} \text{over 2 steps} 80% \hspace{2cm} \text{over 3 steps} 85%

\text{Reagents and conditions: } i. \text{EDC, DMAP, CH}_2\text{Cl}_2, 61%; ii. \text{Pd(OAc)}_2, \text{n-Bu}_3\text{P}, \text{K}_2\text{CO}_3, \text{DMA}, 85%; iii. \text{TBAF, THF}, 90%; iv. \text{K}_2\text{CO}_3, \text{MeOH}, 85%; v. \text{H}_2, 10\% \text{ Pd/C, EtOAc, 58%}.

Scheme 1.10: First total synthesis of graphislactone D (78a)
The following year Abe et al.,\textsuperscript{58} reported the synthesis of ulocladol A (76a) using three different methods based on the methodology developed for the synthesis of graphislactone D (78a). The first route involved a selective demethylation of graphislactone D (78a) with boron tribromide to afford ulocladol A (76a) in 21-73\% yield (Scheme 1.11, route 1). The authors reported that the reaction was difficult to reproduce as the deprotection yield varied greatly (21-73\%). Next, the authors decided to reverse the reaction sequence and attempt to demethylate first followed by debenzylation (Scheme 1.11, route 2). Accordingly, selective demethylation of benzoxepine 97 was achieved using aluminium trichloride to afford intermediate 98 in 83\% yield, followed by hydrogenolysis using Pd/C in ethyl acetate to furnish ulocladol A (76a) in 60\% yield. Finally, the third method reported involved use of previously synthesised intermediate 99 (Scheme 1.11, route 3).\textsuperscript{69} Subsequent reconstruction of the six-membered lactone 99, via ring-opening and closing using potassium carbonate in methanol afforded benzoxepine ring 101 in 82\% yield. Standard hydrogenolysis of benzyl ethers 101 furnished ulocladol A (76a) in 63\% yield.
Reagents and conditions: i. BBr$_3$, CH$_2$Cl$_2$, 27-73%; ii. AlCl$_3$, NaI, CH$_2$Cl$_2$-CH$_3$CN, 83%; iii. H$_2$, Pd/C, EtOAc, 60%; iv. K$_2$CO$_3$, MeOH, 82%; v. H$_2$, Pd/C, EtOAc, 63%.

Scheme 1.11: Frist total synthesis of ulocladol A (76a)

In 2009, Podlech et al.$^{59}$ reported their total syntheses of ulocladol A (76a) and graphislactone D (78a) using a Suzuki cross-coupling reaction to construct the key biaryl bond forming the benzoxepine ring system. Key coupling partner aryl halide 103 and boronate 105 were prepared from 3,4-dihydroxy-5-methoxybenzaldehyde (102) in 75% yield in over 3 steps, and
Introduction

2,4,6-trihydroxybenzoic acid (104) in 75% yield over 3 steps, respectively. (Scheme 1.12). The key Suzuki cross-coupling of boronate 105 and aryl halide 103 using Pd(OAc)$_2$, caesium carbonate and S-Phos in dioxane/H$_2$O (6:1) at 80 °C afforded the benzoxyepine 106 in 65% yield. Subsequent debenzylation using Pd/C in methanol furnished ulocladol A (76a) in 60% yield. Conversely, graphislactone D (78a) was accomplished using the common benzoxyepine intermediate 107, which underwent methylation and subsequent benzyl ether deprotection.

Reagents and conditions: i. DIBAL-H, toluene, -78 °C, 5 min, 99%; ii. Pd(OAc)$_2$, Cs$_2$CO$_3$, S-Phos, dioxane/H$_2$O (6:1), 80 °C, 2 h, 65%; iii. H$_2$, Pd/C, CH$_2$Cl$_2$/MeOH (20:1), 60%; iv. K$_2$CO$_3$, Mel, acetone, reflux, 12 h, 81%; v. H$_2$, Pd/C, CH$_2$Cl$_2$/MeOH (20:1).

Scheme 1.12: Total synthesis of of ulocladol A (76a) and graphislactone D (78a) by Podlech et al.

D. Total synthesis of alterlactone (77)

Having successfully synthesised ulocladol A (76a) and graphislactone D (78a), Podlech and co-workers then reported a seven step convergent total synthesis of alterlactone (77) utilising the Suzuki cross-coupling strategy previously established (Scheme 1.13). The Suzuki coupling
of boronate 105 and aryl bromide 108 was performed using the same conditions previously established to furnish benzoepine 109 in 80% yield. Subsequent deprotection of the benzyl protecting groups furnished alterlactone (77) in quantitative yields.

\[ \text{Reagents and conditions: i. } \text{Pd(OAc)}_2, \text{ S-Phos, Cs}_2\text{CO}_3, \text{ dioxane/H}_2\text{O} (7:1), 20 \text{ h, 80\%. ii. Pd/C, H}_2, \text{ EtOH/EtOAc} (10:1), \text{ quant.} \]

Scheme 1.13: Total synthesis of alterlactone (77)
1.7 Aims of the Current Research

At the onset of this project, no total synthesis of pestalospiranes A (2) and B (3), nor any information regarding their bioactivity had been reported. Thus, the initial aim of this project was to develop an efficient strategy for the total synthesis of pestalospiranes A (2) and B (3). Synthetic access to pestalospiranes A (2) and B (3) will enable confirmation of the reported structure and provide sufficient material for biological testing. The potential biological activity exhibited by structurally-related compounds and the synthetic challenge posed by the heavily unsaturated structures of pestalospirane A (2) and B (3) required a thorough investigation into both known and novel organic transformations.

The key challenge of this work was anticipated to be the construction of the unsaturated tetraoxadispiro ring, which had not been explored by the synthetic community. Our retrosynthetic analysis would hinge on an oxidative radical cyclisation to simultaneously construct both benzoxepine/spiroketal rings of cyclisation precursor 110. Alkene 110 would be available from partial hydrogenation of alkyne 111, which in turn could be accessed via a double Sonogashira cross-coupling of aryl iodide 113 and tetrasubstituted dioxane 112.

Scheme 1.14: Retrosynthetic analysis of pestalospirane B (3)
Chapter Two: Model Study
2.1 Oxidative Radical Cyclisation Strategy

2.1.1 Overview of oxidative radical cyclisation

It was envisioned that a novel double oxidative radical cyclisation would be employed for the construction of both seven-membered rings for the synthesis of pestalospiranes A (2) and B (3). Oxidative radical cyclisations have been utilised for the synthesis of a number of spiroketal-containing natural products as detailed in a recent review.\textsuperscript{70} This methodology is a useful alternative to classical methods such as acid-catalysed spiroketalisation, as it offers a mild cyclisation protocol for substrates which otherwise might be acid-sensitive or contain incompatible functionalities. Our research group has a long-standing interest in the synthesis of aliphatic spiroketalts using oxidative radical cyclisation of cyclic ethers containing a hydroxyalkyl side chain, and have broadened the substrate scope to include benzylic alcohols.\textsuperscript{24,70-72} Inspired by these results we set out to investigate if this strategy could be successfully applied to the synthesis of pestalospiranes A (2) and B (3). A detailed mechanism, as well as the application of the oxidative radical spiroketalisation is discussed later (Section 2.3).

![Figure 2.1: Structure of pestalospirane A (2) and B (3)](image)

2.1.2 Retrosynthetic analysis of the pestalospirane core

The synthetic strategy proposed for pestalospirane A (2) and B (3) hinges on the use of a late stage oxidative radical cyclisation by intramolecular hydrogen abstraction (IHA) to construct both seven-membered spiroketal rings simultaneously. The initial focus of the research was to investigate the formation of the required cyclisation precursor, 1,4-dioxane ring 118 (Scheme 2.1). A model study was devised using a simplified spiroketal 118, which did not contain the phenol groups in order to examine the feasibility of the proposed strategy.
Unfortunately, the most favourable spiroketal configuration cannot be predicted at this initial stage as a multitude of factors including steric effects, intramolecular hydrogen bonding and other chelation interactions may influence the final stereochemistry. As outlined in Scheme 2.1 cyclisation precursor 115 could be obtained by selective reduction of bis-alkyne 116, followed by deprotection. A double Sonogashira cross-coupling reaction between 117 and 118 would provide 116.

Scheme 2.1: Retrosynthetic strategy of the spiroketal core 114 using radical cyclisation

OP = oxygen protecting group
2.2 Synthesis of Substituted 1,4-dioxanes

To apply the oxidative radical cyclisation strategy outlined above to the synthesis of pestalospirane core 114 the first objective was to construct the key 1,4-dioxane intermediate 118. The following section will briefly discuss the literature methods to access substituted dioxanes.

2.2.1 Literature precedent for construction of substituted 1,4-dioxanes

Currently, only a limited number of procedures have been reported for the synthesis of disubstituted 1,4-dioxanes and the main methods will be briefly discussed below. Quaglia et al.,\textsuperscript{73} described the synthesis of a series of α-AR antagonists bearing a 1,4-dioxane ring, which were obtained by the opening of 2,2-diphenyloxirane (119) with allyl alcohol to give 120 or 123 (Scheme 2.2).\textsuperscript{73,74} Epoxidation of olefins 120 and 123 was achieved using \textit{m}-CPBA to furnish epoxides 121 and 124 respectively. Subsequent treatment with 10-camphorsulfonic acid (CSA) afforded the desired dioxanes 122 and 125 in moderate yields.
In search of an alternative procedure for the synthesis of substituted dioxanes, a literature survey revealed several groups have successfully demonstrated the construction of tetrasubstituted 1,4-dioxanes 131-134 by dimerisation of a variety of different epoxides 126-129 at either high temperatures or using either acidic or basic conditions (Scheme 2.3).
Chapter 2: Discussion

Reagents and conditions: i. CHCl₃, r.t., quant.; ii. 180 °C, 4 h, 82%; iii. 150 °C, 30%; iv. NaOH, 0→10 °C, 48 h, 60%.

Scheme 2.3: Examples of substituted dioxane formation via epoxide dimerisation

Lastly, reported procedures for the synthesis of 1,4-dioxanes, constructed via a tandem nucleophilic substitution-intermolecular dimerisation or intramolecular substitution cyclisation are outlined in Scheme 2.4.⁷⁹-⁸³
Reagents and conditions: i. TBAI, 1,2-DCE, 50-55 °C, 47%; ii. K$_2$CO$_3$, DMF, 70 °C, 16 h, 70 °C, 91%; iii. K$_2$CO$_3$, 80 °C, 5 h, 71%; iv. Bu$_2$SnO, reflux, 50%; v. KOH, Et$_2$O, reflux, 4 h, 70-80%.

Scheme 2.4: Literature examples of substituted dioxanes via an S$_\text{N}$_2 dimerisation/cyclisation.$^{79-82}$

2.2.2 Retrosynthetic analysis of disubstituted 1,4-dioxanes

Three different retrosynthetic routes were designed towards 1,4-dioxane 118, exploiting the chemistry discussed in Section 2.2. Route 1 is an adaptation of the method reported by Quaglia et al.$^{73,74}$ Synthesis of 1,4-dioxane 147 could be achieved by ring-opening of known
2-ethylnyloxirane (146) (a (R,R)-tartaric acid derivative), with allylic alcohol 148 under acidic conditions. Further manipulation to install the alkyne would then be required to give the desired product 118 (Scheme 2.5). The second proposed route was designed based on dimerisation of the known 2-ethylnyloxirane (146) to furnish the expected 1,4-dioxane. Finally, route 3 utilises the chemistry described in Scheme 2.4. In this case, we designed a novel approach to the synthesis of 1,4-dioxanes via a tandem S_N2 displacement-intermolecular dimerisation/cyclisation, using 1,2-diol 149 and the corresponding leaving group substrate 150. The 1,2-diol 149 could be obtained from L-tartaric acid derivative 151, which is then modified to introduce an appropriate leaving group such that under basic conditions, substitution by 1,2-diol 149 would provide the desired disubstituted 1,4-dioxane 118 via a S_N2 double intermolecular dimerisation process.

Fortunately, all three routes had a common intermediate; but-3-yn-1,2-diol (149). However, the initial synthetic strategy employed for the construction of the 1,4-dioxane 118 was to employ our novel route 3, in which 1,2-diol 149 undergoes reaction with the corresponding substrate 150 which contains two leaving groups (Scheme 2.5). The decision to construct the dioxane ring via an intermolecular dimerisation was in part motivated by the relative ease of the route as it appeared to be more facile and convergent thus avoiding a laborious multistep synthesis and the need for handling volatile 2-ethylnyloxirane (146) (Scheme 2.5).
2.2.3 Synthesis of but-3-yn-1,2-diol (149)

The first objective was to construct the known 1,2-diol 149 via literature methods using L-tartaric acid as the starting material (Scheme 2.6). Synthesis of 1,2-diol 149 commenced with esterification of the carboxylic acid functionalities of L-tartaric acid (151) using thionyl chloride and ethanol, followed by protection of the vicinal diol as the acetonide using 2,2-dimethoxypropane and catalytic p-toluenesulfonic acid to give ester 153. Reduction of ester 153 using LiAlH₄ afforded the desired 1,4-diol intermediate 154, which underwent mono-benzylation with benzyl chloride to give primary alcohol 155. Alcohol 155 was then converted to chloride 156 under neutral conditions using triphenylphosphine in carbon tetrachloride heated to reflux. The subsequent double base-induced elimination was initially attempted using standard literature conditions. However when chloride 156 was treated with n-BuLi and DMPU, the reaction typically did not go to completion. It was found that the base-induced elimination could also be achieved using LDA as the base. Pleasingly, when the reaction was repeated using LDA, desired propargylic alcohol 157 was obtained in 90% yield. With alcohol 157 in hand, deprotection of the benzyl group was next examined. The NMR data obtained for alcohol 157 was in agreement with the literature values.

Reagents and conditions: i. SOCl₂, EtOH, r.t., 18 h, 94 %; ii. p-TsOH, 2,2-dimethylpropane, r.t., 16 h, 90 %; iii. LiAlH₄, THF, 0 °C, 2 h, quant.; iv. NaOH, DMSO, BnCl, r.t., 2 h, 80%; v. CCl₄, PPh₃, 80 °C, 20 h, quant; vi. LDA, THF, -78 °C, 2 h then -40 °C, 1 h, 90%.

Scheme 2.6: First attempted synthesis of 1,2-diol 149
Initially, propargylic alcohol 157 was treated with BBr₃ in dichloromethane at -78 °C to effect deprotection of the benzyl ether protecting group. Disappointingly, the reaction resulted in the formation of a complex mixture from which no compound was able to be identified accurately by NMR analysis (Table 2.1, entry 1). Next, deprotection was attempted using BCl₃, affording a brown solution containing multiple products as observed by TLC analysis that could not be effectively separated and identified (Table 2.1, entry 2). Lastly, alcohol 157 was subjected to hydrogenolysis conditions in the presence of Pd/C. Even though consumption of the starting material was initially observed by TLC analysis, prolonged reaction times failed to produce any new products (Table 2.1, entry 3). Furthermore, NMR analysis of the reaction mixture showed no formation of the desired diol 149, instead indicating the starting material had undergone degradation.

\[
\begin{array}{c}
\text{OH} & \text{OBn} \\
\text{157} & \rightarrow & \text{OH} \\
\text{149}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BBr₃</td>
<td>CH₂Cl₂</td>
<td>-78</td>
<td>30 min</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>BCl₃</td>
<td>CH₂Cl₂</td>
<td>-78</td>
<td>30 min</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>Pd/C</td>
<td>MeOH</td>
<td>r.t.</td>
<td>18 h</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Table 2.1: Conditions screened for the deprotection of alcohol 157

In order to establish a robust synthetic route to 1,2-diol 149, either a change in protecting group of the terminal alcohol of 157 or exploration of an alternative synthetic strategy was deemed necessary. Despite this route being easily scalable with respectable yields, one major drawback was the use of carbon tetrachloride, a known hepatotoxin which was difficult to obtain and prohibitively expensive in New Zealand. Therefore it was decided to prepare the desired 1,2-diol 149 by an alternative method starting from commercially available d-mannitol 158, which would consequently cut the number of synthetic steps by three.

Synthesis of 1,2-diol 149 began with protection of d-mannitol 158 (Scheme 2.7). Following literature procedures, acetonide protection of the terminal diols of d-mannitol 158 was generally performed using ZnCl₂ and acetone, however, the yield of the reaction was highly variable and generally quite low. Consequently, acetonide protection was instead attempted
using 2,2-dimethoxypropane and catalytic \( p \)-toluenesulfonic acid in DMSO.\(^\text{92}\) Pleasingly, the reaction proceeded smoothly furnishing acetonide \( 159 \) in 90% yield. Sodium periodate cleavage of the diol moiety was carried out using a well-known literature procedure to give the corresponding aldehyde \( 160 \).\(^\text{93}\) Aldehyde \( 160 \) was freshly prepared each time as it would polymerise upon standing. Alkyne \( 162 \) could be prepared via two routes; either by using a Corey-Fuchs reaction (Scheme 2.7, reactions iii and iv)\(^\text{94}\) or using an Ohira-Bestmann homologation (Scheme 2.7, reaction v).\(^\text{95}\)

The Corey-Fuchs reaction is a two-step procedure for the transformation of aldehydes to acetylenes.\(^\text{96}\) The first step is to convert the aldehyde to the homologated dibromoolefin \( 165 \) by treatment of the aldehyde \( 164 \) with dibromo phosphorous ylide \( 163 \), which is generated \textit{in situ} from the reaction of carbon tetrabromide and triphenylphosphine (Scheme 2.8). The second step involves the treatment of dibromoolefin \( 165 \) with two equivalents of \( n \)-BuLi at -78 °C. A lithium-halogen exchange takes place with the first equivalent of \( n \)-BuLi, followed by bromide elimination by the second equivalent of \( n \)-BuLi. The lithium acetylide is then hydrolysed to afford the terminal acetylene \( 166 \).
Alternatively, alkyne 162 could be obtained via a one-pot synthesis using the Ohira-Bestmann reagent via a carbene and carbenoid rearrangement (Figure 2.2). The Ohira-Bestmann procedure is a modification of the Seyferth-Gilbert homologation (Scheme 2.9). Ohira discovered that when phosphonate 168 is treated with potassium carbonate in methanol at 0 °C, dimethyl(diazomethyl)phosphonate (167) is generated in situ for a mild and facile synthesis of alkynes (Scheme 2.9). Bestmann et al. further improved this methodology by a one-pot procedure where phosphonate 168 can be prepared directly from dimethyl-2-oxopropylphosphonate (169) avoiding the multi-step synthesis of dimethyl(diazomethyl)phosphonate (167). Additionally, this method avoids the need for strong bases, low temperatures and oxygen-free techniques.

Mechanistically, the Ohira-Bestmann modified procedure first involves the deacylation of the reagent by methanol (Scheme 2.9). The resulting carbanion attacks the carbonyl group of the aldehyde or ketone and an oxaphosphetane-type intermediate is formed, which then breaks down to afford a thermally unstable diazoalkene and subsequent loss of dinitrogen via α-elimination. The resulting alkylidene carbene then undergoes a 1,2-shift to furnish the desired alkyne.
When applied to aldehyde 160 both the Corey-Fuchs and Ohira-Bestmann homologation furnished the desired propargylic diol 149 in acceptable yields. Both procedures had their own advantages and drawbacks. The Corey-Fuchs methodology requires a two-step process and the use of strong bases, but the reagents are all commercially available. However the by-products of the Corey-Fuchs homologation specifically triphenylphosphine oxide, rendered purification of dibromoalkene 161 and terminal alkyne 162 tedious and time-consuming. Alternatively, use of the Ohira-Bestmann reagent enabled the reaction to be performed as a one-pot procedure, proceeding smoothly at ambient temperatures. It only required the use of mild bases and generated water soluble by-products thereby simplifying purification; alkyne 162 was easily obtained after a quick workup making this procedure very attractive. However, one major drawback of the Ohira-Bestmann reagent was that dimethyl(diazomethyl)phosphonate 168 was expensive to purchase and was therefore synthesised in house.\textsuperscript{99} It was decided to primarily use the Ohira-Bestmann reaction because alkyne 162 was extremely volatile. Hence, the crude alkyne 162 generated using the Ohira-Bestmann reagent was then directly deprotected with Dowex 50W in methanol for 48 h to deliver the desired 1,2-diol 149 without further purification (Scheme 2.7). The NMR data obtained for 1,2-diol 149 was in agreement with the literature values.\textsuperscript{100}
2.2.4 Attempted synthesis of di-substituted dioxane 118

Having successfully synthesised the desired 1,2-diol 149, investigations into an appropriate leaving groups was next examined. Triflate was initially chosen as the leaving group because the triflate anion is a far superior leaving group compared to the tosylate or mesylate anion.\textsuperscript{101} Disappointingly, the reaction of 1,2-diol 149 with triflic anhydride and pyridine in dichloromethane proved unsuccessful, resulting in degradation of the starting material (Scheme 2.10).

\begin{center}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_2_10.png}
\end{center}

\textbf{Reagents and conditions:} i. triflate anhydride, pyridine, CH$_2$Cl$_2$, -78 $\rightarrow$ 0°C, 1 h, 0%.

\textbf{Scheme 2.10: Attempted synthesis of di-triflate 176}

Next, tosylation conditions were explored. Treatment of 1,2-diol 149 with tosyl chloride in the presence of acetonitrile and pyridine resulted in only trace quantities of the desired ditosylate 177 with the majority of the starting material being recovered (Table 2.2, entry 1). Performing the reaction in the presence of triethylamine and DMAP resulted in isolation of desired ditosylate 177 in 19% yield (Table 2.2, entry 2). Despite prolonged reaction times and additional equivalents of both base and tosyl chloride, no difference in the yield of ditosylate 177 was observed. A slight elevation in temperature resulted in decomposition and no desired product was observed by TLC analysis (Table 2.2, entry 3). Finally, it was found that changing the solvent from acetonitrile to dichloromethane facilitated smooth conversion, giving ditosylate 177 as the sole product in a respectable 80% yield.
Table 2.2: Conditions screened for synthesis of ditosylate 177

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Solvent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>TsCl</td>
<td>Acetonitrile</td>
<td>Pyridine</td>
<td>0</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>TsCl</td>
<td>Acetonitrile</td>
<td>Triethylamine + DMAP</td>
<td>0 → r.t.</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>TsCl</td>
<td>Acetonitrile</td>
<td>Triethylamine</td>
<td>0 → 40</td>
<td>Degradation</td>
</tr>
<tr>
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<td>TsCl</td>
<td>Pyridine</td>
<td>Pyridine</td>
<td>0</td>
<td>Trace</td>
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<tr>
<td>5</td>
<td>TsCl</td>
<td>CH$_2$Cl$_2$</td>
<td>Triethylamine + DMAP</td>
<td>0 → r.t.</td>
<td>80</td>
</tr>
</tbody>
</table>

With both 1,2-diol 149 and ditosylate 177 in hand, attention now focused on the key dimerisation step for construction of the desired 1,4-dioxane 118. A mixture of 1,2-diol 149 and ditosylate diol 177 (1:1) was subjected to a wide range of basic conditions with the hope of promoting the S$_N$2 dimerisation (Scheme 2.11).

Scheme 2.11: Proposed dimerisation of 1,2 diol 149 with ditosylate 177

Investigations towards dimerisation began using potassium carbonate as base, in various solvent systems (Table 2.3, entries 1-3). Using THF as the solvent resulted in no reaction, and only starting materials were observed by TLC analysis. Further addition of potassium carbonate made no significant difference, with starting material being recovered from the reaction (Table 2.3, entry 1). Changing the solvent to DMF resulted in the initial formation of a promising new spot as observed by TLC analysis, however, the reaction failed to go to completion. The use of acetonitrile as the solvent also produced trace amounts of the same spot observed in entry 2 (Table 2.3, entry 3). Unfortunately, the isolated fractions from both entries 2 and 3 afforded a complex mixture from which no compounds could be accurately identified by $^1$H NMR analysis.
Next, alternative bases were explored in anticipation of effecting dimerisation. Unfortunately the use of caesium carbonate, 2,6-lutidine or pyridine also resulted in no reaction and starting materials were recovered (Table 2.3 entries 4-6).

The use of solid sodium hydroxide resulted in both the starting materials being consumed, producing multiple spots as revealed by TLC analysis (Table 2.3, entries 6 and 7). However, none of the compounds isolated exhibited characteristic peaks associated with 1,4-dioxane formation in the $^1$H NMR.

When the reaction was attempted using sodium hydride as the base in DMF, prolonged heating resulted in the appearance of a new spot right below the ditosylate spot as observed by TLC. Disappointingly, the NMR and mass spectra of the isolated compound did not exhibit any peaks that corresponded to the desired product. In all cases, prolonged reaction times and high temperatures resulted in decomposition of both starting materials.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>THF</td>
<td>reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t→130</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>acetonitrile</td>
<td>r.t→100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t→100</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>2,6-lutidine</td>
<td>-</td>
<td>r.t→100</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>pyridine</td>
<td>-</td>
<td>r.t→100</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>NaOH</td>
<td>DMSO</td>
<td>r.t→100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>NaOH</td>
<td>toluene</td>
<td>r.t→100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>9</td>
<td>NaH</td>
<td>DMF</td>
<td>r.t→100</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 2.3: Conditions screened for the dimerisation of 1,2-diol 149 and ditosylate 177

In light of these difficulties with the dimerisation of 1,2-diol 149 via a double S$_2$N$_2$ process using base, a simplified model system was devised with the use of commercially available ethylene...
glycol (178) as the diol substrate, as it was suspected that the monosubstituted 1,4-dioxane 179 would be easier to access (Scheme 2.12).

![Scheme 2.12: Proposed synthesis of model mono-substituted 1,4-dioxane 179](image)

Investigations towards the formation of model dioxane 179 began with the screening of potassium carbonate in DMF, however, no reaction was observed by TLC analysis and the starting material ditosylate 177 was recovered (Table 2.4, entry 1). When the dimerisation was repeated using either sodium hydride or caesium carbonate as the base at elevated temperatures, TLC analysis suggested no reaction had occurred and starting material was recovered again (Table 2.4, entries 2 and 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>100→130</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>DMF</td>
<td>100→130</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Cₛ₂CO₃</td>
<td>DMF</td>
<td>100→130</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

*Table 2.4: Conditions screened for the attempted synthesis of model mono-substituted dioxane 179*

Even with the use of the simpler diol ethylene glycol (178), the desired double SN2 nucleophilic displacement proved challenging. As such a new synthetic approach to substituted dioxanes was required.
2.2.5 Revised approach for the synthesis of di-substituted dioxane 118

To avoid the problematic dimerisation step for the construction of the 1,4-dioxane 118 ring, a modified strategy was examined. We envisioned the 1,4-dioxane 118 ring could be constructed via intramolecular S_N2 displacement/cyclisation of tosylate 180, which would in turn be accessed via an acetylide addition to lactol 182 and subsequent tosylation of the resulting diol 181 (Scheme 2.13).^{102-104} Lactol 182 would be obtained by reduction of lactate 183, which itself could arise from a step-wise etherification of ethyl bromoacetate 186 with mono-TBS protected alcohol 185 and subsequent acid-catalysed lactonisation of alcohol 184.^{105,106}

Scheme 2.13: Revised retrosynthetic strategy for the synthesis of di-substituted 1,4-dioxane 118

The synthesis commenced with mono-TBS protection of previously synthesised 1,2-diol 149. Disappointingly, standard conditions for TBS protection using TBSCl and imidazole resulted in low yields for the desired mono-protected diol 185, along with significant quantities of di-protected diol 188 (Table 2.5, entry 1). In order to circumvent this problem, the synthesis of mono-protected diol 185 via its corresponding stannylene acetal was explored (Scheme 2.14). This protocol, first reported by Shanzer et al.,^{107} involves the treatment of diols with stoichiometric amounts of dibutyltin oxide and subsequent removal of solvent (water or methanol) to afford the desired stannylene acetal 187. These stannylene acetals can then undergo various selective alkylation, acylation, sulfonylation and phosphorylation reactions, usually selectively at the primary alcohol. One disadvantage of this method is the unavoidable production of stoichiometric amounts of dibutyltin oxide, which is only separable by chromatography. By employing this method, the stannylene acetal 187 of 1,2-diol 149 was
prepared, followed by treatment with tert-butylidemethylsilyl chloride resulting in regioselective silylation to afford the desired silyl ether 185 in excellent yield (Scheme 2.14, Table 2.5, entry 2.\textsuperscript{107,108})

\[
\begin{align*}
\text{HO} \quad \text{OH} & \quad \xrightarrow{\text{Entry 1, Table 2.5}} \quad \text{HO} \quad \text{OTBS} \\
149 & \quad + \quad \text{TBSO} \quad \text{OTBS} \\
\text{BuSnO} & \quad \xrightarrow{\text{Entry 2}} \quad \text{BuSnO}
\end{align*}
\]

Scheme 2.14: Selective mono TBS-protection of 1,2-diol 149

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents\textsuperscript{a}</th>
<th>Yield % (185)</th>
<th>Yield % (188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSCl (1 eq), Imidazole (1 eq)</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Bu\textsubscript{2}SnO, then TBSCl (1 eq), Imidazole (1 eq)\textsuperscript{b}</td>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}TBS-protection was performed at room temperature for 12 hours, \textsuperscript{b}diol 149 and dibutyltin oxide were heated under reflux in methanol until a homogenous solution was observed.

Table 2.5: Conditions screened for mono-TBS protection of 1,2-diol 149

With an established route to access mono-TBS protected alcohol 185, intermolecular etherification with commercially available ethyl bromoacetate (186) was next attempted (Scheme 2.15).

\[
\begin{align*}
\text{Br} \quad \text{O} & \quad \xrightarrow{\text{HO}} \quad \text{O} \\
186 & \quad + \quad \text{185} \\
\text{184}
\end{align*}
\]

Scheme 2.15: Attempted coupling of bromo-ester 186 with mono-protected alcohol 185
To effect etherification of alcohol 185 with ethyl bromoacetate (186) a range of different bases, solvents and temperature were examined (Table 2.6). Investigations began using sodium hydride as the base in either THF or DMF (Table 2.6, entries 1 and 2). Unfortunately, no reaction was observed with both starting materials being recovered. The addition of catalytic sodium iodide under these conditions resulted in degradation of starting materials (Table 2.6, entry 3). Use of either potassium carbonate or caesium carbonate with TBAI as an additive and heating to 100 ºC in DMF, resulted in no reaction (Table 2.6, entries 4-7). Interestingly, when the solvent was changed to acetone, degradation of both starting materials was observed (Table 2.6, entry 8). The use of KOH (solid or ground) also resulted in no reaction as observed by TLC analysis (Table 2.6, entries 10 and 11).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Additives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (1.2 eq)</td>
<td>THF</td>
<td>Reflux</td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>NaH (1.2 eq)</td>
<td>THF</td>
<td>Reflux</td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>NaH (2 eq)</td>
<td>DMF</td>
<td>40→100</td>
<td>NaI (cat)</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>Reflux</td>
<td>TBAI</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>100</td>
<td>TBAI</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃ (2 eq)</td>
<td>DMF</td>
<td>40→100</td>
<td>TBAI</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Cs₂CO₃ (2-10 eq)</td>
<td>DMF</td>
<td>40→100</td>
<td>TBAI</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Cs₂CO₃ (2 eq)</td>
<td>Acetone</td>
<td>100</td>
<td>TBAI</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>Cs₂CO₃ (2 eq)</td>
<td>Acetone</td>
<td>Reflux</td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>KOH (pellets)</td>
<td>DMSO</td>
<td>r.t.</td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>KOH (ground)</td>
<td>DMSO</td>
<td>r.t.→50</td>
<td></td>
<td>No reaction</td>
</tr>
</tbody>
</table>

*aBase was added last. *bAlcohol and base were premixed for an hour before addition of ester 186. *cReaction was performed in a pressure tube

**Table 2.6: Conditions screened for the attempted etherification of alcohol 185 with ethyl bromoacetate (186)**
Failure to effect etherification under the various conditions (bases, solvent and temperature) screened led to speculation that the secondary alcohol was not reactive enough to undergo intermolecular etherification with ethyl bromoacetate (186) and consequently an alternative substrate was examined (Scheme 2.16).

Given that the reaction did not proceed with the secondary alcohol, the conditions in Table 2.6 were used to screen the intermolecular esterification of 1,2-diol 149 with both 2-bromoacetyl bromide (189a) and 2-chloroacetyl bromide (189b) in parallel (Scheme 2.16). Unfortunately, all attempted conditions were again unsuccessful and the reaction resulted in degradation of starting material (Scheme 2.16).

![Scheme 2.16: Attempted synthesis of ester 190](image)

**2.2.6 Synthesis of monosubstituted 1,4-dioxane (179)**

In light of the difficulties encountered in constructing the disubstituted 1,4-dioxane 118 (Sections 2.2.4 and 2.2.5), it was next decided to simplify the model once again by focusing on forming the mono-substituted dioxane 179 (Scheme 2.17). It was envisioned that dioxane 179 could be obtained by TBS deprotection and subsequent intramolecular SN2 cyclisation of tosylate 200, which itself is available via acetylide addition to aldehyde 201. Mono protection of commercially available diethylene glycol 202, followed by oxidation would provide the required aldehyde 201.
Following literature procedure, synthesis of aldehyde 201 began with mono-TBS protection of diethylene glycol 202 followed by Swern oxidation (Scheme 2.18). In order to avoid the work-up procedure and unpleasant dimethyl sulfide by-product obtained during the Swern oxidation, an alternative oxidation of alcohol 203 was performed using IBX in ethyl acetate heated to reflux. Unfortunately IBX oxidation generally gave lower yields in comparison to the Swern oxidation, thus the Swern oxidation was preferred despite its drawbacks. Tediously, aldehyde 201 proved to be unstable upon storage at 4 °C beyond 24 hours, and therefore needed to be used immediately after isolation by treatment with ethynylmagnesium bromide to give alcohol 204. Treatment of alcohol 204 with tosyl chloride afforded tosylate 200 and subsequent deprotection was achieved using buffered TBAF (TBAF/acetic acid 1:1) furnishing the cyclisation precursor, primary alcohol 205. It is worth noting that it was necessary to buffer the deprotection reaction with stoichiometric acetic acid as treatment with TBAF alone led to decomposition of the starting material.

Scheme 2.17: Proposed retrosynthesis of mono-substituted dioxane 179

Reagents and conditions: i. TBSCl, imidazole, CH₂Cl₂, 18 h, r.t., 65%; ii. DMSO, (COCl)₂, Et₃N, CH₂Cl₂, -78 → r.t. 96% or IBX, EtOAc, refluxed 70%; iii. ethynylmagnesium bromide, THF, 9 h, 0 °C → r.t., 67%; iv. TsCl, Et₃N, DMAP, CH₂Cl₂, 18 h, r.t., 71%; v. TBAF/AcOH(1:1), THF, 12 h, 0 °C → r.t., 75%.
Chapter 2: Discussion

With tosylate 205 in hand, investigation into cyclisation could now be attempted. A number of different bases and temperatures were trialled in an attempt to induce cyclisation, however under these reaction conditions, only degradation of starting material was observed, resulting in unidentifiable and/or unstable side products (Table 2.7). It was next decided to perform the reaction under acidic conditions as tosylate 205 was speculated to be unstable under basic conditions (Table 2.8).

![Chemical structure](image)

Table 2.7: Conditions screened for cyclisation of mono-substituted dioxane (179) under basic conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>DMF</td>
<td>r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>r.t.-80</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>CsCO₃</td>
<td>DMF</td>
<td>r.t.-80</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Treatment of alcohol 204 with TBAF afforded diol 206 which, was expected to undergo acid-catalysed condensation to furnish the desired dioxane 179 (Table 2.8). Unfortunately, upon treatment with p-toluenesulfonic acid, no reaction took place, with only starting material being recovered as observed by TLC and NMR analysis (Table 2.8, entry 1). The use of the stronger Brønsted acids TFA or HCl (4.0 M) resulted in decomposition of the starting material (Table 2.8, entries 2 and 3).
Chapter 2: Discussion

Reagents and conditions: i. TBAF, THF, 0 °C, 5 min, 65%.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH</td>
<td>Toluene</td>
<td>r.t → reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>1,2-DCE</td>
<td>0 → r.t</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>HCl (4.0 M)</td>
<td>1,2-DCE</td>
<td>0 → r.t</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Table 2.8: Conditions screened for cyclisation of mono-substituted dioxane 179 under acidic conditions

It was speculated that if any dioxane was formed under the conditions mentioned above, the product was suspected to be volatile and/or unstable to prolonged heating. Therefore, this method may not be a viable option as high temperatures were required to effect reaction. We therefore considered an alternative method to construct the desired dioxane 179.

2.2.7 Sonogashira coupling of aryl halide 210 and alkyne 204

Upon consideration of the problems previously encountered during the attempted synthesis of 1,4-dioxanes mentioned above (Sections 2.2.2-2.2.6), it was decided to increase the molecular weight of the dioxane precursor 209 to overcome any suspected volatility issues. Consequently, the Sonogashira cross-coupling would be performed first, followed by oxidative radical cyclisation in hopes of delivering the desired 1,4-dioxane 207 (Scheme 2.19). It was envisaged that the spiroketal core 207 would be established using an oxidative radical cyclisation reaction from 1,4-dioxane 208. 1,4-Dioxane 208 would in turn be accessed via partial hydrogenation followed by cyclisation of intermediate 209. Sonogashira cross-coupling of aryl halide 210 with alkyne 204 would provide intermediate 209.
A. The Sonogashira cross-coupling

The Sonogashira cross-coupling reaction is a coupling between an aryl or vinyl halide with a terminal alkyne to generate a new sp²-sp carbon-carbon bond in the process. The reaction is catalysed by a transition metal species, most commonly a palladium complex, in the presence of a base and often alongside a copper(I) co-catalyst. Under classical Sonogashira cross-coupling conditions, the copper(I) co-catalyst is required to accelerate the reaction by forming a π-complex with the alkyne, increasing the acidity of the terminal proton, thus allowing the base to deprotonate the alkyne and copper-acetylide (1A) to be formed in situ. This is followed by transmetalation with palladium complex B to give complex C which, after cis/trans isomerisation to D, undergoes reductive elimination to give the final coupled alkyne E product (Scheme 2.20). A potential complication of this procedure is the competing homo-coupling (Glaser cross-coupling, Scheme 2.20), that may outcompete the Sonogashira cross-coupling if the reaction is not performed under anaerobic conditions; copper can bind and activate atmospheric oxygen and promote homocoupling in preference. Consequently, all reactions were performed under strict anaerobic conditions by degassing and flushing all glassware with nitrogen before use.
Having earlier established a robust route to alkyne 204 (Scheme 2.18), attention then focused on synthesis of the aryl halide 210 coupling partner. Accordingly, the synthesis commenced with commercially available 2-iodobenzoic acid (211) which underwent reduction using BH$_3$-DMS in THF to afford the benzyl alcohol 212 in excellent yields, and subsequent EOM protection using chloromethyl ethyl ether and sodium hydride in DMF furnished aryl halide 210 (Scheme 2.21).
Chapter 2: Discussion

**Reagents and conditions**: i. BH$_3$·DMS, THF, 16 h, 0 ºC, 90%; ii. EOMCl, NaH, DMF, 18 h, 0 ºC, 90%.

Scheme 2.21: Synthesis of aryl halide 210

With both alkyne 204 and aryl halide 210 in hand, attention now shifted to the Sonogashira cross-coupling (Table 2.9). Initially, standard Sonogashira cross-coupling conditions (Table 2.9, entry 1) were attempted using triethylamine as both the base and solvent which has been shown to be effective at minimising Glaser coupling. Unfortunately, conducting the reaction under these cross-coupling conditions resulted in an incomplete conversion of starting materials (204 and 210), even after extended reaction times and using an increased catalyst loading (Table 2.9, entry 2). Altering the solvent system to either DMF or THF as co-solvents (Table 2.9, entries 3 and 4) made little difference to the yield of the desired product 213. However, pleasingly, under these conditions no Glaser coupling was observed.

In an effort to improve the yield of the Sonogashira cross-coupled product 213, alternative conditions were sought. The use of sterically hindered, electron-rich phosphine ligands, in place of triphenylphosphine, has been shown to facilitate oxidative insertion to aryl halides and have been successfully employed in copper-free Sonogashira coupling conditions (Scheme 2.20).
Mechanistically the copper-free Sonogashira cross-coupling reaction is not well-understood, despite extensive study (Scheme 2.22). However, a general mechanism is described herein. The catalytic cycle begins with oxidative insertion of Pd(0) complex to the aryl halide to give A. The second step involves the complexation of the alkyne to the Pd-complex A via ligand displacement to give intermediate complex B, followed by deprotonation to form complex C. Subsequent reductive elimination would then generate the coupled product D and regeneration of the active Pd(0)-catalyst.

**Table 2.9: Conditions screened for Sonogashira cross-coupling of aryl halide 210 with alkyne 204**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(^{11}) Catalyst (mol%)</th>
<th>Cu(^1) Catalyst (mol%)</th>
<th>Ligand (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh(_3))(_2)Cl(_2) (2)</td>
<td>CuI (2)</td>
<td>-</td>
<td>Et(_3)N</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh(_3))(_2)Cl(_2) (10)</td>
<td>CuI (10)</td>
<td>-</td>
<td>Et(_3)N</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh(_3))(_2)Cl(_2) (5)</td>
<td>CuI (5)</td>
<td>-</td>
<td>Et(_3)N /DMF (1:1)</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh(_3))(_2)Cl(_2) (5)</td>
<td>CuI (2.5)</td>
<td>PPh(_3) (2.5)</td>
<td>Et(_3)N /THF (1:1)</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc(_2)) (5)</td>
<td>-</td>
<td>X-Phos (20)</td>
<td>Et(_3)N</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc(_2)) (5)</td>
<td>-</td>
<td>X-Phos (10)</td>
<td>NMP + K(_2)CO(_3) (5 eq)</td>
<td>62</td>
</tr>
</tbody>
</table>
The reaction was repeated using palladium(II) acetate and X-Phos in triethylamine which provided a slight increase in the yield of 213 to 50% (Table 2.9, entry 5). Next, replacing triethylamine with potassium carbonate and using N-methyl-2-pyrrolidone (NMP) as solvent (Table 2.9, entry 6) further improved the yield of the desired coupled product 213 to a modest 62% yield.

Given the successful formation of Sonogashira coupled product 213, investigation into the formation of the 1,4-dioxane could now commence. Therefore, the secondary alcohol was converted to the tosylate 209 using 4-toluenesulfonyl chloride, triethylamine and DMAP in dichloromethane. Subsequent treatment with TBAF concomitantly deprotected the silyl ether and induced the desired 6-exo-tet cyclisation via S_n2 displacement of the tosylate group. Gratifyingly, this reaction sequence afforded the desired dioxane 214 with an overall yield of 50% over two steps (Scheme 2.23).

**Reagents and conditions:** i. TsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 18 h 67%; ii. TBAF, THF, 0 °C → r.t., 6 h, 75%.
2.3 Oxidative Radical Cyclisation

Having successfully synthesised the desired monosubstituted 1,4-dioxane 214, the key spirocyclisation via an intramolecular hydrogen abstraction (IHA) was investigated next. The oxidative radical cyclisation is a versatile method to construct spiroketals and is also a useful alternative to traditional acid-catalysed spirocyclisation of dihydroxyketones, in particular for acid-sensitive substrates (Scheme 2.24).70

The first use of this methodology for the synthesis of spiroketals was reported in 1961 by Mićović et al.116, whereby a series of terminal diols 215A were treated with lead tetraacetate in benzene and heated to reflux (Scheme 2.24). The diols were demonstrated to undergo double intramolecular hydrogen abstraction affording a series of 5,5-, 5,6- or 6,6- spiroketals 215B.

Scheme 2.24: Double IHA of aliphatic diols using lead tetraacetate by Mićović et al.,116 and acid-catalysed spiroketalisation

In 1983, Suárez et al.,117 investigated the oxidative radical spirocyclisation of 26-hydroxyfurostan 216 to sapogenin-spiroketal 217 via the formation of a hypoiodite intermediate and subsequently elucidated the likely mechanism of this reaction (Scheme 2.25). The acetyl hypoiodite is generated in situ from the reaction between lead tetraacetate and iodine, which then reacts with the alcohol 216 to generate the alkyl hypoiodite 216A. It was initially suspected that the alkoxy radical was formed via a thermally or photochemically induced homolytic cleavage of the O-I bond in alkyl hypoiodite 216A. The cyclisation was believed to then proceed exclusively via a 1,6-hydrogen shift, which was confirmed by deuterium-labelled (OD) NMR studies during cyclisation.70,117 For successful IHA cyclisation to occur, two general requirements need to be considered. Firstly, the optimum distance between the O-radical and abstractable hydrogen is around 3 Å and secondly, the reactivity of
the abstractable hydrogen atom increases with the degree of substitution at the carbon atom. Tertiary hydrogens are therefore more reactive towards IHA than secondary hydrogens.\textsuperscript{117,118}

\begin{center}
\begin{tikzpicture}

\node (216) at (0,0) {\includegraphics[width=0.2\textwidth]{216.png}};

\node (216A) at (0,-2) {\includegraphics[width=0.2\textwidth]{216A.png}};

\node (217) at (4,0) {\includegraphics[width=0.2\textwidth]{217.png}};

\node (PbOAc4) at (2,-2) {\includegraphics[width=0.2\textwidth]{PbOAc4.png}};

\node (I2) at (2,0) {\includegraphics[width=0.2\textwidth]{I2.png}};

\node (cyclohexane) at (2,-4) {\includegraphics[width=0.2\textwidth]{cyclohexane.png}};

\draw[->] (216) -- (216A) node[midway,above] {2AcO\text{I}};
\draw[->] (216) -- (PbOAc4) node[midway,above] {Pb(OAc)\text{4}};
\draw[->] (PbOAc4) -- (I2) node[midway,above] {I\text{2}};
\draw[->] (I2) -- (cyclohexane) node[midway,above] {hv};
\draw[->] (216A) -- (217) node[midway,above] {Pb(OAc)\text{2}};
\draw[->] (216) -- (217) node[midway,above] {i};
\draw[->] (217) -- (PbOAc4) node[midway,above] {2AcO\text{I}};
\draw[->] (217) -- (I2) node[midway,above] {I\text{2}};
\draw[->] (217) -- (cyclohexane) node[midway,above] {hv};
\draw[->] (217) -- (216A) node[midway,above] {Pb(OAc)\text{2}};
\draw[->] (217) -- (216) node[midway,above] {i};
\draw[->] (217) -- (PbOAc4) node[midway,above] {2AcO\text{I}};
\draw[->] (217) -- (I2) node[midway,above] {I\text{2}};
\draw[->] (217) -- (cyclohexane) node[midway,above] {hv};
\end{tikzpicture}
\end{center}

**Reagents and conditions:** i. Pb(OAc)\text{4}, I\text{2}, hv (100 W), cyclohexane, reflux 20 mins, 80%

Scheme 2.25: Proposed mechanism of the oxidative radical spitketalisation.\textsuperscript{117}

Shortly after their initial discovery, in 1984, Suárez et al.\textsuperscript{119} reported a major breakthrough for this methodology during the synthesis of spiroketal 217, where photolytic oxidative radical cyclisation of alcohol 216 was achieved using the non-toxic hypervalent iodine reagent iodobenzene diacetate PhI(OAc)\text{2} (Scheme 2.26). More impressively, only one equivalent of both PhI(OAc)\text{2} and iodine were required for complete conversion, in contrast to the use of
excess lead tetraacetate and iodine.\textsuperscript{116,120} The use of iodobenzene diacetate has since proven to be a more efficient and convenient protocol than \(\text{Pb(OAc)}_4/\text{I}_2\) in other syntheses.\textsuperscript{121}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Improved methodology with the use of iodobenzene diacetate.\textsuperscript{119}}
\end{figure}

The success of IHA in late-stage construction of spiroketal moiety has been reviewed extensively, illustrating the synthetic value of this approach for the synthesis of complex natural products.\textsuperscript{70} Our research group has a long-standing interest in the synthesis of spiroketals using oxidative radical cyclisation of cyclic ethers containing hydroxyalkyl side chains.\textsuperscript{71,122,123} In the synthesis of the bis-spiroketal moiety of spirolides B and D, Brimble et al.,\textsuperscript{124,125} used \(\text{PhI(OAc)}_2\) and iodine to perform two consecutive IHA reactions to first give a 5,6-spiroketal 219, followed by the desired 5,5,6-bispiroketal 220, in excellent yields for both transformation (Scheme 2.27).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Synthesis of the fully functionlised 5,5,6-bis-spiroketal moiety by Brimble et al.\textsuperscript{124}}
\end{figure}

The chemistry has also been employed for the construction of a series of 5,5-, 5,6-, 6,6-monobenzannulated spiroketals from alcohols.\textsuperscript{72,123} The use of \(\text{PhI(OAc)}_2/\text{I}_2\) afforded the
monobenzannulated spiroketals 222 in variable yields. Formation of the 5-membered rings usually resulted in higher yields than the corresponding 6-membered rings.

\[
\begin{align*}
\text{221} & \xrightarrow{\text{i.}} \text{222} \\
\end{align*}
\]

Reagents and conditions: i. PhI(OAc)\textsubscript{2}, I\textsubscript{2}, hv, cyclohexane, 7 °C, 2-3 h, 40-92%.

Scheme 2.28: Synthesis of monobenzannulated spiroketals by Brimble et al.\textsuperscript{123}

Of particular relevance to the current work is the preliminary work by Brimble et al.,\textsuperscript{71} who demonstrated an oxidative radical cyclisation procedure for the synthesis of spiroacetal 224 from benzylic alcohol 223 (Scheme 2.29). This is the only example known to date where oxidative radical cyclisation was successfully employed using a benzylic alcohol.

\[
\begin{align*}
\text{223} & \xrightarrow{\text{i.}} \text{224} + \text{225} \\
\end{align*}
\]

Reagents and conditions: i. PhI(OAc)\textsubscript{2}, I\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, hv, r.t., 2 h, 61%.

Scheme 2.29: Example of oxidative radical cyclisation of a benzylic alcohol as reported by Brimble et al.\textsuperscript{71}

Encouraged by this recent literature precedent for successful oxidative radical cyclisation using a benzylic alcohol moiety, investigation of the crucial radical cyclisation of alcohol 223 could now be carried out.

2.3.1 Saturated ring formation

To the best of our knowledge, IHA reactions which proceed through either an eight or higher membered transition state remain relatively unexplored.\textsuperscript{118} Therefore it was decided to perform preliminary experiments on a model substrate to verify the feasibility of this methodology. It
is difficult to predict what influence the unsaturated bond could have on the oxidative radical cyclisation, as no examples of this type of unsaturated ring system have been reported to date. Thus, it was thought that the use of the saturated model analogue 226 would be more appropriate to investigate the IHA via a putative eight-membered transition state and therefore offer a potentially novel route to access the 7,6-membered spiroketal ring system (Scheme 2.30).

Accordingly, dioxane 213 was subjected to hydrogenation conditions using Pd/C in ethyl acetate under an atmosphere of hydrogen to afford alkane 228 in 90% yield (Scheme 2.31). Deprotection of alkane 228 was successfully achieved using p-toluenesulfonic acid in methanol to give the key cyclisation precursor, alcohol 226 in 75% yield.

Treatment of alcohol 226 with iodobenzene diacetate (2 equiv.) and iodine (2 equiv.) in cyclohexane at room temperature produced a bright purple solution and TLC analysis indicated complete consumption of the starting material and the appearance of two non-polar spots after one hour. Gratifyingly, one of the compounds isolated was the desired spiroketal 227; the compound corresponding to the other TLC spot was found to be the aldehyde 229 (Scheme 2.31). The reaction was then repeated with irradiation by a 40 W light source, however, neither improvement in the yield of spiroketal 227 nor a decrease in the yield of aldehyde 229 was observed. Nevertheless, this model study demonstrates the ability for a radical spiroketalisation to occur via the postulated eight-membered transition state (Scheme 2.32).
Structural assignment of spiroketal 227 was established by analysis of the $^1$H NMR and $^{13}$C NMR spectra along with the identification of an appropriate molecular ion in the mass spectra. The appearance of a new quaternary $^{13}$C signal at δ 96.4 ppm corresponding to the spiroketal anomeric carbon and the disappearance of the corresponding methine multiplet signal at δ 3.84-3.57 ppm corresponding to the abstractable hydrogen are consistent with the formation of the new quaternary centre of the spiroketal 227. Additionally, an increase in complexity of the overlapping multiplet peaks corresponding to the CH$_2$ groups in the $^1$H NMR spectrum was consistent with the conversion from a linear to a cyclic system.

The aldehyde side product was identified by both its mass spectrum and the $^1$H NMR spectrum; the compound showed a new resonance at δ 10.26 ppm replacing the assigned signal for the benzylic CH$_2$O at δ 4.69 ppm, which is consistent with oxidation of the alcohol to the proposed aldehyde 229. Furthermore, the mass spectrum exhibited a molecular ion of m/z 243.0992 which is consistent with the loss of two hydrogens thus further confirming that oxidation to aldehyde 229 had taken place. The formation of the aldehyde 229 is not entirely unexpected as Jay-Smith et al.,$^{71}$ also reported the observation of trace amounts of aldehyde 225 during their studies (Scheme 2.29). The eight-membered transition state as we know isn’t as favoured as the six or seven-membered transition state and the oxidation of the alcohol might be equally as favoured as the 1,7-H shift, hence resulting in a roughly 1:1 mixture of spiroketal and aldehyde. The proposed mechanism for formation for the desired spiroketal 227 and undesired aldehyde 229 are outlined in Scheme 2.32. The acetyl hypoiodite is formed in situ from a reaction between iodosobenzene diacetate and iodine, which then reacts with the alcohol 226 to give the
intermediate alkyl hypoiodite $226\text{B}$. The alkoxy radical $226\text{A}$ is formed via homolytic cleavage, initiated by photochemical irradiation of $226\text{B}$. Subsequent 1,7-hydrogen abstraction on intermediate $226\text{A}$ could occur along with competing benzylic hydrogen abstraction on intermediate $229\text{A}$ to furnish the desired spiroketal $227$ and undesired aldehyde $229$, respectively.

Scheme 2.32: Postulated competing mechanism for the formation of spiroketal $227$ and aldehyde $229$

2.3.2 Attempted unsaturated ring formation using oxidative radical cyclisation

With the successful outcome of the oxidative radical cyclisation of the saturated dioxane $226$ to form spiroketal $227$, we were eager to extend this methodology to the unsaturated alcohol $208$ to install the unsaturated seven-membered ring system of pestalospiranes A (2) and B (3)
We anticipated that unsaturated alcohol 208 could be obtained by partial hydrogenation of alkyne 213 (Table 2.10).

The Lindlar catalyst is one of the most popular catalyst systems employed for hydrogenation of alkynes to alkenes.\textsuperscript{101,126} The Lindlar catalyst is a palladium\textsuperscript{0} species supported on calcium or barium carbonate poisoned with lead acetate. It has been found that palladium coated on BaSO\textsubscript{4} is superior to CaCO\textsubscript{3} due to the stability of the solid support towards acid.\textsuperscript{126} The lead acts to control the degree of hydrogenation by reducing the amount of hydrogen absorbed onto the surface of the catalyst.\textsuperscript{126} Unfortunately, when partial hydrogenation of dioxane 213 was attempted using Lindlar catalyst, only over reduction to alkane 228 was observed (Table 2.10, entry 1). It was found that the catalyst alone was not sufficiently selective to effect partial hydrogenation and the addition of quinoline was required to give unsaturated dioxane 230 (Table 2.10, entry 2).

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
Entry & Catalyst\textsuperscript{a} & Solvent & Additive & Yield (\%) \\
\hline
1 & Lindlar & MeOH & & 228 (90) \\
2 & Lindlar & EtOAc or hexanes & Quinoline (0.25 M) & 230 (quant) \\
\hline
\end{tabular}
\caption{Conditions screened for partial hydrogenation of alkyne 213 using Lindlar catalyst.}
\end{table}

\textsuperscript{a}0.3 w/w loading

Quinoline acts by inhibiting the alkene-catalyst surface interaction, thus further enhancing the ability of the catalyst to partially reduce alkynes selectively (Scheme 2.33).\textsuperscript{101,126} It is proposed that the stereoselective reduction of alkynes to cis-alkenes is a consequence of one face of the triple bond being blocked by the Lindlar catalyst so that hydrogen transfer can occur from the other side of the triple bond.\textsuperscript{126} Furthermore, it was found that the choice of solvent used in the reaction was of crucial importance. Protic solvents such as methanol and ethanol are conventionally used in hydrogenation reactions, however, for optimal stereoselective partial syn-hydrogenation ethyl acetate or hexanes were found to be the ideal solvents.\textsuperscript{126}
Scheme 2.33: Proposed mechanism of alkyne hydrogenation using Lindlar catalyst and quinoline.$^{126}$

With the desired cis-alkene dioxane 230 in hand, deprotection with p-toluenesulfonic acid in methanol/ethanol (1:1) furnished the desired alcohol 208 in quantitative yield (Scheme 2.34).

Reagents and conditions: i. p-TsOH, MeOH/EtOH (1:1), 50 °C, 14 h, quant.

Scheme 2.34: Synthesis of unsaturated alcohol 208.

Given the successful oxidative radical cyclisation of the saturated alcohol 226, it was expected the cyclisation of the unsaturated alcohol 208 would be facile. We suspected the tertiary dioxane hydrogen would be more reactive towards intramolecular hydrogen abstraction (IHA), as the adjacent double bond was expected to confer additional stability to the tertiary carbocation due to its resonance stabilisation (Scheme 2.35).

Reagents and conditions: i. PhI(OAc)$_2$, I$_3$, hv.

Scheme 2.35: Expected resonance stabilisation of unsaturated dioxane 208
The unsaturated alcohol 208 was therefore subjected to oxidative radical cyclisation using the previously established conditions (Section 2.3.1) of iodobenzene diacetate and iodine, in cyclohexane. Once again a bright purple solution was observed and TLC analysis indicated, two products had formed. However, after 24 h a large proportion of the starting material still remained, and no other components were able to be isolated (Table 2.11, entry 1).

![Diagram](Table 2.11)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidants (eq)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)2 (1), I2 (1)</td>
<td>Cyclohexane</td>
<td>0</td>
<td>Recovered SM,</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OAc)2 (3)</td>
<td>CH2Cl2</td>
<td>0-40</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>PhI(OAc)2 (3), I2 (1)</td>
<td>CH2Cl2\cyclohexane</td>
<td>0-r.t.</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OCOCF3)2 (2), I2 (2-3)</td>
<td>Cyclohexane</td>
<td>r.t.</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)4 (2.5), I2 (2)</td>
<td>Cyclohexane</td>
<td>0-r.t.</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>HgO (1), I2 (1)</td>
<td>Cyclohexane</td>
<td>r.t.</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>DDQ (2)</td>
<td>CH2Cl2\water (1:1)</td>
<td>r.t-40</td>
<td>Recovered SM</td>
</tr>
<tr>
<td>8</td>
<td>DDQ (2)</td>
<td>toluene</td>
<td>r.t.-40</td>
<td>Recovered SM</td>
</tr>
</tbody>
</table>

Table 2.11: Attempted oxidative radical cyclisation conditions.

Disappointed by the insubstantial conversion, alternative conditions were examined using several different oxidants both with and without the presence of iodine (Table 2.11). Investigations began using promising conditions of excess iodobenzene diacetate employed within our group for cyclisation of spiroketals. Disappointingly, when these conditions were applied to alcohol 208 only starting material was recovered (Table 2.11, entry 2). The addition of iodine to this reaction saw an immediate consumption of starting material, and the appearance of a new non-polar spot by TLC analysis (Table 2.11, entry 2). After painstaking isolation of this spot ¹H NMR analysis revealed it to be multiple products that were not able to be effectively separated and definitively characterised (Table 2.10, entry 3).
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At this stage, alternative oxidants were also trialled. Use of bis(trifluoroacetoxy)iodobenzene, also lead to the formation of complex mixtures of unidentifiable products (Table 2.11, entry 4). Next the reaction was attempted using lead tetraacetate (Table 2.11, entry 5) and mercuric oxide (Table 2.11, entry 6), at room temperature which both resulted in formation of complex mixtures. It was evident that the desired spiroketal 207 had not been formed as determined by TLC and NMR analysis.

Given the unsatisfactory results obtained using the traditional oxidant/I₂ systems, an alternative procedure was sought. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a strong oxidant and has been successfully employed for cyclisation reactions. Jay-Smith et al., observed that when cyclisation precursor 231 was subjected to PMB deprotection using an excess of DDQ, spiroketal 233 was formed directly (Scheme 2.36). Not only did the DDQ unmask the alcohol it also effected oxidative cyclisation to furnish the desired spiroketal 233 in one step. These positive results encouraged us to investigate DDQ induced cyclisation for alcohol 208.

When a solution of unsaturated alcohol 208 was treated with DDQ in a solvent mixture of dichloromethane and water (1:1), no reaction was observed (Table 2.11, entry 7). To investigate the effects of increased reaction temperatures, the reaction was next attempted in refluxing toluene (Table 2.11, entry 8). Again, no reaction was observed and only starting material was recovered.

![Chemical structure](image)

Reagents and conditions: i. DDQ (3 equiv), CH₂Cl₂/H₂O, 1.5 h, 95%.

Scheme 2.36: Concomitant PMB deprotection-spiroketalisation formation using DDQ reported by Jay-Smith et al. It was suspected that the presence of the double bond was hindering the oxidative radical cyclisation rather than promoting it. Perhaps the more stable radical generated is able to undergo undesired reactions or rearrangements.
2.3.3 Dehydrogenation of dioxane 227

In light of the difficulties encountered with the above cyclisation, attempts to simply install the double bond via dehydrogenation of saturated spiroketal 227 were next examined (Scheme 2.37). The oxidative dehydrogenation of hydrocarbons to alkenes is an important chemical transformation in organic chemistry, with DDQ being one of the most versatile reagents to effect the reaction as it combines high oxidation potential with relative stability and ease of handling.\textsuperscript{131} This reagent is particularly useful for benzylic dehydrogenation to form conjugated aryl alkenes.\textsuperscript{131,132}

![Scheme 2.37: Proposed dehydrogenation of saturated dioxane 227](image)

Initially, dehydrogenation using DDQ was attempted in either toluene or benzene (Table 2.12, entries 1 and 2), however only starting material was recovered. Prolonged reaction times resulted in degradation of starting material.

Another commonly used reagent used for dehydrogenation is Pd/C, employed at elevated temperatures.\textsuperscript{133,134} Accordingly, dehydrogenation using Pd/C in two different solvents at 200 °C was attempted (Table 2.12, entry 3 and 4). Disappointingly, no desired product was observed and only starting material was recovered.

As an alternative method, a stepwise procedure of radical bromination followed by dehydrobromination was investigated (Table 2.12, entry 5 and 6). The saturated dioxane 227 contains two benzylic carbons, however, it was hoped the bromination would selectively occur at the desired position rather than next to the oxygen. NBS is a commonly used brominating reagent used to effect allylic and benzylic bromination.\textsuperscript{135} It is proposed that the N-Br bond undergoes homolytic cleavage either by photolysis or thermolysis or through addition of radical initiators such peroxides, forming bromine \textit{in situ} in low concentrations which may then act as the brominating agent.\textsuperscript{135,136} Standard conditions to effect benzylic bromination were then attempted with saturated dioxane 227 using NBS with either AIBN or benzyl peroxide as the
Chapter 2: Discussion

Unfortunately, treatment of NBS to saturated dioxane \(227\) only resulted in recovery of starting materials as determined by TLC or NMR analysis (Table 2.12, entries 5 and 6).

\[
\begin{array}{cccc}
\text{Entry} & \text{Conditions}\text{a} & \text{Solvent} & \text{Temp (°C)} & \text{Yield (%)} \\
1 & DDQ & Toluene & reflux & 0 \\
2 & DDQ & Benzene & reflux & 0 \\
3 & Pd/C & Benzene & 200 & 0 \\
4 & Pd/C, K\(_2\)CO\(_3\) & DMF & 200 & 0 \\
5 & NBS, AIBN & CCl\(_4\) & reflux & 0 \\
6 & NBS\text{b} & CCl\(_4\) & reflux & 0 \\
7 & MnO\(_2\) & Toluene & reflux & 5 \\
\end{array}
\]

\(\text{a}\)reagents were added in excess (5-30 eq) amounts and reactions were stirred for 24-72 h. \(\text{b}\)catalytic dibenzoyl peroxide was added to reaction.

Table 2.12: Conditions screened for dehydrogenation of saturated dioxane \(227\)

Next, activated manganese dioxide was investigated as a potential reagent to effect dehydrogenation.\(^{138}\) Saturated dioxane \(227\) was treated with a large excess of manganese dioxide (10-20 eq) and the heterogeneous mixture was heated to reflux in toluene for 48 hours (Table 2.12, entry 7). TLC analysis of the reaction mixture revealed the formation of a new spot possessing similar polarity and \(R_t\) to the starting material, however, the new spot stained a different colour with vanillin stain. Investigation of the \(^1\)H NMR and \(^{13}\)C NMR spectra of this product provided immediate confirmation that dehydrogenation was successful due to the appearance of two doublets at \(\delta\) 6.68 ppm and \(\delta\) 5.75 ppm, assigned to a \(\text{cis}\)-di-substituted alkene possessing a vinylic coupling constant of 12.4 Hz. In the \(^{13}\)C NMR spectrum a shift from \(\delta\) 96.4 ppm for the spiroketal quaternary carbon in the starting material to \(\delta\) 109.5 ppm was also observed. This downfield shift is consistent with the installation of an adjacent \(sp^2\) carbon. Furthermore, the high resolution mass spectrum exhibited a molecular ion at \(m/\varepsilon\) 243.0996, corresponding to a molecular formula of \(C_{13}H_{16}O_6Na\), further confirming the formation of desired unsaturated dioxane \(207\).
Despite the successful installation of the double bond using activated manganese dioxide, the reaction was extremely poor yielding affording unsaturated dioxane 207 in only 5% yield at best. Furthermore, this low yield was difficult to reproduce and often a large excess (20-30 eq) of activated manganese oxide was required to effect any reaction. Nevertheless, having established a route to unsaturated dioxane 207, construction of substituted dioxane was revisited.

2.3.4 Summary of the synthesis of unsaturated dioxane

With the successful synthesis of the key oxidative radical cyclisation precursor, mono-substituted dioxane 213, investigation into the construction of a 7-membered ring via this method was conducted. 1,4-dioxane 213 underwent both complete hydrogenation and partial hydrogenation and deprotection to provide saturated dioxane 226 and unsaturated dioxane 208 respectively. The saturated dioxane 226 underwent oxidative radical cyclisation to furnish the desired 7-membered spiroketal 227. The unsaturated dioxane 208 on the other hand, under the same conditions resulted in a complex mixture. Efforts to circumvent this problem through revised synthetic sequences revealed that 207 could be accessed via dehydrogenation of saturated dioxane 227 as outlined in Scheme 2.38.

\[
\text{Scheme 2.38: Reagents and conditions: i. Pd/C, H}_2, \text{ Ethyl acetate, 1 h, r.t, 90%; ii. p-TsOH, MeOH, 55 }^\circ \text{C, 75%; iii. } \text{Phi(OAc)}_2, \text{ I}_2, \text{ hv, r.t., cyclohexane, 227 40% and 229 41%; iv. Lindlar’s catalyst, EtOAc, quinoline, r.t., 1 h, quant.; v. p-TsOH, MeOH/EtOH (1:1), 50 }^\circ \text{C, 14 h, quant.; vi. MnO}_2, \text{ toluene, reflux, 48 h, 5%.}
\]
2.4 Revised Synthetic Strategy for Substituted 1,4-Dioxane

2.4.1 Overview

Given the successful radical cyclisation and subsequent dehydrogenation to construct the desired unsaturated dioxane 207 (Section 2.3.3), synthesis of the pestalospirane core 114 was re-examined by employing the fully substituted dioxane precursor 235 (Scheme 2.39). A review of the literature revealed a potentially useful approach to the pestalospirane core 114 whereby α-hydroxyketones or α-hydroxy dimethyl acetics were dimerised under acidic conditions to give 1,4-dioxanes hemiacetal and 1,4-dioxane acetics respectively. Therefore we decided to construct the pestalospirane core 114 via dimerisation of α-hydroxy dimethyl acetal precursor 237 (Scheme 2.39).

Retrosynthetically, pestalospirane core 114 could be available from double dehydrogenation of saturated dimer 234, following the key oxidative radical cyclisation of advanced precursor 235. Dimerisation of α-hydroxy dimethyl acetal 237 and subsequent reduction of acetal functionality would provide precursor 235. α-Hydroxy dimethyl acetal 237 could in turn be accessed by acetal formation, following hydrogenation of α-hydroxyketone 238, which itself is available from the addition of alkyne 239 to Weinreb amide 240.

![Scheme 2.39: Revised retrosynthetic analysis of pestalospirane core 114 by double oxidative radical cyclisation](image-url)
This new strategy provides flexibility in the sequence of the dimerisation step to generate pestalospirane core 114. As previously discussed in the model study, oxidative radical cyclisation in the presence of the double bond and dehydrogenation of saturated dioxane proved challenging (Section 2.3.3). Therefore an alternative route was envisaged upon successful construction of the 1,4-dioxane ring 241 using this new method (Scheme 2.40). This route would allow direct access to the desired pestalospirane core 114 using acid-catalysed cyclisation/spiroketalisation of 1,4-dioxane 241. 1,4-Dioxane 236 would in turn be accessed via partial hydrogenation, following dimerisation of α-hydroxy dimethyl acetal 242. α-Hydroxy dimethyl acetal 242 can in turn be accessed by acetal formation of common α-hydroxyketone 238. This alternative method was to be attempted in parallel to the oxidative radical cyclisation route discussed above (Scheme 2.40).

![Scheme 2.40: Alternative acid-catalysed cyclisation of dioxane 241 to synthesise pestalospirane core 114](image)

2.4.2 Literature examples for dimerisation of α-hydroxyketones and α-hydroxy dimethyl acetals

In 1984, Moriarty et al.,\textsuperscript{143} discovered conditions under which α-hydroxy dimethyl acetals could be converted to 1,4-dioxanes via bimolecular loss of methanol (Scheme 2.41, A-C). This approach has since been applied to a variety of substrates (Scheme 2.41).\textsuperscript{140,141,143,144}
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Reagents and conditions: i. p-TsOH, MeOH, reflux, 30 min, 72%; ii. CDCl₃, 2 months, 60%; iii. p-TsOH, MeOH, reflux, 30 min, 69%; iv. 3.5 months; v. TMSOTf, CH₂Cl₂, 63%; vi. HCl, MeOH, 120 ºC, 45 min, 95%.

Scheme 2.41: Examples of dimerisation of α-hydroxyketone or their α-hydroxy acetals to give 1,4-dioxanes.¹⁴⁰,¹⁴¹,¹⁴³,¹⁴⁴

The rearrangement of α-hydroxy dimethyl acetals has been extensively studied by Creary and Rollins. During their studies they obtained dioxane 254 (Scheme 2.41, F) which then allowed them to elucidate the mechanism for this transformation (Scheme 2.42).¹⁴⁰ Mechanistically, an α-hydroxyacetal in the presence of acid provides carbocation intermediate 255A by a loss of methanol. Intermediate 255A then undergoes dimerisation to furnish intermediate 256. Subsequent intramolecular cyclisation of 256 via loss of another molecule of methanol provides dioxane 257.

Scheme 2.42: Mechanism of acid-catalysed 1,4-dioxane formation.¹⁴⁰
Given the difficulties encountered during the initial attempts to synthesise disubstituted 1,4-dioxane 118 under basic conditions (Section 2.2.4), a new synthetic approach was required, this time using dimethyl substituted dioxane precursor 238. Encouraged by the literature precedent for α-hydroxyketone and α-hydroxy dimethyl acetal motifs to undergo dimerisation, we sought to apply this methodology to the synthesis of the pestalospirane core 114 (Scheme 2.39).

2.4.3 Synthesis of α-hydroxyketone 265

The initial aim of this model study was to synthesise the key common intermediate α-hydroxyketone 238 from coupling of alkyne 239 and Weinreb amide 240 (Scheme 2.43).

![Scheme 2.43: Retrosynthesis of α-hydroxyketone 240](image)

Accordingly, the synthesis commenced with previously synthesised alcohol 212 which underwent Sonogashira cross-coupling with commercially available ethynyltrimethylsilane in triethylamine using Pd(PPh₃)₂Cl₂ and CuI to furnish the coupled alkyne product 258 in 95% yield (Scheme 2.44). Subsequent deprotection of the silyl ether group was achieved using potassium carbonate in methanol to furnish terminal alkyne 259 which then underwent TBDPS protection using TBDPSCl, DMAP and imidazole to afford alkyne 260 in 90% yield.
Reagents and conditions: i. Pd(PPh_3)_2Cl_2, CuI, Et_3N, ethynyltrimethylsilane, 15 h, r.t. 95%; ii. K_2CO_3, MeOH, 1.5 h, 40 °C, 90%; iii. TBDPSCI, DMAP, imidazole, CH_2Cl_2, 0 °C → r.t. 90%.

Scheme 2.44: Synthesis of alkyne coupling partner 260

With alkyne 260 in hand, attention then turned to the synthesis of Weinreb amide 262. For the purposes of this model study (S)-methyl lactate (261a) (100g, $57) was employed despite possessing the opposite stereochemistry that of the natural product, to avoid unnecessary use of the more expensive (R)-methyl lactate (100g, $162). It has been reported that Weinreb amide 262 could be synthesised directly from (S)-methyl lactate (261a) using either trimethylaluminium in toluene or isopropylmagnesium chloride in dichloromethane.145,146 Numerous attempts to reproduce these conditions proved unsatisfactory for our purposes (Scheme 2.45). Usually, only 10-20% conversion to the desired Weinreb amide 262a was observed by NMR analysis and further efforts to push the reaction to completion through added equivalents of reagents and prolonged reaction times were unsuccessful. Furthermore, (S)-methyl lactate (261a) and Weinreb amide 262 were found to have identical R_f values in all eluents tested and as such isolation of the desired product 262 proved difficult. As an alternative, hydroxyl protection of (S)-methyl lactate (261a) was investigated prior to Weinreb amide formation.

Reagents and conditions: i. HN(OMe)Me-HCl, toluene or HN(OMe)Me, i-PrMgCl, CH_2Cl_2

Scheme 2.45: Attempted synthesis of Weinreb amide 262a using either AlCl_3 or iPrMgCl
After careful consideration of suitable protecting groups for (S)-methyl lactate (261a), it was decided that an orthogonal protecting group strategy would be most suitable for the envisaged reaction sequence. Silyl ethers are among the most commonly used protecting groups, notable for the relatively mild reaction conditions required for their formation, and for their lability under a diverse range of deprotection conditions. Both steric and electronic properties govern the relative lability of different silyl protecting groups in multi functionalised substrates. Given that an orthogonal protecting group strategy was required, the use of two different silyl ether groups in the same molecule was appropriate. As a general rule the size of substituents on the silicon atom is directly related to the rate of deprotection with the smaller silyl substituents allowing easier cleavage under acidic conditions. Encouraged by literature examples of deprotection of primary TBS ethers in the presence of a primary TBDPS ether, the difference in reactivity of these two silyl ethers was taken advantage of during the synthesis of pestalospirane core 114. Hence, (S)-methyl lactate (261a) was protected using TBSCI, imidazole and DMAP to furnish ester 263a, which then upon treatment with isopropylmagnesium chloride and N,N-dimethyl-hydroxylamine hydrochloride in THF was smoothly converted to the desired Weinreb amide 264a in near quantitative yields (Scheme 2.46). The NMR data obtained for Weinreb amide 264a was in agreement with literature values.

\[
\begin{align*}
261a & \xrightarrow{i} 263a & \xrightarrow{ii} 264a
\end{align*}
\]

*Reagents and conditions:* i. TBSCI, imidazole, DMAP, CH\(_2\)Cl\(_2\), r.t., 16 h, quant; ii. HN(OMe)Me·HCl, i-PrMgCl, THF, 0 °C, 2 h, 99%.

Scheme 2.46: Synthesis of Weinreb amide coupling partner 264a

With both Weinreb amide 264a and alkyne 260 coupling partners in hand, subsequent n-BuLi-mediated alkynylation was performed in THF at -78 °C to give α-hydroxyketone 265 (Scheme 2.48). Consistent execution of this coupling to achieve reproducible yields was challenging, as all glassware, solvents and reagents were required to be rigorously dried immediately before use. With scalable access to α-hydroxyketone 265 established, selective deprotection of the TBS ether group was explored. Pleasingly, selective TBS deprotection of
bis-silyl ether \( \text{265} \) was achieved using \( p \)-toluenesulfonic acid and trimethyl orthoformate in methanol to furnish \( \alpha \)-hydroxy dimethyl acetal \( \text{266} \) in 60% yield.

\[
\begin{array}{c}
\text{261a} \\
\text{OTBDPS} \\
\end{array}
+ 
\begin{array}{c}
\text{264a} \\
\text{OTBS} \\
\end{array}
\xrightarrow{\text{i}} 
\begin{array}{c}
\text{265} \\
\text{OTBDPS} \\
\text{OTBS} \\
\end{array}
\xrightarrow{\text{ii}} 
\begin{array}{c}
\text{266} \\
\text{MeO} \\
\text{MeO} \\
\end{array}
\]

*Reagents and conditions*: i. \( n \)-BuLi, THF, -78 °C, 1 h, then \( \text{264a} \), -78-0 °C, 1 h, 60%; ii. \( p \)-TsOH, CH(OCH\(_3\))\(_3\), MeOH, 1 h, 60%.

**Scheme 2.47**: Synthesis of hydroxy dimethyl acetal \( \text{266} \)

In a parallel route \( \alpha \)-hydroxyketone \( \text{265} \) was subjected to hydrogenation using Pd/C in ethyl acetate to give protected ketone \( \text{267} \) (Scheme 2.48), which then underwent selective TBS deprotection to give either \( \alpha \)-hydroxy dimethyl acetal \( \text{268} \) or \( \alpha \)-hydroxyketone \( \text{269} \) by manipulation of the reaction solvent system. With access to both \( \alpha \)-hydroxy dimethyl acetals (\( \text{266} \) and \( \text{268} \)) and \( \alpha \)-hydroxyketone \( \text{269} \) established, the dimerisation reaction of all three substrates could be thoroughly investigated.

\[
\begin{array}{c}
\text{265} \\
\text{OTBDPS} \\
\end{array}
\xrightarrow{\text{i}} 
\begin{array}{c}
\text{266} \\
\text{MeO} \\
\text{MeO} \\
\end{array}
\]

*Reagents and conditions*: i. Pd/C, H\(_2\), EtOAc, 1 h, 90%; ii. TsOH, CH(OCH\(_3\))\(_3\), MeOH, 1 h, 80%; iii. TsOH, THF/H\(_2\)O, 30 min, 80%.

**Scheme 2.48**: Synthesis of \( \alpha \)-hydroxy dimethyl acetal \( \text{268} \) and \( \alpha \)-hydroxy ketone \( \text{269} \)
2.4.4 Attempted dimerisation of $\alpha$-hydroxyketone 269 and $\alpha$-hydroxy dimethyl acetals 266 and 268

Literature reports indicated that $\alpha$-hydroxyketone and $\alpha$-hydroxy dimethyl acetal functionalities could undergo dimerisation simply upon standing or exposure to anhydrous acids.\textsuperscript{140,143,150} Encouraged by this precedent, conditions to induce dimerisation of both $\alpha$-hydroxyketone 269 and $\alpha$-hydroxy dimethyl acetal (266 and 268) were investigated.

Investigation began by exposing $\alpha$-hydroxy dimethyl acetal 266 to a variety of either Brønsted or Lewis acids in an array of solvents. When $\alpha$-hydroxy dimethyl acetal 266 was treated with $p$-toluenesulfonic acid in THF/H$_2$O (1:1), no reaction was observed and only starting material was recovered (Table 2.13, entry 1). Altering the solvent system to methanol, dichloromethane or toluene using $p$-toluenesulfonic acid, led to consumption of starting material to afford a complex mixture of side products that were not able to be effectively separated and identified (Table 2.13, entries 2-4). When HCl (4 M) was employed as the acid, rapid decomposition of the starting material was observed by TLC and NMR analysis (Table 2.13, entry 5). When $\alpha$-hydroxy dimethyl acetal 266 was treated with either CSA in methanol or PPTS in ethanol, no reaction was observed and only starting material was recovered (Table 2.13, entries 6 and 7). When the Lewis acid, BF$_3$·OEt$_2$ was used, rapid degradation of starting material was observed by TLC and NMR analysis (Table 2.13, entry 8).
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Table 2.13: Attempted dimerisation of α-hydroxy dimethyl acetal 266

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH</td>
<td>THF/H₂O (1:1)</td>
<td>r.t.→60</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH</td>
<td>MeOH</td>
<td>r.t.→reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOH</td>
<td>CH₂Cl₂</td>
<td>r.t.→reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>p-TsOH</td>
<td>Toluene</td>
<td>r.t.→reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>HCl (2 M)</td>
<td>MeOH</td>
<td>0→ r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>CSA</td>
<td>MeOH</td>
<td>r.t.→60</td>
<td>SM recovered</td>
</tr>
<tr>
<td>7</td>
<td>PPTS</td>
<td>EtOH</td>
<td>r.t.→reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>8</td>
<td>BF₃·OEt₃</td>
<td>CH₂Cl₂</td>
<td>0→ r.t.</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

α-Hydroxy dimethyl acetal 268 (Table 2.14) and α-hydroxyketone 269 (Table 2.15) were submitted to a range of reaction conditions in parallel, with no success. Treatment with acids resulted in recovered starting material and decomposed by-products as detected by TLC and NMR analysis in most cases.
Chapter 2: Discussion

Table 2.14: Attempted dimerisation of α-hydroxy dimethyl acetal 269

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH</td>
<td>THF/H₂O (1:1)</td>
<td>r.t. → 60</td>
<td>SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH</td>
<td>MeOH</td>
<td>r.t. → reflux</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>HCl (2M)</td>
<td>MeOH</td>
<td>0 → r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>MeOH</td>
<td>r.t. → 60</td>
<td>SM recovered</td>
</tr>
<tr>
<td>5</td>
<td>PPTS</td>
<td>EtOH</td>
<td>r.t. → reflux</td>
<td>SM recovered</td>
</tr>
<tr>
<td>6</td>
<td>TFA</td>
<td>CH₂Cl₂</td>
<td>0 → r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>7</td>
<td>BF₃·OEt₃</td>
<td>CH₂Cl₂</td>
<td>0 → r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf</td>
<td>CH₂Cl₂</td>
<td>-78 → -20</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>TiCl₄</td>
<td>CH₂Cl₂</td>
<td>-78 → -20</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Interestingly, the α-hydroxy dimethyl acetals 266 (Table 2.13, entries 1, 6 and 7) and 268 (Table 2.15, entries 1, 4 and 5) were unexpectedly stable under certain acidic conditions in comparison to α-hydroxyketone 269, which primarily underwent degradation in non-methanolic solvent systems. In methanol, however, α-hydroxyketone 269 underwent conversion to the corresponding α-hydroxy dimethyl acetal 268 as observed by TLC and NMR analysis (Table 2.14, entries 2-4). Additionally, it was also observed that α-hydroxyketone 269 existed in equilibrium with α-hydroxy dimethyl acetal 268 in the presence of p-toluenesulfonic acid in methanol (Table 2.15, entry 2). Disappointingly, no dimerisation products were isolated with reactions returning starting material or giving complex mixtures from which no compounds were able to be identified upon analysis of the NMR spectra and mass of the crude product mixtures (Table 2.15, entry 2).
Despite the literature precedent for successful dimerisation of α-hydroxyketones and α-hydroxy dimethyl acetal functionalities, all attempts to form the 1,4-dioxane from α-hydroxyketone 269 and α-hydroxy dimethyl acetal 266 and 268 proved unsuccessful. In light of this setback, an alternative method for the construction of the 1,4-dioxane ring system was required.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH</td>
<td>THF/H\textsubscript{2}O (1:1)</td>
<td>r.t. → 60</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH</td>
<td>MeOH</td>
<td>r.t. → reflux</td>
<td>α-hydroxyacetal 268 + SM</td>
</tr>
<tr>
<td>3</td>
<td>HCl (2M)</td>
<td>MeOH</td>
<td>0 → r.t.</td>
<td>α-hydroxyacetal 268*</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>MeOH</td>
<td>r.t. → 60</td>
<td>α-hydroxyacetal 268</td>
</tr>
<tr>
<td>5</td>
<td>PPTS</td>
<td>EtOH</td>
<td>r.t. → reflux</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>TFA</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0 → r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>7</td>
<td>BF\textsubscript{3},OE\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0 → r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78 → -20</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>TiCl\textsubscript{4}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78 → -20</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

*Trace amounts of α-hydroxy dimethyl acetal 268 were isolated

Table 2.15: Attempted dimerisation of α-hydroxyketone 269
2.5 Synthesis of Methoxybenzoxepin 273

Given that the desired dimer 271 was inaccessible from α-hydroxyketone 269 or α-hydroxy dimethyl acetals 266 and 268, direct dimerisation of protected α-hydroxyketone 265 to 1,4-dioxane 271 was attempted with the hope that a one-pot deprotection-dimerisation could be achieved (Scheme 2.49). Disappointingly, no dimerisation product 271 was observed. However, upon prolonged exposure of protected α-hydroxyketone 265 to p-toluenesulfonic acid and trimethyl orthoformate in methanol, complete consumption of the starting material 265 took place and the appearance of two new polar spots were detected by TLC analysis that were separable by column chromatography.

The two isolated compounds (ca. 1:1) had the same molecular mass and shared a similar proton distribution by analysis of the $^1$H NMR spectra. In both cases the silyl ether groups had been cleaved and the region where the adjacent benzylic methylene protons appeared as a singlet at δ 4.72 ppm in the starting material 265, now two new doublets were observed in the $^1$H NMR spectra for both products at δ 4.33 ppm and δ 3.90 ppm, and δ 5.09 ppm and δ 4.27 ppm respectively. This observation is consistent with the intramolecular cyclisation having taken place, as this increases the restriction of the degrees of freedom around the ring compared to the acyclic structure thus giving rise to diastereotopic methylene signals. In the $^{13}$C NMR spectra, the disappearance of the carbonyl carbons at δ 213.0 ppm and appearance of new quaternary carbons at δ 102.8 ppm and δ 103.4 ppm respectively were also consistent with intramolecular cyclisation. Lastly, in the presence of a new singlet at δ 3.44 ppm and 3.34 ppm in the respective spectra were consistent with a methoxy group being introduced at the site of cyclisation. Hence, the new structures were concluded as being the methoxybenzoxepine diastereomers 273a and 273b (Scheme 2.49). Pleasingly, this reaction was reliable and reproducible.
Reagents and conditions: i. p-TsOH, CH(OCH₃)₃, MeOH, r.t., 5 h, 273a 37% and 273b 30%.

Scheme 2.49: Synthesis of methoxybenzoxepine 273a and 273b

The stereochemical configuration of the more polar spot, methoxybenzoxepine 273b was determined using NOESY experiments to establish the configuration of the spiroacetal core in relation to the alcohol group of known (S)-configuration. The resultant 2-D spectrum clearly showed a diagnostic positive nOe correlation between the methoxy group (δ 3.34 ppm) and benzylic H-1'a protons (δ 5.09 ppm) (Figure 2.3), whereas no nOe correlation was observed between the methine proton (H-1, δ 4.01 ppm) and the methoxy protons (δ 3.34 ppm). Thus the stereochemical configuration of the spiroketal centre was tentatively established as (1R, 3'S)-273b at the spiroketal centre (Figure 2.3). Consequently, the stereochemistry for the less polar diastereoisomer, methoxybenzoxepine 273a was established as (1S, 3'S)-273a.
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Figure 2.3: NOESY spectrum of methoxybenzoxepin 273b

It had become increasingly apparent that dimerisation of α-hydroxyketone 269 or α-hydroxy dimethyl acetals 266 and 268 to access the desired tetrasubstituted dioxane 271 was no longer a feasible strategy and further investigation into this methodology was abandoned.
2.6 Biomimetic-Inspired Approach to Pestalospiranes core 114

Initial attempts at synthesising pestalospirane core 114 using an oxidative radical cyclisation approach had proved unsuccessful, failing to construct the required substituted dioxane intermediate 271. However the observation of hemiketal 10 during the isolation of pestalospiranes A (2) and B (3) reported by Kesting et al.,¹⁸ and a structurally related natural product, heptacyclosordariolone (73),⁵⁴ prompted us to suspect that these monomers 273a and 273b were the likely biosynthetic precursors to pestalospiranes A (2) and B (3) (Sections 1.2 and 1.5.2).⁵⁴ Consequently, our initial plan to use oxidative radical cyclisation to form the seven-membered ring was abandoned and we considered pursuing a biomimetic approach instead.

Using nature as inspiration to guide a chemical synthesis by following or mimicking a hypothetical or proven biosynthetic pathway has proven to be an effective method.¹⁵¹,¹⁵² Robinson’s landmark synthesis of tropinone (274) in 1917 pioneered this approach (Figure 2.5).¹⁵²,¹⁵³ This precedent has since catalysed the construction of many natural products by chemical methods inspired by nature’s biosynthetic pathways, as reflected by the increasing number of total syntheses that have been termed “biomimetic” or “bioinspired” during the last 20 years.¹⁵¹,¹⁵⁴,¹⁵⁵
While it is desirable to have an established biosynthesis pathway elucidated for a natural product before embarking on a biomimetic synthesis, no biosynthesis had been proposed in the report describing the isolation of pestalospiranes A (2) and B (3). However, we believe it to be a reasonable assumption that methoxybenzoxepins 273a and 273b are the monomeric precursors for pestalospiranes A (2) and B (3). The elegance with which nature assembles complex molecular frameworks from simple monomeric units is remarkable and therefore we sought to take advantage of synthetic methoxybenzoxepins 273a and 273b as our building blocks in designing a precursor-directed biomimetic synthetic approach.

We next considered how the natural product structure could be constructed using the synthesised monomeric precursors 273a and 273b (Scheme 2.50). A survey of the literature uncovered di-D-fructose dianhydrides (DAFs) that contain a similar substituted 1,4-dioxane central core and we hypothesised that the construction of the desired tetrasubstituted dioxane could be achieved using di-D-fructose dianhydride (DAF) chemistry as inspiration.\textsuperscript{156}

![Scheme 2.50: Proposed biomimetic dimerisation of methoxybenzoxepins 273a and 273b](image)

2.6.1 Di-D-fructose dianhydrides (DAFs)

Di-D-fructose dianhydrides (DFAs) comprise a diverse family of mono- or di-spiro cyclic acetals (Figure 2.6).\textsuperscript{156-159} DFAs are a major component in caramel and other foodstuffs such as roasted chicory, heat-dried fruits, natural sugar-roasted torrefacto coffee and traditional tequila. The chemical transformation leading to the formation of DFAs is universally accepted to be caramelisation, which is a non-enzymatic process where sugars undergo dehydration and self-condensation upon heating to furnish oligosaccharides, among which DFAs are present. Generally, DFAs are constructed via dimerisation of D-fructose with the loss of two water molecules and generation of two reciprocal glycosidic linkages upon thermal or acid activation. The unique and complex architecture of DFA’s evoked much interest in evaluating new spiroketal methodologies (Figure 2.6).\textsuperscript{156-159}
2.6.2 Synthesis of DFAs by acid activation

Chemical methods such as the acid-catalysed activation of d-fructose with HF have proved extremely efficient in promoting the conversion of sugars to DFAs, mimicking the caramelisation process.\textsuperscript{159} Comparison of HF and heat-induced caramelisation has allowed for the elucidation of a possible mechanism (Scheme 2.51).\textsuperscript{156,159} The relative abundance of individual DFA diastereomers in the final products is dependent on the starting cyclic forms of d-fructose in addition to caramelisation conditions.\textsuperscript{159} Most reported DFAs are artificially synthesised with the use of protecting group strategies to exclude certain cyclic forms of fructose during the dimerisation/spiroketalisation process. This is followed by treatment with anhydrous acids to afford the DFA tricyclic core containing a central 1,4-dioxane ring system.\textsuperscript{156,157,160} Spiroketalisation is a reversible process under normal caramelisation conditions, resulting in a complex distribution of isomers, ring size, linking position and stereochemistry at the anomeric carbon.\textsuperscript{156} The diastereomeric distribution of DFA mixtures can be described in terms of kinetic and thermodynamic control.\textsuperscript{156,161}

The proposed mechanism for DFA formation under acidic conditions involves the formation of fructosyl oxonium cation 276A, which undergoes \textit{in situ} glycosylation to the corresponding keto-disaccharide by reaction with a second fructose molecule (Scheme 2.51). Intramolecular
ring closure/spiroketalisation closes the central 1,4-dioxane ring to furnish the DFA tricyclic core 278.

Scheme 2.51: Mechanism of protic acid-catalysed dimerisation of ketose.\textsuperscript{156}

2.6.3 Synthesis of the pestalospirane core 275

Investigation into dimerisation conditions for the synthesis of pestalospirane core 114 were chosen based on literature procedures that had been successfully employed for the synthesis of DFAs.\textsuperscript{156}

With the key dimerisation precursor 273 now readily accessible, attention now turned to their dimerisation to form the pestalospirane core. Investigations commenced by stirring methoxybenzoxepins 273a and 273b with BF\textsubscript{3}·OEt in either toluene or dichloromethane (Table 2.16, entries 1 and 2). Instead of the expected product 275, multiple spots were observed by TLC, none of which indicated successful construction of a 1,4-dioxane ring by NMR analysis. Treatment of diastereomers 273a and 273b with HCl (4 M) immediately resulted in formation of a brown slurry, resulting only in decomposition of starting material (Table 2.16,
Dimerisation was next attempted in the presence of TFA (Table 2.16, entry 4). TLC analysis indicated the formation of two new non-UV active products which were visualised with vanillin stain. Despite these initially encouraging results, prolonged reaction times resulted in degradation of starting material. Gratifyingly, treatment of 273a and 273b with trifluoromethanesulfonic acid for one hour at -78 °C resulted in complete consumption of all starting material producing two separable non-polar compounds by TLC analysis. After purification by column chromatography, the NMR spectra obtained from the newly isolated compounds immediately indicated the successful construction of the desired 1,4-dioxane ring (Table 2.16, entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃.OEt</td>
<td>Toluene</td>
<td>-78→0</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>BF₃.OEt</td>
<td>CH₂Cl₂</td>
<td>-78→0</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>HCl (2M)</td>
<td>CH₂Cl₂</td>
<td>-20→0</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>CH₂Cl₂</td>
<td>-78→0</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>TfOH</td>
<td>CH₂Cl₂</td>
<td>-78</td>
<td>275a 37%: 275b 30%</td>
</tr>
</tbody>
</table>

Table 2.16: Conditions screened for acid catalysed dimerisation of 275a and 275b

The structures of the products were assigned using NMR and mass spectral analysis. The mass spectra of both isolated compounds exhibited a molecular ion at m/z at 403.1866 consistent with the formation of the desired dimers. For both the new compounds the ¹H NMR and ¹³C NMR spectra showed the absence of the methoxy moiety and both compounds contained the same kind of resonance patterns, except that all resonances were doubled for the more polar dimer 275b (Figure 2.7). This is consistent with both dimers 275a and 275b exhibiting a 2-fold C2 symmetry through the 1,4-dioxane core axis. The details of the NOESY spectrum allowed
for differentiation of the possible dimers exhibiting isochronous NMR peaks, and thus assignment of the stereochemistry.

Figure 2.7: $^1$H NMR spectra comparison of less polar dimer 275a vs more polar dimer 275b

NOESY experiments were conducted for determination of absolute stereochemistry of less polar dimer 275a, using the fixed (S)-configuration of the methyl side chain as the reference point. The NOESY spectra of dimer 275a exhibited a diagnostic nOe correlation between the methyl protons (H-12/H-12') and H-1a/H-1'a proton and in addition a correlation between the methine protons (H-3/H-3') and the H-1a/H-1'a protons. For H-1/H-1' methylene protons and methyl protons to be close enough in proximity to exhibit the nOe correlation, the spiroketal must adopt a syn-relationship between both the methyl group in the dioxolane ring to the C-4/C-4' and C-5/C-5' methylene protons (Figure 2.8). Furthermore, the methyl groups (H-12 and H-12') exhibited correlations with H-4ab/H-4'ab and H-5ab/H-5'ab consistent with the syn-relationship. Therefore it was concluded that dimer 275a contained the stereochemistry shown in Figure 2.9 and assigned as pestalospirane core A 275a.
Chapter 2: Discussion

Figure 2.8: NOESY of sym-dimer 275a

Figure 2.9: Structure of pestalospirane core A 275a and pestalospirane core B 275b

Analysis of the NOESY spectra of more polar dimer 275b exhibiting anisochronous NMR signals (Figure 2.10), revealed a correlation between only one of the methyl protons (H-12) to one of the anisochronous H-1a protons, as previously observed for pestalospirane core A 275a,
whereas no such correlation was observed for the other methyl group (H-12') to H-1'a. Therefore it was concluded that one methyl group in the dioxolane ring was syn and the other anti to the C-4/C-4' and C-5/C-5' methylene protons, which is consistent with the structure proposed for pestalospirane core B 275b (Figure 2.9)

In comparison, in the NOESY spectra of pestalospirane core B 275b (Figure 2.10), one of the methyl protons exhibited a correlation to one of the anisochronous benzyl CH₂a protons similarly to pestalospirane core A 275a, whereas no such correlation was observed for the other methyl group. Therefore it was concluded that one methyl group of syn and the other was anti to the C-4/C-4' substituent which is consistent with the structure proposed for pestalospirane core B 275b (Figure 2.10)

Figure 2.10: NOESY of pestalospirane core B 275b
2.6.4 X-ray structure of pestalospirane core A 275a

In order to confirm the absolute stereochemistry of the pestalospirane core A 275a unambiguously, X-ray crystallography was performed. Sufficiently ordered and pure crystals for single crystal X-ray diffraction were obtained by the slow evaporation technique in THF (Figure 2.11). X-ray crystallography subsequently confirmed the absolute stereochemistry and structure of pestalospirane core A 275a where both the spiroketals displayed an $R$-configuration in comparison to the methyl groups that are fixed in the $S$-configuration (Figure 2.8). The absolute configuration and a twisted boat conformation of 275a was unambiguously confirmed by single X-ray analysis.

![OTREP diagram of pestalospirane core A 275a](image)

Figure 2.11: OTREP diagram of pestalospirane core A 275a. The crystal structure data is listed in the Appendix (Section 5.2.1)

Having successfully demonstrated the construction of the carbon skeletons of both pestalospirane A (2) and B (3) and having established a robust method, investigations towards the synthesis of pestalospirane A (2) and B (3) could now be conducted.

2.6.5 Summary of the synthesis of pestalospirane core A 275a and B 275b

The synthesis of pestalospirane core A (275a) and B (275b) using a bioinspired route towards the natural products has been accomplished in 9 steps from commercially available (2-iodophenyl)methanol (211) and methyl (S)-2-hydroxypropanoate (261a). The key reaction in this synthesis was the acid-catalysed cyclisation to provide the monomers 273a and 273b.
that prompted a change towards a precursor-directed biomimetic synthetic approach. As a result the double oxidative radical cyclisation approach was abandoned. Another highlight of this synthesis was the dimerisation to construct the novel 1,9,11,18-tetraoxadispiro[6.2.6.2]octadecane skeleton. The overall approach is scalable and should be readily amenable towards synthesis of pestalospirane A (2) and B (3). The successful strategy employed to construct the pestalospirane core 275 is outlined in Scheme 2.52.

\[ \text{Scheme 2.52: Reagents and conditions:} \]

- i. TBSCl, imidazole, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 16 h, quant;
- ii. HN(OMe)Me·HCl, i-PrMgCl, THF, 0 °C, 2 h, 99%;
- iii. Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}, CuI, Et\textsubscript{3}N, ethynyltrimethylsilane, 15 h, r.t. 95%;
- iv. K\textsubscript{2}CO\textsubscript{3}, MeOH, 1.5 h, 40 °C, 90%;
- v. TBDPSCI, DMAP, imidazole, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C \rightarrow r.t. 90%;
- vi. n-BuLi, THF, -78 °C, 1 h, then 264b -78-0 °C, 1 h, 60%;
- vii. Pd/C, H\textsubscript{2}, EtOAc, 1 h, 90%;
- viii. p-TsOH, CH(OCH\textsubscript{3})\textsubscript{3}, MeOH, r.t., 5 h, 273a 37% and 273b 30%;
- ix. TfOH, CH\textsubscript{2}Cl\textsubscript{2}, -78 °, 275a 37% and 275b 30%.
Chapter Three: Synthesis of Pestalospiranes A & B
3.1 Overview

Given the successful construction of pestalospirane cores A 275a and B 275b (Section 2.6.3), it was anticipated that our established methodology could be extended towards the total synthesis of pestalospiranes A (2) and B (3). Although the above studies laid the foundation for a robust method for the synthesis of the unusual dispiro-1,4-dioxane motif, concerns regarding the identification of an appropriate protecting group for the phenols still remained. The phenol protecting group would have to be cleaved easily and cleanly in order to avoid excessive manipulation of the final product.\textsuperscript{162,163} The introduction and subsequent removal of a protecting group would lengthen the reaction sequence and could encounter unforeseen difficulties during the deprotection procedure.\textsuperscript{162,164,165} It was therefore decided to investigate an acid-catalysed concomitant deprotection/cyclisation sequence for the construction of the dimerisation precursor 279 by employing an acetonide protecting group strategy (Scheme 3.1).\textsuperscript{162,164,165}

Our new retrosynthetic route would hinge on the key dimerisation of acetal 279 to provide the natural product 3 (Scheme 3.1). Acetal 279 would be accessed \textit{via} deprotection of the acetonide protected ketone 280, unmasking both the phenolic and benzylic alcohol moieties at the same time, thus enabling cyclisation. Lithium-mediated alkynylation of Weinreb amide 262b would provide ketone 280. The following section describes in detail the efforts made towards the synthesis of pestalospiranes A (2) and B (3).
Scheme 3.1: Retrosynthetic analysis of acetonide protecting group strategy
3.2 Acetonide protecting group strategy

The initial focus of the acetonide protecting group strategy was on the synthesis of alkyne 281 which could be accessed from commercially available 2,6-dihydroxybenzoic acid (282) (Scheme 3.2). Reduction of 2,6-dihydroxybenzoic acid (282) would provide triol 283, which can undergo acetonide protection followed by triflation to furnish intermediate 284. Triflate 284 can then undergo Sonogashira coupling with trimethylsilylacetylene and deprotection of the silyl group would provide the desired alkyne 281 (Scheme 3.2).

![Scheme 3.2: Proposed synthesis of alkyne 281](image)

The first attempt at the synthesis of alkyne 281 commenced with the reduction of 2,6-dihydroxybenzoic acid (282) using BH₃·DMS in dichloromethane, however these conditions failed to effect any reaction, with only starting material being recovered (Table 3.1, entry 1). Reduction using LiAlH₄ was attempted next, however no reaction was observed at room temperature, and consequently the reaction was repeated using excess LiAlH₄ (4-10 eq) and heated to reflux (Table 3.1, entry 2). Disappointingly, only starting material was recovered again. Similarly, no reaction was observed using either DIBAL-H or NaBH₄ (Table 3.1, entries 3 and 4).
Chapter 3: Discussion

Table 3.1: Conditions screened for reduction of acid 283

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH$_3$·DMS</td>
<td>CH$_2$Cl$_2$</td>
<td>-78 → r.t.</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH$_4$</td>
<td>THF</td>
<td>r.t. → reflux</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL·H</td>
<td>CH$_2$Cl$_2$</td>
<td>-78 → r.t.</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>NaBH$_4$</td>
<td>EtOH</td>
<td>r.t.</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

It was postulated that the inability to reduce 2,6-dihydroxybenzoic acid (282) without a protecting group maybe due to intramolecular hydrogen-bonding interactions hindering the reduction process. Therefore, protection of the free acid was thought to be necessary prior to reduction. The shortest linear sequence for the preparation of known alkyne 281 was reported by Jennings et al.,$^{167}$ (Scheme 3.3). Following this literature procedure, the synthesis began with protection of acid 282 using thionyl chloride, DMAP and acetone in 1,2-dimethoxyethane to afford acetonide 285 in 70% yield.$^{167}$ This particular step, however, was difficult to perform on larger scales as the work up protocol often resulted in formation of an emulsion. Additionally, if the reaction failed to completely consume the starting material, recovery of acid 282 was not possible due to its solubility in the aqueous layer. Recovery by flash chromatography was similarly not possible as acid 282 was unable to be recovered despite a range of column eluents trialled. Therefore, the protection of acid 282 was performed in small batches of three grams. With access to acetonide protected ester 285 established, formation of triflate 284 was achieved using either trifluoromethanesulfonic anhydride or N-phenyl-bis(trifluoromethanesulfonimide). Use of N-phenyl-bis(trifluoromethanesulfonimide) was preferred because the reaction did not require vigorous drying or an inert atmosphere and as a result was operationally simpler to perform. Subsequent, Sonogashira cross-coupling of triflate 284 with commercially available ethynyltrimethylsilane was performed in the presence of catalytic PdCl$_2$(PPh$_3$)$_2$ and CuI in triethylamine-NMP (1:5) affording alkynylsilane 286 in 80% yield. Silane 286 was then treated with TBAF, followed by reduction using LiAlH$_4$ in THF to furnish the desired diol 288 in near quantitative yields. At this stage, the diol was again protected as an acetonide using 2,2-dimethoxypropane, p-toluenesulfonic acid in acetone to
give alkyne 281 in 90% yield. The NMR data obtained for alkyne 281 was in agreement with literature values.\(^{102}\)

**Reagents and Conditions:** i. SOCl\(_2\), acetone, DMAP, DCE, 0 °C, 24 h, 70%; ii. NaH, DMAP, PhNTf\(_2\), DMF, 0 °C, 2 h, 90%; iii. PdCl\(_2\)(PPh\(_3\))\(_2\), CuI, Et\(_3\)N/NMP, trimethylsilylacetylene, r.t., 2 h, 80%; iv. TBAF, THF, 0 °C, 15 min, 99%; v. LiAlH\(_4\), THF, 0 °C, 30 min, 99%; vi. 2,2-dimethoxypropane, p-TsOH, acetone, r.t, 16 h, 90%.

Scheme 3.3: Synthesis of acetonide-protected alkyne 281

### 3.2.1 Attempted cyclisation using alkene 289

With alkyne 281 in hand, focus then shifted towards the synthesis of the key acid-catalysed cyclisation precursor, alkene 289. Alkene 289 could be accessed via a lithium-mediated coupling of the alkyne 281 to the Weinreb amide 264b, which possessed the requisite (R)-methyl stereochemistry present in the natural products, followed by partial hydrogenation (Scheme 3.4).

Scheme 3.4: Retrosynthetic analysis of alkene 289a
The alkynylation reaction was first attempted using $n$-BuLi at -78 °C for an hour, followed by the addition of Weinreb amide 264b, then warmed to room temperature. Unfortunately no reaction was observed and only starting material was recovered. Pleasingly, exchanging $n$-BuLi with LiHMDS under otherwise same reaction conditions, allowed the reaction to proceed smoothly affording ketone 290 in 80% yield (Scheme 3.5).\textsuperscript{168}

Partial reduction of alkynyl ketone 290 was next attempted to install the double bond present in pestalospiranes A (2) and B (3). Accordingly, ketone 290 was subjected to partial hydrogenation using Lindlar’s catalyst and catalytic amounts of quinoline in ethyl acetate. Under these reaction conditions the desired cis-alkene 289a was formed along with trace quantities of trans-alkene 289b. Elimination of the trans-alkene 289b during the reaction proved unsuccessful, however the amount present in the mixture was considered inconsequential and subsequent synthetic steps were not expected to be hindered by its presence.

![Scheme 3.5: Synthesis of acid-catalysed cyclisation precursor 289a](image)

\textbf{Reagents and conditions}: i. LiHMDS, THF, -78 °C, 1 h, then Weinreb amide 264b, r.t., 1 h, 80%; ii. Lindlar catalyst, quinoline (0.2), H$_2$, EtOAc, 1h, 90% 289a:289b(9:1).

Having successfully synthesised the key cyclisation precursor 289a, investigation into the key acid-catalysed deprotection/cyclisation sequence could now be conducted. The acid-catalysed cyclisation was attempted using the conditions previously established in the model study (Section 2.5). Unfortunately, when alkene 289a was treated with $p$-toluenesulfonic acid and trimethyl orthoformate in methanol, the reaction resulted in degradation of starting material, as determined by both TLC and NMR analysis (Table 3.2, entry 1). Alternative acids were then examined to effect cyclisation. Alkene 289a was then treated with HCl (4.0 M in dioxane), however, no desired cyclised product 279 was observed and degradation of starting material...
was observed (Table 3.2, entry 2). Trifluoromethanesulfonic acid was next investigated in hope of effecting a one-pot deprotection-cyclisation-dimerisation sequence via *in situ* generation of the acetal 279, as the model study suggested trifluoromethanesulfonic acid was the only acid able to effect dimerisation. Disappointingly, these reaction conditions also resulted in degradation of the starting material (Table 3.2, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid(^a)</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>p</em>-TsOH</td>
<td>MeOH</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>HCl (4.0 M)</td>
<td>MeOH</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>TfOH</td>
<td>DCM</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

\(^a\)1.2 eq of \(\text{CH(OCH}_3\text{)}\)_3 was added to reaction

*Table 3.2: Conditions screened for acid cyclisation of alkene 289a*

At this stage, the difficulties encountered during the acid-catalysed deprotection/cyclisation were unable to be explained. However, it was noted that no previous cyclisation studies were conducted in the presence of an olefin functionality. It was postulated that the presence of the double bond may have contributed to the failures described above and it was therefore decided to examine the acid-catalysed cyclisation reaction with the saturated analogue 292 (Scheme 3.6).

*Scheme 3.6: Proposed synthesis of alkane analogue 292*
3.2.2 Attempted cyclisation using alkane 291

To generate the alkane analogue 291, alkylnyl ketone 290 was subjected to hydrogenation conditions in the presence of Pd/C under an atmosphere of hydrogen to afford alkane 291 in 90% yield (Scheme 3.7).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{i. Pd/C, H}_2, \text{ EtOAc, 1 h, 90\%.} \\
\end{align*}
\]

Scheme 3.7: Preparation of alkane 291 for cyclisation studies

Previously established acid-catalysed deprotection/cyclisation conditions using p-toluenesulphonic acid and trimethyl orthoformate in methanol were then applied to alkane 291. Consumption of the starting material was observed along with the appearance of multiple polar spots by TLC analysis (Table 3.3, entry 1). Isolating a pure compound without contamination of by-products with similar polarity proved difficult. It was found that multiple purifications by flash chromatography were required using ethyl acetate/toluene (1:2) as eluent to separate any compounds of interest from undesired by-products. One of the isolated compounds was identified and characterised by NMR and mass spectroscopic analysis. The \(^1\)H NMR spectrum exhibited a singlet at \(\delta 3.47\) ppm indicating the presence of a methoxy group and the high resolution mass spectrum exhibited a molecular ion of \(m/z\) of 261.1090 consistent with the proposed cyclised product 292. However, an unexpected peak at \(\delta 4.73\) ppm corresponding to the benzylic \(\text{CH}_2\text{O}\) exhibited no AB\(_q\) splitting and appeared as a singlet, whereas the cyclised product 292 was expected to exhibit an AB\(_q\) splitting pattern. Our suspicions were confirmed by the \(^{13}\)C NMR spectrum which displayed a peak at \(\delta 211.6\) ppm characteristic of a carbonyl moiety that would not be present in the desired product 292. Rather, it was proposed that compound 293 had been isolated, whereby the benzylic alcohol was unexpectedly methylated (Table 3.3).
In light of this unexpected methylation, different acids were screened to investigate whether the cyclisation was feasible in the presence of an unmasked phenol. When the acid-catalysed cyclisation was performed using either HCl (4.0 M) or Dowex 50W, the reaction appeared cleaner with the formation of fewer by-products as observed by TLC analysis, thereby simplifying purification (Table 3.3, entries 2 and 3). Unfortunately, in both instances methyl ether 293 was isolated again.

![Chemical structures](image)

**Table 3.3:** Conditions screened for acid cyclisation of alkane 291

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>p</em>-TsOH</td>
<td>MeOH</td>
<td>293 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>HCl (4 M)</td>
<td>MeOH</td>
<td>293 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>Dowex 50W</td>
<td>MeOH</td>
<td>293 (50%)</td>
</tr>
<tr>
<td>4</td>
<td>Dowex 50W</td>
<td>THF/H&lt;sub&gt;2&lt;/sub&gt;O (1:1)</td>
<td>294 (50%)</td>
</tr>
<tr>
<td>5</td>
<td><em>p</em>-TsOH</td>
<td>THF/H&lt;sub&gt;2&lt;/sub&gt;O (1:1)</td>
<td>294 (30%)</td>
</tr>
<tr>
<td>6</td>
<td>Amberlyst-15</td>
<td>Acetonitrile</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>TFA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Degradation</td>
</tr>
<tr>
<td>8</td>
<td>Acetic acid</td>
<td>-</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were performed at r.t. <sup>b</sup>TFA was added at -20 °C and then warmed to r.t.

All acids employed using methanol as solvent consistently afforded methyl ether 293. In order to avoid formation of undesired ether 293 and effect cyclisation, different solvents were screened next. When the solvent was changed to THF/H<sub>2</sub>O (1:1), the reaction also failed to provide the desired cyclisation product 292, instead resulting in the formation of triol 294 (Table 3.3, entries 4 and 5). The formation of triol 294 was confirmed by NMR and mass
spectroscopic analysis. The observation of a characteristic carbonyl carbon at δ 212.1 ppm along with the absence of a methoxy group in the $^{13}$C NMR served to demonstrate that only deprotection of the acetonide had occurred. Furthermore, the absence of a methoxy group and no characteristic AB$_{q}$ splitting of the OCH$_2$ at δ 4.93 ppm was consistent with the proposed structure 294. Lastly, the presence of a molecular ion peak at $m/z$ 247.0945 confirmed that the proposed triol 294 had formed rather than the desired cyclised product 292.

The reaction was then repeated using Amberlyst-15 in acetonitrile affording a complex mixture from which only a small amount of impure triol 294 could be isolated (Table 3.3, entry 6). It was found that repeating the acid-catalysed conditions of entries 1-6 with greater number of equivalents of the various acids made little difference to the reaction, yielding only undesired methyl ether 293 or triol 294 in each case. When the reaction was performed using either TFA in dichloromethane or neat acetic acid, the reaction resulted in degradation of the starting material (Table 3.3, entries 7 and 8). Despite our best efforts to effect cyclisation of alkane 291 to the desired dimerisation precursor 292, all conditions trialled were unrewarding. Interestingly, both methyl ether 293 and triol 294 demonstrated remarkable stability under the harsh acidic conditions, used with prolonged reaction times with no signs of degradation or formation of the desired cyclised product 292.

Having been unable to effect cyclisation of 291 in the presence of the free phenol and unable to proceed further into the reaction sequence using methoxy 292 and triol 293 as intermediates, work on this synthetic route was halted and investigations into an alternative protecting group for the phenol group were explored.
3.3 Tosyl Protecting Group Strategy

The initial retrosynthetic approach towards pestalospirane A (2) and B (3) hinged on the absence of a protecting group on the phenol moiety, however, it soon became apparent that the acid-catalysed cyclisation was not possible in the presence of an unmasked phenol. The need to protect the phenol functionality until after the acid-catalysed cyclisation determined that the protecting group selected had to be acid-stable yet easily removed in the presence of sensitive functionality at the late stage of the synthetic sequence. The O-tosyl protecting group is most commonly associated with carbohydrate synthesis, however, it has emerged as a highly valuable addition to the existing range of protecting group strategies as it is stable towards both acidic and basic conditions. Additionally, deprotection can be conducted under mild one-electron reductive conditions making it ideal for our purposes. An O-tosyl group was therefore incorporated into the modified synthetic plan (Scheme 3.8). Tosyl protected alkyne 295 was envisioned to be synthesised from previously synthesised acetonide 286, followed by lithium-mediated alkynylation and partial hydrogenation to provide alkene 296. Tosyl protected alkene 296 was anticipated to undergo cyclisation and dimerisation, followed by late-stage deprotection to deliver the natural product 3.

![Scheme 3.8: Proposed alternative protective group strategy](image)

The modified synthesis began with the preparation of alkyne 295. Concurrent deprotection and esterification of previously synthesised acetonide 286 was achieved using potassium carbonate.
in methanol giving ester 300, which in turn was treated with p-toluenesulfonyl chloride in the presence of potassium carbonate to furnish alkyne 301 in 80% yield (Scheme 3.9).

Reduction of the ester functionality of alkyne 301 was initially attempted with LiAlH₄ in THF. Unfortunately, no reaction was observed with only starting material being recovered despite using prolonged reaction times (Table 3.4, entry 1). Surprisingly, no reduction of the tosyl or ester moieties were observed, even when alkyne 301 was treated with excess LiAlH₄ in THF and heated under reflux for 48 h (Table 3.4, entry 2). Finally, treatment of ester 301 with DIBAL-H in dichloromethane afforded benzylic alcohol 302 in 80% yield (Table 3.4, entry 3). Subsequent TBS protection of benzylic alcohol 302 furnished the desired alkyne 303 in quantitative yields (Scheme 3.9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (eq.)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄ (2)</td>
<td>THF</td>
<td>0 °C → r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄ (4-6)</td>
<td>THF</td>
<td>reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL-H (1.5)</td>
<td>CH₂Cl₂</td>
<td>-78 °C</td>
<td>80%</td>
</tr>
</tbody>
</table>

Table 3.4: Conditions screened for reduction of alkyne 302
Chapter 3: Discussion

With both alkyne 303 and previously prepared Weinreb amide 264b in hand, attention then shifted to union of the two fragments via generation of the corresponding lithium acetylide of alkyne 303 employing the optimised conditions previously established (Section 3.2.1). The reaction was conducted with caution as the use of n-BuLi and/or LiHMDS was reported to cause the cleavage of the carbon-sulfur bond of the tosyl group. Alkyne 303 was treated with LiHMDS at -78 °C for one hour to form the lithium acetylide, to which was added Weinreb amide 264b and the mixture was then warmed to room temperature for a further hour (Table 3.5). No change was detected by TLC analysis and the reaction was continued stirring for a further 16 h, however longer reaction times resulted in no further development and only starting materials were recovered from the reaction (Table 3.5, entry 1). Next, the reaction was attempted with n-BuLi; again only starting materials were detected by TLC analysis (Table 3.5, entry 2). Changing the base to t-BuLi did not result in formation of the desired product and only starting materials were again recovered (Table 3.5, entry 3).

Table 3.5: Conditions screened for the alkynylation of alkyne 303 with Weinreb amide 264b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78 → r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>THF</td>
<td>-78 → r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-78 → r.t.</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Having been unable to effect alkynylation of 303, an alternative method to unite the two fragments was sought without needing to revise the protecting group strategy, as alkyne 303 was still considered synthetically useful.
3.3.1 Cross-coupling strategy

Given that alkyne 303 was unreactive in the previous alkynylation procedure, transition metal-catalyzed cross-coupling reactions were next examined as these reactions have proven to be one of the most powerful methodologies for selective C-C bond formation. Retrosynthetically, it was proposed that the assembly of the desired ketone intermediate 304 could be accessed via a cross-coupling of the triflate 305 and alkyne 306 fragments (Scheme 3.10). A Sonogashira cross-coupling was therefore initially attempted to generate the desired sp²-sp carbon-carbon bond (Section 2.2.7).

![Scheme 3.10: Revised retrosynthetic approach for the synthesis of ketone 304](image)

A. Sonagashira cross-coupling

In order to apply the Sonogashira cross-coupling strategy to the synthesis of ketone 304 (Scheme 3.10), the preparation of the aryl triflate coupling partner 305 was required (Scheme 3.11A). Previously synthesised triflate 284 underwent concurrent acetonide deprotection and esterification using methanol and potassium carbonate to give ester 307, followed by protection of the phenol with p-toluenesulfonyl chloride to furnish tosylate 308 in excellent yield. Subsequent reduction of the ester moiety using DIBAL-H afforded the desired Sonogashira aryl cross-coupling partner, triflate 305.

With aryl triflate 305 in hand, attention shifted towards the synthesis of alkyne 306. The alkyne cross-coupling partner 306 was prepared in one step in 78% yield by treatment of previously synthesised Weinreb amide 264b with commerically available ethynylmagnesium bromide (Scheme 3.11B).
Investigations into the Sonogashira cross-coupling began by applying standard literature conditions using aryl triflate 305 in the presence of Pd(PPh$_3$)$_2$Cl$_2$ and CuI in triethylamine/NMP (1:1), followed by the addition of alkyne 306. The resulting reaction mixture turned a murky brown colour and TLC analysis showed only degradation of both starting materials had occurred (Table 3.6, entries 1 and 2). Upon further investigation, it was found that the alkyne 306 was unstable in triethylamine and afforded a complex mixture as observed by TLC analysis. Consequently triethylamine was excluded from reactions henceforth. It was postulated that the α-proton of alkyne 306 might be abstracted by the base leading to degradation of the alkyne 306 and thus the use of milder and/or bulkier bases were examined.

The use of the sterically bulky 1,1′-bis(di-tert-butylphosphino)ferrocene (D'BuPF) ligand in the presence of potassium carbonate as the base and Pd(OAc)$_2$ under copper-free conditions was investigated next. These reaction conditions have been routinely used within our group due to their generally reliable outcomes for various Sonogashira coupling reactions. However, when these conditions were applied to our substrates, the reaction was unrewarding as degradation of starting material occurred (Table 3.6, entry 3). Subsequently, the reaction was attempted using Pd(PPh$_3$)$_2$Cl$_2$ and CuI in NMP, which again resulted in degradation of starting materials (Table 3.6, entry 4). Changing the solvent to THF offered no improvements and also resulted in degradation of starting materials (Table 3.6, entry 5). Interestingly, using DMF as the solvent led only to the recovery of both starting materials (Table 3.6, entries 6-8).
Regrettably, the union of aryl triflate 305 and alkyne 264b via Sonogashira cross-coupling proved challenging and unsuccessful, with no evidence for the formation of the coupled product 304 as observed by $^1$H NMR analysis. At this point, it was decided this approach was no longer feasible and an alternative method was sought, specifically using a modified Negishi cross-coupling.

**B. Modified Negishi cross-coupling**

In 1977, Negishi and co-workers reported a novel procedure for the direct synthesis of terminal alkynes via a Pd-catalysed cross-coupling of an alkynyl-zinc complex with organic halides (Scheme 3.12). 170,171
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Reagents and conditions: i Pd (cat), THF, 0→25 °C, 83-87%.

Scheme 3.12: Negishi alkyne-zinc coupling.\(^\text{170}\)

In 2001, this methodology was extended to include the generation of the alkynyl zinc derivative \textit{in situ}, thus making this procedure readily accessible and attractive from a synthetic standpoint.\(^\text{172}\) Two efficient procedures (procedure A and B) for the Pd-cross coupling of aryl halides with terminal alkynes via an \textit{in situ} conversion to the zinc acetylide were reported (Scheme 3.13).\(^\text{172}\) Procedure A used LDA, and consequently, required the rigorous exclusion of moisture from the reaction mixture. Procedure B using a premixed solution of zinc and a base (4:1) in THF was initially preferred for our investigation.

\begin{align*}
&\text{Procedure A} \\
&\text{Procedure B}
\end{align*}

Reagents and conditions: i. LDA, ZnX\(_2\), cat. Pd\(_{\text{Lag}}\); ii. Et\(_3\)N\,ZnX\(_2\) (4:1), ArX, cat. Pd\(_{\text{Lag}}\).

Scheme 3.13: Negishi’s \textit{in situ} alkynyl zinc procedure.

Although aryl triflates were not discussed or explored as coupling partners in the original paper,\(^\text{172}\) in general, Negishi crossing-coupling can be performed using aryl triflates, and hence our synthesis continued with the previously prepared aryl triflate 305.\(^\text{101}\)

Before applying the modified Negishi reaction conditions, aryl triflate 305 underwent silyl ether protection with TBSCl to prevent quenching of the zinc acetylide intermediate formed \textit{in situ} to give 309 (Table 3.7). The zinc alkyne complex was generated using a mixture of ZnBr\(_2\), alkyne 306 and DBU in THF, followed by addition of triflate 309 and Pd(PPh\(_3\))\(_4\) (Table 3.7, entry 1). Unfortunately, none of the expected product was isolated, but instead phenol 310, resulting from hydrolysis of the triflate group was isolated. From the \(^1\)H NMR spectrum, it was clearly evident that hydrolysis had occurred rather than cross-coupling to give
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product 310, notably, due to an absence of the aromatic resonances from the triflate (δ 7.37-7.33 ppm and δ 7.24 ppm) and the appearance of a new phenol proton resonance at δ 8.17 ppm. The high resolution mass spectrum exhibited a molecular ion at m/z 431.1323 corresponding to a molecular formula of C_{20}H_{28}O_{5}SNa, consistent with the proposed structure 310.

Reagents and conditions: i. TBSCI, imidazole, CH_{2}Cl_{2}, r.t., 16 h, 90%.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp °C</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh_{3})_{4}</td>
<td>DBU</td>
<td>THF</td>
<td>r.t.</td>
<td>310</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh_{3})_{2}Cl</td>
<td>DBU</td>
<td>THF</td>
<td>r.t.</td>
<td>310</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh_{3})_{4}</td>
<td>Cs_{2}CO_{3}</td>
<td>THF</td>
<td>r.t.</td>
<td>310^{b}</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh_{3})_{4}</td>
<td>LDA^{a}</td>
<td>THF</td>
<td>-78- r.t.</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh_{3})_{4}</td>
<td>K_{2}CO_{3}</td>
<td>DMF</td>
<td>r.t.</td>
<td>310^{b}</td>
</tr>
</tbody>
</table>

^{a}Procedure B was employed to generate the zinc acetylide complex. ^{b}Trace quantities of 310 was observed by ^{1}H NMR

Table 3.7: Conditions screened for Negishi cross-coupling of triflate 309 with alkyne 306

Next, Pd(PPh_{3})_{2}Cl_{2} was trialled as the catalyst in place of Pd(PPh_{3})_{4}, however, it failed to provide any improvement to the reaction and phenol 310 was again recovered (Table 3.7, entry 2). Cesium carbonate, LDA and potassium carbonate were subsequently examined as they have been shown to promote the Negishi cross-coupling reaction.^{172} However these conditions were also fruitless and did not deliver any of the desired cross-coupled product 304. In most cases, cleavage of the triflate 309 took place affording phenol 310. It was becoming evident that the use of triflate 310 as the aryl substrate for the modified Negishi cross-coupling was no longer worthwhile pursuing due to its inherent preference to undergo hydrolysis rather than undergo cross-coupling.
3.3.2 Summary of attempted synthesis of ketone 304

Upon consideration of the problems encountered thus far, it was concluded that the tosyl protecting group strategy was no longer a feasible route for the synthesis of ketone 304. Alkyne 295 proved unreactive towards conventional alkynylation procedures as starting materials were primarily recovered (Scheme 3.14, route A). In order to circumvent this problem, an alternative method to synthesise ketone 304 via crossing-coupling of aryl triflate 305 and alkyne 306 fragments also proved unrewarding and no coupled product 304 was observed during the trials conducted (Scheme 3.14, route B). At this point, it was decided that it was no longer sensible to commit both time and material to further investigate the methods mentioned above. The synthetic strategy was therefore abandoned and investigation of a new protecting group strategy was initiated.

Scheme 3.14: Attempted synthesis of ketone 304
3.4 \textit{i}Pr Protecting Group Strategy

3.4.1 Revised protecting group

The initial revised protecting group strategy using the \textit{O}-tosyl protecting group failed to furnish the desired ketone 304 and consequently prevented the synthesis of pestalosirpane A (2) and B (3). Therefore a more traditional phenol protecting group was employed.

Alkyl ethers are among the most common protecting groups used for phenol functionalities, with the most popular of them being the methyl ether. However methyl ethers are often difficult to deprotect, as harsh reaction conditions are regularly used to effect cleavage, often in the presence of other sensitive functionalities. Consequently, it was decided to use the more labile isopropyl ether as an alternative protecting group.\textsuperscript{165} The use of the isopropyl ether as a protecting group was first introduced by Simpson \textit{et al.},\textsuperscript{173} and quickly became popular due to being both robust under a wide variety of reaction conditions and readily installed under mild conditions in comparison to the methyl ether. The revised synthetic strategy incorporates one key change to the alkyne coupling partner 311 namely the use of an isopropyl protecting group (Scheme 3.15). Isopropyl protected alkyne 311 was envisioned to be synthesised from previously synthesised ester 300, followed by lithium-mediated alkynylation with Weinreb amide 264b and partial hydrogenation to provide alkene 312. Isopropyl protected alkene 312 was anticipated to undergo cyclisation and dimerisation, followed by late-stage deprotection to deliver the natural product 3.

\begin{center}
\textbf{Scheme 3.15: Proposed revised synthetic route towards pestalosirpane B (3)}
\end{center}
The preparation of isopropyl protected alkyne 311 was achieved in a route analogous to that of the tosyl protected alkyne 303 (Scheme 3.9). Treatment of previously synthesised ester 300 with isopropyl bromide and potassium carbonate furnished alkyne 315 with excellent yields (Scheme 3.16). Reduction of the methyl ester of alkyne 315 and subsequent TBS protection of the resulting benzyl alcohol afforded alkyne 316, which in turn underwent lithiation using LiHMDS, followed by the addition of the Weinreb amide 264b in THF at -78 °C to give ketone 317 in 79% yield.

Reagents and conditions: i. K$_2$CO$_3$, isopropyl bromide, DMF, r.t., 16 h, 96%; ii. LiAlH$_4$, THF, 0 °C, 2 h, 95%; iii. TBSCl, imidazole, DMAP (0.2 eq), CH$_2$Cl$_2$, r.t., 16 h, 99%; iv. LiHMDS, THF, -78 °C→r.t., 2 h, 79%.

Scheme 3.16: Synthesis of ketone 317

3.4.2 Stereoselective partial reduction

C. Use of a Heterogeneous catalyst

With ketone 317 in hand, partial hydrogenation to the desired acid-catalysed cyclisation precursor 312 was next investigated (Scheme 3.17). The first attempt at partial hydrogenation was trialled using Lindlar’s catalyst and catalytic amounts of quinoline in ethyl acetate, under an atmosphere of hydrogen.\textsuperscript{126}
Unfortunately, the reaction failed to give alkene 312 exclusively, but instead resulted in an inseparable mixture of alkene 312 and over hydrogenated alkane 318 (ca. 1:1) (Table 3.8, entry 1). It was thought that increasing the amount of quinoline may suppress over reduction to give alkene 312 exclusively, however, this resulted in increased reaction times while the relative amount of undesired alkane 318 formed remained unchanged (Table 3.8, entry 2).

Ethylenediamine is also known to be useful for minimising over-reduction in partial hydrogenation reactions by poisoning the Pd-catalyst thus lowering its reactivity towards the alkene product compared to alkyne substrate.\textsuperscript{174} However, when the reaction was repeated using ethylenediamine in place of quinoline, the reaction was unsuccessful and only starting material was observed by TLC and \textsuperscript{1}H NMR analysis (Table 3.8, entry 3).
Lindlar’s catalyst had thus far failed to furnish the desired alkene 312 in a viable yield, hence another heterogeneous catalyst system was examined. In 1963, Brown described the use of sodium borohydride with nickel acetate in ethanol as a selective nickel cis-hydrogenation catalyst. Brown reported two forms of nickel boride (NiB) arising from the reaction of sodium borohydride with nickel acetate in either aqueous solvent (P-1) or an alcoholic solvent (P-2). Both of these catalysts are non-pyrophoric and non-magnetic compared to Raney nickel. Subtle differences between the P-1 and P-2 forms of nickel boride exist as the catalytic activity was determined by their contamination of NaBO₂ absorption on the catalyst surface. P-1 was reported to be insensitive to steric hindrance of the side chains on the substrate and was found to be more active than P-2 (based on the t₁/₂ measured for hydrogenation of several alkenes). P-1 type NiB was usually preferred for complete hydrogenation of unsaturated hydrocarbons, whereas the P-2 type NiB catalyst is more selective for partial hydrogenation of
alkynes. As a result the P-2 catalyst was chosen, in anticipation of delivering the desired alkene exclusively.

The P-2 NiB catalyst was prepared via borohydride reduction of nickel acetate in ethanol forming a nearly black colloidal suspension under an atmosphere of nitrogen. When the reaction was complete as indicated by the cessation of hydrogen evolution (observed by the effervescence of reaction), ketone 317 was added and the reaction was placed under an atmosphere of hydrogen (1 atm) (Table 3.8, entry 4). Disappointingly, TLC analysis of the reaction after 5 hours revealed only starting material, thus the reaction was stirred for a further 12 h, after which point only alkane 318 was isolated with none of the desired alkene 312 being observed. It was presumed that the reaction was proceeding slowly with catalytic amounts of P-2 NiB and that isolation of the desired alkene 312 would be difficult, given that use of prolonged reaction times led to complete hydrogenation. Consequently, excess P-2 NiB catalyst (1-3 eq) was prepared and the reaction was repeated under otherwise similar conditions. Unfortunately, this procedure consistently resulted in a mixture of alkene 312 and alkane 318 being obtained (Table 3.8, entry 5). No change was observed when the reaction was attempted using methanol instead of ethanol as the solvent (Table 3.8, entry 6). Next, the reaction was repeated with the addition of quinoline as a catalyst modifier. Although this partially suppressed the formation of the undesired alkane 318, we were still unable to obtain alkene 312 in a workable yield (Table 3.8, entry 7). Alternative amine bases were examined with the hope of increasing the amount of alkene 312. Disappointingly, the addition of ethylenediamine prevented alkyne hydrogenation altogether (Table 3.8, entry 8), while the use of pyridine as the additive made no significant impact in minimising reduction to the undesired alkane 318 (Table 3.8, entry 9).

Extensive studies have been carried out on partial hydrogenation using a heterogeneous catalytic system. The use of Lindlar’s catalyst with quinoline and P2-NiB with quinoline produced the best results (Table 3.8, entries 3 and 7), however further attempts to improve the reaction conditions proved unsuccessful. Given the constant frustration encountered with the formation of the undesired alkane 318, alternative procedures were sought.
D. Hydroboration-protonolysis

An alternative procedure for the partial hydrogenation of alkynes is a one-pot hydroboration-protonolysis to afford the desired alkene (Scheme 3.18).\textsuperscript{180-182} This approach can be used for both terminal and internal alkynes and often affords excellent stereoselectivity. Boron hydride reagents have been utilised extensively in organic synthesis for a variety of transformations such as selective reduction of carbonyl compounds and hydroboration of alkenes and alkynes. The chemoselectivity of alkyne addition versus ketone reduction can be manipulated depending on the borane reagent employed, as they are reagent and substrate dependent. Furthermore, it has been reported that the reaction of boranes with alkynes proceeds faster in certain substrates which also contain a ketone motif.\textsuperscript{180,182-187} Protonolysis is typically achieved using excess acetic acid (7-9 eq.) however Brown, has described the use of methanol for acid-sensitive substrates, making this procedure tolerant to a wide range of functional groups.\textsuperscript{182} Therefore it was decided to investigate this procedure for the synthesis of alkene 312. As it could not be predicted with absolute certainty if the alkyne or ketone moiety of ketone 317 would react in preference; a range of different borane reagents were surveyed.

![Scheme 3.18: Hydroboration-protonolysis reaction.](https://placehold.it/300x300)

The hydroboration of ketone 317 was first attempted using BH$_3$·DMS and BH$_3$·THF in THF, however, these resulted in no reaction (Table 3.9, entries 1 and 2).

Miller \textit{et al.},\textsuperscript{185} reported that the use of dicyclohexylborane (DCHB) was far superior to other borane reagents for this transformation and required no heating to achieve complete protonolysis making it an attractive reagent.\textsuperscript{184,185} Accordingly, dicyclohexylborane was freshly prepared by the addition of BH$_3$·THF to cyclohexene at 0°C and ketone 317 was then added to this slurry and the mixture stirred for 5 h (Table 3.9, entry 3). These reaction conditions also failed to effect hydroboration of ketone 317 and only starting material, was recovered.
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The reaction was next attempted with commercially available 9-borabicyclo[3.3.1]nonane in dichloromethane (Table 3.9, entry 4). However, none of the desired alkene 312 was observed, with starting material being recovered. Hydroboration was then attempted using either 9-borabicyclo[3.3.1]nonane or pinacolborane with the inclusion of catalytic amounts of dicyclohexylborane as an additive to enhance the reactivity of the active reducing agent (Table 3.9, entry 5 and 6). Unfortunately, these conditions failed to produce the desired alkene 312, resulting again in no reaction. Finally, catecholborane was trialled, but again no reaction was observed by TLC or NMR analysis (Table 3.9, entry 7).

![Diagram](chart.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Additive</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH₃·DMS</td>
<td></td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>BH₃·THF</td>
<td></td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Cy2BH</td>
<td></td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>9-BBN</td>
<td></td>
<td>CH₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>9-BBN</td>
<td>Cy2BH</td>
<td>CH₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>pinacolborane</td>
<td>Cy2BH</td>
<td>CH₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>catecholborane</td>
<td></td>
<td>CH₂Cl₂</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

<sup>a</sup>protonolysis was attempted with acetic acid at 0 ºC → 60 ºC

Table 3.9: Conditions screened for hydroboration-protonolysis for ketone 317

All efforts to synthesise alkene 312 via hydroboration-protonolysis proved unsuccessful with no evidence of hydroboration and only starting material being recovered in all cases. Consequently no further reaction conditions were pursued, and this method was abandoned.
E. Catalytic system using palladium complexes

Since selective partial hydrogenation of internal alkynes is an important transformation in organic chemistry, a plethora of methodologies have been developed with ongoing research to improve both the chemo and regioselectivity of reaction conditions.\textsuperscript{182} Due to its operational simplicity, one particularly attractive set of conditions involves the use of catalytic transfer hydrogenation using organic hydrogen donors. In 2003, Wei \textit{et al.},\textsuperscript{182,188} reported the use of Pd(OAc)$_2$ with sodium methoxide and triphenylphosphine could selectively reduce alkynes to the corresponding alkenes. The proposed mechanism, shown in Scheme 3.19, involves the formation of a palladium methanolate complex \textit{A} followed by β-hydride elimination to give metallo-hydride \textit{B}. Subsequent migratory insertion of an alkyne to the metal-hydride bond of \textit{B} gives adduct \textit{C} which may then undergo ligand exchange with sodium methoxide to give complex \textit{D}. Finally, β-hydride elimination of adduct \textit{D} gives complex \textit{E}, which undergoes reductive elimination to produce the corresponding alkene and regenerate the Pd(0) species.

\begin{center}
\textbf{Scheme 3.19: Proposed mechanism of partial-hydrogenation using Pd(OAc)$_2$ and NaOCH$_3$}\textsuperscript{188}
\end{center}

Another variation of transfer hydrogenation with hydrogen donors was reported by Tao \textit{et al.},\textsuperscript{182,189} using Pd(OAc)$_2$ in conjunction with DMF/ KOH, which undergoes Pd(II) catalysed decomposition to generate formic acid \textit{in situ}. It was found that KOH greatly accelerated the reaction conditions as it promotes hydrolysis of DMF in the presence of KOH to form formic
acid *in situ* which is the true hydrogen donor source (Scheme 3.20). The proposed mechanism involves the oxidative addition of Pd into the formic acid O-H bond to give a palladium hydride complex B, followed by stereoselective insertion of the alkyne into the metal-hydride bond to give intermediate C. Subsequent decarboxylation of complex C forms hydride complex D generating carbon dioxide, then reductive elimination finally affords the *cis*-alkene and regenerates the Pd(0) species (Scheme 3.20). The use of transfer hydrogenation is becoming increasingly popular, due to safer operation and better control of chemoselectivity towards alkynes over alkenes. Encouraged by this literature precedent, it was decided to investigate these reaction conditions on ketone 317.

Our investigations commenced with a solution of ketone 317 in DMF in the presence of Pd(OAc)$_2$ and KOH and was heated to a 150 °C for 17 hours. Unfortunately, no reaction was observed after this time and only starting material was detected by TLC analysis (Table 3.10, entry 1). Next, ketone 317 was treated with Pd(OAc)$_2$, triphenylphosphine and sodium methoxide (Scheme 3.19), however, no reaction was observed again (Table 3.10, entry 2).

Hauwert *et al.*, reported a Pd catalysed semi-hydrogenation using Pd(OAc)$_2$ and sodium methoxide/triethylamine as the hydrogen donor source. However, when alkene 312 was subjected to these conditions, no conversion to the desired alkene 312 had occurred and only
starting material was recovered from the reaction (Table 3.10, entry 3). Furthermore, when the above mentioned trials were conducted at elevated temperatures up to 200 °C, reactions resulted in decomposition of the starting material.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Result(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)(_2)</td>
<td>KOH</td>
<td>DMF</td>
<td>No reaction</td>
</tr>
<tr>
<td>2(^b)</td>
<td>Pd(OAc)(_2)</td>
<td>NaOCH(_3)</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)(_2)</td>
<td>NaOCH(_3)/Et(_3)N</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)(_2)</td>
<td>NaOCH(_3)/Et(_3)N</td>
<td>CH(_2)Cl(_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td>5(^c)</td>
<td>Pd(OAc)(_2)</td>
<td>Et(_3)N</td>
<td>CH(_2)Cl(_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>PdCl(_2)</td>
<td>KOH</td>
<td>DMF</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

\(^a\) Heating to 100-150 °C resulted in no reaction while temperatures above 200 °C led to degradation of starting material.

\(^b\) PPh\(_3\) was added to reaction, \(^c\) formic acid was added.

**Table 3.10: Conditions screened for Pd-catalysed partial-hydrogenation of ketone 317.**

Given that the most promising conditions reported had failed to produce the desired alkene 312, alternative bases for these reactions were examined in hopes of effecting partial hydrogenation. Changing the solvent to dichloromethane, offered no improvement with starting material being recovered again (Table 3.10, entry 4). Changing the base to triethylamine also resulted in no reaction (Table 3.10, entry 5). Lastly, PdCl\(_2\) was substituted for Pd(OAc)\(_2\), however no significant change was observed with starting material being recovered (Table 3.10, entry 6).

It was suspected that ketone 317 was insufficiently reactive towards the active palladium(II) complex due to steric hindrance from the neighbouring aromatic ring and/or the high degree of conjugation of the carbon-carbon triple bond and thus any approach toward alkene 312 via partial hydrogenation would continue to be unsuccessful. Therefore, alternative routes for construction of the desired alkene 312 were subsequently considered.
F. Synthesis of alkene 312 via vinyl bromide 322 and Weinreb amide 264b

In order to circumvent the inaccessibility of alkene 312 via the partial hydrogenation, it was thought that installation of the alkene prior to the coupling of Weinreb amide 264b may yield better results. It was envisaged that alkene 312 could be readily accessed via a coupling of previously synthesised Weinreb amide 264b with the corresponding vinyl lithiate generated in situ from vinyl bromide 322 (Scheme 3.21). Vinyl bromide 322 should be accessible from alkynyl bromide 323, which in turn could be prepared from previously synthesised alkyne 316.

Scheme 3.21 Alternative retrosynthetic analysis of alkene 312

N-bromosuccinimide (NBS) is a well-known brominating agent and in combination with silver nitrate can be used to convert terminal alkynes into alkynyl bromides in high yielding and mild reaction conditions. Accordingly, the previously synthesised terminal alkyne 316 was successfully converted to the corresponding alkynyl bromide 323 with NBS and catalytic amounts of silver nitrate in acetone in quantitative yields (Scheme 3.22)

Reagents and conditions: i. NBS, AgNO₃ (0.1 eq), acetone, 0 ºC, 2 h. quant.

Scheme 3.22: Synthesis of bromo alkyne 323
With alkynyl bromide 323 in hand, attention then turned to partial hydrogenation to provide vinyl bromide 322. The partial hydrogenation was first attempted via hydrobroration-prontonolysis using either dicyclohexylborane or 9-BBN followed by protonolysis with acetic acid at reflux, however, only starting material was recovered (Table 3.11, entries 1 and 2).

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%) 322:324</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C_{12}H_{23}B</td>
<td></td>
<td>THF</td>
<td>r.t</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>9-BBN</td>
<td></td>
<td>THF</td>
<td>r.t</td>
<td>0</td>
</tr>
<tr>
<td>3^a</td>
<td>p-TsNHNH₂</td>
<td>NaOAc</td>
<td>MeOH</td>
<td>reflux</td>
<td>40:40</td>
</tr>
<tr>
<td>4^a</td>
<td>p-TsNHNH₂^b</td>
<td>NaOAc</td>
<td>MeOH</td>
<td>reflux</td>
<td>90:3</td>
</tr>
</tbody>
</table>

^a p-TsNHNH₂ (3 eq), NaOAc (4 eq), ^b quinoline (1 eq) was added to reaction

Table 3.11: Conditions screened for partial hydrogenation of alkynylbromide 323

The reaction was next attempted using p-toluenesulfonyl hydrazine (TSH) in conjunction with sodium acetate to generate diimide in situ as an alternative reagent for the desired partial hydrogenation. Diimide is an unstable hydrogen donor that can only be generated in situ and is used for alkyne and alkene reduction. This is a remarkable reaction as hydrogen is transferred to a carbon-carbon multiple bond without the aid of any catalysts (Scheme 3.23).\textsuperscript{195,196} This reagent predominantly reduces unpolarized carbon–carbon double or triple bonds thus leading to their high stereoselectivity and low observation of undesired over-reduced products.\textsuperscript{182,195,197}

Mechanistically the reaction proceeds through a 6-membered transition state with transfer of two hydrogen atoms to the alkyne substrate. A major drawback of using diimide is its ability to undergo competing disproportion (autohydrogenation) and decomposition reactions generating hydrazine, hydrogen and nitrogen by-products (Scheme 3.23).\textsuperscript{195,197,198} However, the use of excess reagents is often sufficient to push the reaction to completion to obtain the desired product.
When alkynyl bromide 323 was treated with *p*-toluenesulfonyl hydrazine and sodium acetate in methanol, partial hydrogenation was achieved to deliver the desired vinyl bromide 322, as an inseparable mixture containing the over-reduced product bromoalkane 324 (Table 3.11, entry 3). Next, the reaction was repeated with the addition of quinoline in order to reduce the amount of over hydrogenated bromoalkane 324. Pleasingly, this set of reaction conditions resulted in a smooth conversion to the desired vinyl bromide 322 with only trace amounts of bromoalkane 324 (Table 3.11, entry 4). Even though the production of bromoalkane 324 was inevitable under these reaction conditions, the amount formed was considered negligible and the mixture was then subjected to lithiation conditions (Scheme 3.24).

With vinyl bromide 322 in hand, addition to Weinreb amide 264b was explored using lithium-halogen exchange. Exposing vinyl bromide 322 to LiHMDS in THF at -78 °C for 30 min in attempts to generate the corresponding vinyl lithiate *in situ*, which after Weinreb amide 264b was added. The reaction was then allowed to be warmed to room temperature. Unfortunately, this procedure failed to give the desired alkene 312 and only starting materials were isolated.
Chapter 3: Discussion

Increasing the reaction time for lithium-halogen exchange, resulted in no improvement, returning only starting materials again (Table 3.12, entry 2).

Next, treatment of vinyl bromide 322 with n-BuLi resulted in isolation of the desired alkene 312 in 5% yield (Table 3.12, entry 3). Desiring to improve the yield of alkene 312, it was postulated that a stronger base was required to effect complete lithium-halogen exchange therefore t-BuLi was employed.191,199 Accordingly, when the reaction was repeated using t-BuLi in THF at -78 °C for the lithiation step, with addition of Weinreb amide 264b after an hour, both alkene 312 (5%) and de-brominated alkyne 316 (30%) were isolated (Table 3.12, entry 3). Changing the solvent system to diethyl ether caused a slight increase in the yield from 5% to 10% of the desired alkene 312 (Table 3.12, entry 5). Further investigations into the reaction conditions revealed that decreasing the time for lithium-halogen exchange with near immediate addition of Weinreb amide 264b after only 30 seconds drastically improved the yield of the desired alkene 312 to 40% (Table 3.12, entry 7).

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Pre-mix times</th>
<th>Yield 312 (%)</th>
<th>Yield 316 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LIHMDS</td>
<td>THF</td>
<td>-78→r.t.</td>
<td>30 min</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>LIHMDS</td>
<td>THF</td>
<td>-78→r.t.</td>
<td>1 h</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi</td>
<td>THF</td>
<td>-78→r.t.</td>
<td>1 h</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-78→r.t.</td>
<td>1 h</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>t-BuLi</td>
<td>Ether</td>
<td>-78→r.t.</td>
<td>1 h</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>t-BuLi</td>
<td>Ether</td>
<td>-78→r.t.</td>
<td>15 min</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>t-BuLi</td>
<td>Ether</td>
<td>-78→r.t.</td>
<td>30 sec</td>
<td>40</td>
<td>10-20</td>
</tr>
</tbody>
</table>

*Pre-mix times before addition of Weinreb amide 264b. *I*2 and 1,2-dibromoethane were added to initiate the reaction.

Table 3.12: Conditions screened for lithium-halogen exchange of alkene 312
The use of t-BuLi also led to unwanted side reactions where alkyne 316 was isolated in 10-30% yield using all conditions attempted with this base. It was deduced that the base was strong enough to effect proton abstraction in preference of lithium-halogen exchange leading to increasing alkyne 316 formation the longer the lithium-halogen exchange was allowed to occur (Scheme 3.25). Decreasing the time for lithium-halogen exchange resulted in an increase in desired alkene 312 in modest yields, thus minimising the formation of the alkyne 316 side product to a more manageable quantity.

Scheme 3.25: Proposed mechanism for production of alkyne 316

To further improve the yield of alkene 312 with the hope of avoiding formation of alkyne 316 an alternative method was sought. Accordingly, the use of a milder protocol, namely Br/Mg exchange was attempted. Standard Grignard conditions were attempted first using magnesium turnings to form the organomagnesium species 325 (Scheme 3.26). Unfortunately, upon addition of Weinreb amide 264b no desired product 312 was detected by TLC analysis and the vinyl bromide 322 was recovered (Table 3.13, entry 1).

Scheme 3.26: Attempted Grignard reaction to synthesis alkene 312
Generation of Grignard reagent using \(^t\)PrMgCl has shown to afford high yields compared to standard Grignard conditions.\(^{201}\) However, treatment of vinyl bromide 322 with \(^t\)PrMgCl, also resulted in no reaction and starting material was recovered (Table 3.13, entry 2).

Br/Mg exchange reactions have been reported to proceed significantly slower than Br/Li exchange reactions, therefore the use of catalytic salts can be of advantage to accelerate the reaction. Knochel and co-workers,,\(^{202}\) concluded that an equimolar equivalent of LiCl with the Grignard reagent delivered the best results. Knochel’s reaction conditions for the formation of the Grignard reagent was applied to our vinyl bromide 322. Disappointingly these reaction conditions were unrewarding and only starting materials were isolated (Table 3.13, entry 3).

![Chemical structure](image)

**Table 3.13: Conditions screened for magnesium-halogen exchange of alkene 312**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Pre-mix times(^a)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg-turnings(^b)</td>
<td>Ether</td>
<td>0→r.t.</td>
<td>16 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>(^t)PrMgCl</td>
<td>THF</td>
<td>0→r.t.</td>
<td>1→16h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>(^t)PrMgCl·LiCl</td>
<td>THF</td>
<td>0→r.t.</td>
<td>1→16 h</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Despite our best efforts to improve the conditions of lithium halogen exchange or find alternative Grignard conditions, pure alkene 312 could only be obtained in 40% yield. While only a moderate yield of alkene 312 was obtained, sufficient material to continue further with the synthesis of pestalospires A (2) and B (3) was available.

**G. H-Cube\(^\oplus\) flow hydrogenation**

In parallel with investigations into the coupling of vinyl bromide 322 with Weinreb amide 264b, partial hydrogenation of alkynyl ketone 317 using an H-cube\(^\oplus\) flow reactor was attempted. The H-cube\(^\oplus\) has the advantage of using a solid-supported catalyst such that
purification from the catalyst is not necessary, and precise control of temperature, flow rate and pressure is also possible. Ketone 317 and excess quinoline (5-10 eq) in hexanes was subjected to hydrogenation using H-cube® hydrogenation equipment (THALES Nanotechnology Inc) with a Lindlar’s catalyst cartridge (Scheme 3.27). The pressure was set to 10 bar and temperature to 20 ºC with a flow rate of 1 ml/min. To our delight the desired alkene 312 was obtained in 80% yield with only trace amounts of alkane 318. Despite best efforts we were unable to stem the production of alkane 318 completely and the hydrogenation remained poorly reproducible and unpredictable, especially on scales larger than 500 mg where production undesired alkane 318 became more prominent. Disappointingly, at the time of this research, the H-cube® had hardware problems that prohibited ongoing access to the machine.

\[
\begin{align*}
\text{Reagents and conditions: } & \text{i. H-Cube® (10 bar), hexanes, quinoline (4 eq), 20 ºC, 80%}.
\end{align*}
\]

\textbf{Scheme 3.27: Synthesis of alkene 312 using H-Cube®}

### 3.4.3 Summary of synthesis of alkene 312

Two parallel routes for the synthesis for alkene 312 have been accomplished. Alkene 312 could be obtained from either coupling of vinyl bromide 322 to Weinreb amide 264b or the use of the H-cube® to effect partial hydrogenation of ketone 317 (Scheme 3.28). At this stage having established access to desired alkene 312, the key acid cyclisation of alkene would now be investigated.
Reagents and conditions: i. H-Cube® (10 bar), Hexanes, quinoline, 20 °C, 80%; ii. t-BuLi, Et₂O, 30 seconds, then 264b, 1 hr, -78°C→r.t., 40%.

Scheme 3.28: Successful conditions for the synthesis of alkene 312
3.5 Acid-catalysed cyclisation

Despite the challenges faced in synthesising the crucial cyclisation precursor alkene 312, a viable route was eventually established and attention now shifted towards the key acid-catalysed cyclisation. It was anticipated that the desired alcohols 313a and 313b could be readily synthesised by employing the previously successful intramolecular acid-catalysed cyclisation conditions established in the preliminary investigations (Section 2.5). Thus, alkene 312 was treated with p-toluenesulfonic acid and trimethyl orthoformate in methanol which resulted in complete conversion of the starting material and the appearance of a new non-polar spot observed by TLC analysis (Scheme 3.29). Examination of the NMR and mass spectroscopic data of the product isolated were not consistent with the desired cyclised products 313a and 313b, indicating that an unanticipated side reaction had occurred. The high resolution mass spectrum of the isolated product exhibited a molecular ion at m/z ion at 299.1259, corresponding to a molecular formula of C_{16}H_{20}O_{4}Na. This corresponds to two hydrogens less than the expected desired products 313 but is consistent with the formation of ketal 326 (Scheme 3.29).

![Scheme 3.29: Acid-catalysed cyclisation of alkene 312](image)

**Reagents and conditions:** i. p-TsOH, CH(OMe)₃, MeOH, 7 h, r.t., 50%.

The $^1$H NMR spectrum of ketal 326 showed characteristic features of intramolecular cyclisation, such as AB₄ splitting of the benzylic OCH₂. The benzylic OCH₂ of starting material at 4.67 ppm, resonating as a singlet was resolved into doublets $\delta$ 5.31 ppm and $\delta$ 4.15 ppm and observation of a methoxy group at $\delta$ 3.30 ppm for 326 was consistent with the cyclised product. In addition, the appearance of the anomeric spiro carbon resonating at $\delta$ 105.3 ppm was observed in the $^{13}$C NMR spectrum. The absence of a key CH quartet, previously resonating at
Chapter 3: Discussion

4.12 ppm in the $^1$H NMR spectrum for starting material 312 and a downfield shift of the methyl group singlet now resonating at $\delta$ 2.03 ppm, were consistent with the proposed ketal structure 326. Furthermore, a presence of the characteristic carbonyl resonance at $\delta$ 205.1 ppm in the $^{13}$C NMR spectrum led us to conclude that oxidation of the chiral alcohol to give ketal 326 had indeed occurred, resulting in loss of the previously established stereochemistry.

The formation of ketal 326 was not observed in model experiments as cyclisation of the saturated model benzo[c]oxepine ring system had been successful (Section 2.5). This served to highlight that the conjugation of the ketone in the starting material 312 results in a markedly different outcome for the cascade reaction. Intriguingly, Kesting et al.\textsuperscript{18} described hemiketal 10 as one of the metabolites observed during their isolation of pestalospirane A (2) and B (3) using the HPLC-PDA-MS-SPE-NMR hyphenated system. However, due to the instability of hemiketal functionality the hemiketal 10 (Figure 3.1) was not in fact isolated (Section 1.2). Nevertheless, as a result of isolating the more stable methyl acetal analogue 326, it was suspected that these monomers were intermediates involved in the biosynthetic pathway of pestalospiranes A (2) and B (3).

Figure 3.1: Structure of monomeric benzo[c]oxepine 10 characterised by Kesting et al.\textsuperscript{18}

Following the mechanism elucidated by Creary and Moriarty for rearrangement of $\alpha$-hydroxy dimethyl acetate functionalities, a likely mechanism for the formation of ketal 326 is presented in Scheme 3.30. Mechanistically, we propose that ketal 326 formation proceeds through a $\alpha$-hydroxy dimethylacetate 327A which upon loss of methanol generates oxonium ion 327B (Scheme 3.30).\textsuperscript{140,143} Intermediate 327B then either undergoes acid-catalysed rearrangement to give enol ether 327C or cyclisation to the desired product 313. However, under acidic conditions, the anomeric carbon of 313 undergoes epimerisation and can exist in equilibrium with the acyclic enol species 327C, favouring the competing reaction pathway and enol 327C forms as a result of extended conjugation. Enol 327C then undergoes tautomerisation to give
intermediate 327D, which is susceptible to oxonium ion formation as a result of increased conjugation to provide 327E. Subsequent attack by the OH at the oxonium centre delivers ketal 326. It is postulated that ketal 326 is more thermodynamically stable and the equilibrium is driven towards formation of ketal 326 due to increased conjugation and facile tautomerisation of the acyloin moiety. To the best of our knowledge this observation is unprecedented in the literature and we can offer no further explanation for this phenomenon at this time.

Scheme 3.30: Proposed mechanism of ketal 326 formation.

As our previous model studies showed that saturated acetals undergo successful cyclisation to form the saturated model benzo[c]oxepine ring system (Section 2.5), we sought to investigate a similar cyclisation using alkane analogue 318. This study could be used to support our hypothesis that formation of the ketal 326 was due to the presence of unsaturation and does not result from the presence of more highly functionalised aromatic ring (Scheme 3.31). Access to saturated acetals 328 would also allow investigation into the subsequent dehydrogenation reaction with the hope of delivering the desired product 313 with retention of the established secondary alcohol stereocentre.

Scheme 3.31: Proposed revised route to desired alcohol 313
Previously synthesised alkyne 317 was subjected to hydrogenation conditions in the presence of Pd/C (10% w/w) in ethyl acetate, providing alkane 318 in excellent yield (Scheme 3.32). The cyclisation was then carried out using p-toluenesulfonic acid and trimethyl orthoformate in methanol, resulting in consumption of starting material and the appearance of two new polar spots as detected by TLC analysis. The formation of the desired diastereomeric acetics 328a and 328b (ca. 1:1) that were separable by column chromatography, was confirmed by NMR and mass spectra analysis. The structural assignment was supported by 1H NMR data that showed the characteristic loss of both silyl protecting group signals and the appearance of two doublets at δ 5.02 ppm and δ 4.71 ppm which were assigned to the two diastereotopic benzylic CH₂O protons in the seven-membered ring. Additionally, the mass spectrum established a molecular ion at m/z 303.1560, corresponding to a molecular formula of C₁₆H₂₄O₄Na, further supporting the formation of desired diastereomeric alcohols 328a and 328b. No observation of oxidation of the remaining secondary alcohol functionality was observed by TLC or NMR analyses. Similar nOe correlations from previously synthesised intermediates 273a and 273b were observed in the NOESY spectrum of the desired diastereomers 328a and 328b, thus enabling the elucidation and confirmation of the stereochemistry (Section 2.5 and Appendix).

\[ \text{Reagents and conditions: } H_2, \text{Pd/C (10\% w/w), EtOAc, r.t., 1 h, 95\%; ii. } p-\text{TsOH, } CH(OMe)_3, \text{MeOH, r.t., 6 h, 328a } 44\%, \text{328b } 36\%. \]

Scheme 3.32: Synthesis of 328a and 328b via acid-catalysed cyclisation of ketone 318

The successful acid-catalysed cyclisation of alkane 318 to afford diastereoisomers 328a and 328b serves to highlight the unexpected reactivity of the ketone in the unsaturated starting material 312 as a result of its conjugation (Scheme 3.33). With access to saturated acetics 328a and 328b dehydrogenation conditions could now be investigated.
Dehydrogenation of saturated acetals 328a and 328b was initially attempted using previously established conditions (Section 2.3.3). A mixture of acetals 328a and 328b was treated with a large excess of MnO₂ in toluene and heated to reflux for 48 hours (Table 3.14, entry 1), however, only starting material was recovered. Extending the reaction time, only led to degradation of the starting material.¹³⁸

Next, dehydrogenation was attempted in the presence of Pd/C in xylene (Table 3.14, entry 2). Heating the suspension to 150 °C for 48 hours, failed to effect the desired reaction and again only degradation of starting material was observed.²⁰³ Gao et al.,²⁰⁴ reported a successful dehydrogenation using Pd(OAc)₂/K₂CO₃ in DMF. Therefore this protocol was applied to our substrate, saturated acetal 328. Accordingly, a solution of alcohol 328 in DMF was treated with Pd(OAc)₂ and K₂CO₃ and heated to a 150 °C (Table 3.14, entry 3). Disappointingly, this procedure offered no promising results, only resulting in degradation of the starting material.

Following these attempts at transition metal-catalysed dehydrogenation, a step-wise bromination/dehydrobromination was next investigated. Saturated acetal 328 was treated with
NBS and AIBN in benzene and heated to reflux (Table 3.14, entry 4), however, no reaction was observed and only starting material was recovered.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (eq)</th>
<th>Base (eq)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MnO₂ (excess)</td>
<td>-</td>
<td>Toluene</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>Pd/C (excess)</td>
<td>-</td>
<td>Xylene</td>
<td>150</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂ (0.06), K₂CO₃ (0.10)</td>
<td></td>
<td>DMF</td>
<td>60</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>AIBN (0.10), NBS (1)</td>
<td>K₂CO₃ (1)</td>
<td>Benzene</td>
<td>reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>I₂ (1.5)</td>
<td>-</td>
<td>DMSO</td>
<td>90</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>DDQ (3)</td>
<td>-</td>
<td>Toluene</td>
<td>100</td>
<td>Ketal 326 60%</td>
</tr>
</tbody>
</table>

Table 3.14: Conditions screened for dehydrogenation of saturated acetal 328

In recent times, molecular iodine has received much attention for dehydrogenation due to its inexpensive, non-toxic and environmentally safe nature. The use of I₂ for dehydrogenation was first reported in 1980 by Tamura and Yoshimoto and this procedure has since been modified and improved. In particular the I₂/DMSO system was found to be the most efficient system for the dehydrogenation reaction as reported independently by Lokhande et al. and Humne et al. However, when these conditions were applied to our saturated acetal 328, degradation of starting material 328 was observed (Table 3.14, entry 5).

Dehydrogenation of saturated acetal 328 was next attempted using DDQ. Surprisingly, when saturated acetal 328 in toluene was treated with excess DDQ and heated to a 100 °C, a clean transformation of the starting material to a new non-polar compound was observed by TLC analysis (Table 3.14, entry 6). NMR analysis revealed that ketal 326, which was previously isolated via acid-catalysed cyclisation of alkene 312 was again isolated under these reaction
conditions (Scheme 3.29). Dehydrogenation of the desired benzylic position had occurred in tandem with oxidation of the secondary alcohol to afford ketal 326. Oxidation of secondary alcohols using DDQ generally does not take place, however DDQ does oxidise allylic and propargylic alcohols as reported by Burn et al.,\textsuperscript{211,212} in 1960. The authors demonstrated that DDQ was able to perform regioselective oxidation of allylic sterols in the presence of saturated alcohols in dioxanes or benzene at room temperatures (Scheme 3.34). We therefore postulated that the unsaturation was introduced first, followed by oxidation of alcohol.

![Scheme 3.34: Regioselective allylic sterol oxidation by Burn et al.\textsuperscript{211}](image)

Reagents and conditions: i. DDQ, benzene, r.t., 75%.

Mechanistically, the formation of ketal 326 was attributed to successful installation of the unsaturated bond, thus resulting in subsequent oxidation of allylic alcohol via the corresponding tautomeric enol (Scheme 3.35).\textsuperscript{211} Attempts to isolate the desired acetal 313 without over oxidation proved unsuccessful as a decrease in the equivalents of DDQ used resulted in incomplete conversion of starting material to ketal 326 with no observation of the desired acetal 313 as detected by TLC or NMR analysis.

![Scheme 3.35: Proposed mechanism of DDQ oxidation of an allylic alcohol.\textsuperscript{211}](image)

Due to the difficulties encountered in the installation of the double bond on alcohol 328, we decided to revise the reaction sequence by attempting to install the double bond after dimerisation to give 314 (Scheme 3.36). The revised retrosynthetic analysis relies on the
dehydrogenation of advanced precursor 331, which in turn is available from dimerisation of previously synthesised saturated acetal 328.

The dimerisation of previously prepared saturated acetal 328, using the previously established protocol (Section 2.5) was treated with TFA in dichloromethane at -78 °C for 1 hr afforded diastereomers 331a and 331b (ca. 1:1) in an unexpectedly low 20% yield (Table 3.15, entry 1). Therefore further optimisation was required to improve the yield and to avoid the production of unidentifiable side products. Gratifyingly, when TFA was used in place of TfOH, dimerisation proceeded smoothly affording the desired diastereomers 331a and 331b (ca. 1:1) in 77% yield which were then separable by column chromatography (Table 3.15, entry 2). Similar nOe correlations from previously synthesised intermediates 275a and 275b were observed in the NOESY spectrum of the desired diastereomers 328a and 328b, thus enabling the elucidation and confirmation of the stereochemistry (Section 2.6.3 and Appendix).

Following the successful dimerisation of acetal 328 to generate the desired dimers 331a and 331b, attention next turned to dehydrogenation to install the required double bonds (Table 3.16). Dimer 331 was subjected to a wide range of oxidation conditions in an effort to
effect double dehydrogenation (Table 3.16). Unfortunately, the dehydrogenation conditions trialled failed to provide the desired product 314, with all reactions resulting in degradation of starting material (Table 3.16, entries 1-5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (eq)</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MnO₂ (excess)</td>
<td>-</td>
<td>Toluene</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>Pd/C (excess)</td>
<td>-</td>
<td>Xylene</td>
<td>150</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂ (0.06), K₂CO₃ (0.10)</td>
<td>DMF</td>
<td>60</td>
<td>Degradation</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I₂ (1.5)</td>
<td>-</td>
<td>DMSO</td>
<td>90</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>DDQ (3)</td>
<td>-</td>
<td>Toluene</td>
<td>100</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Table 3.16: Conditions screened for dehydrogenation of dimer 331

Given that we were unable to access the desired acetal 328 or dimer 331 without the loss of stereochemistry of the alcohol group, further investigation into dehydrogenation was abandoned. Consequently, our synthetic strategy for the synthesis of pestalospiranes A (2) and B (3) was reconsidered using ketal 326 to access the desired dimerisation precursor (±)-313. The successful racemic synthesis of dimerisation precursor (±)-313 and elaboration to racemic pestalospirane A ((±)-2) and B ((±)-3) would then lay the foundation for enantioselective investigations to re-install the prerequisite methyl group stereochemistry of the natural products.
3.5.2 Racemic reduction of ketal 326 for synthesis of isopropyl protected pestalospirane B ((±)-3)

Two parallel approaches for the synthesis of ketal 326 were established: the first being an acid catalysed cyclisation of alkene 312; and the second via DDQ oxidation of acetal 328 (Scheme 3.38). Both routes were used interchangeably to access gram quantities of ketal 326, thus enabling further synthetic investigations towards the synthesis of the natural products.

**Reagents and conditions:** i. p-TsOH, CH(OMe)_3, MeOH, 7 h, r.t., 50%; ii. DDQ, toluene, 100 °C, 4 h, 60%

With ketal 326 now readily available, racemic reduction of the ketone moiety was next examined, with a view to undertake a racemic synthesis of pestalospiranes A (2) and B (3), before investigation into enantioselective reduction would be examined.

Accordingly, reduction of ketal 326 was successfully achieved under Luche conditions using sodium borohydride in methanol to give the corresponding alcohol (±)-313 (Scheme 3.39). The
diastereoselectivity of the reduction could not be precisely quantified by analysis of the $^1$H NMR or $^{13}$C NMR spectra due to the overlap of key resonances. Following the promising results obtained from dimerisation of alkane 328 (Table 3.15), alcohol (±)-313 was treated with TFA in dichloromethane at -78 °C for 1 hour. TLC analysis of the reaction revealed consumption of the starting material and the appearance of two non-polar spots as anticipated. The two spots were isolated and the structures of the product were elucidated using NMR and mass spectra analysis. Interestingly, both dimers exhibited isochronous NMR peaks, however, no dimer exhibiting an anisochronous NMR peak was detected as expected based on the dimerisation studies conducted on the saturated analogues (Section 3.5.1). The products from the reaction were assigned as dimers (±)-314a and (±)-314b (4:1).

**Scheme 3.39: Synthesis of dimers (±)-314a and (±)-314b**

The less polar, major symmetrical product isolated, exhibited a diagnostic NOESY correlation between the olefinic proton (H-4/H-4') and the methyl group, confirming a syn-relationship between these two substituents, consistent with the proposed structure (±)-314a (Figure 3.2). Additionally, no nOe correlation between the olefinic proton (H-4/H-4') and the methine proton (H-2/H-2') was observed, which was also consistent with the syn-arrangement of the methyl and double bond in dimer (±)-314a.
Chapter 3: Discussion

The $^1$H NMR spectrum of the more polar minor product isolated exhibited similar resonances pattern as the above less polar dimer ($\pm$)-314a. However, the NOSEY spectra showed no correlation between the methyl group and olefinic protons (H-4/H-4'), whereas a correlation between the methine proton (H-2/H-2') and olefinic proton (H-4/H-4') was observed. It was therefore concluded that dimer ($\pm$)-314b contains an anti-relationship between the methyl group and olefinic protons (H-4/H-4'), consistent with the proposed structure ($\pm$)-314b (Figure 3.3).

It was postulated that the major isomer obtained from dimerisation would be the kinetically controlled spirocyclisation product. Isolation of dimer ($\pm$)-314b was unexpected as an unsymmetrical dimer ($\pm$)-314c was anticipated. This again served to highlight certain idiosyncrasies between the saturated and unsaturated ring system. It was postulated that the extra rigidity acquired due to the presence of the unsaturated ring favours formation of two symmetrical dimers ($\pm$)-314a and ($\pm$)-314b, with a preference for the syn-arrangement as the

![Figure 3.2 NOSEY correlation of proposed dimer ($\pm$)-314a](image)
methyl groups have no steric interaction with the benzylic CH₂O groups (Figure 3.2). On the other hand, the dimer (±)-314b is less favoured due to steric interactions between the methyl groups and benzylic CH₂O groups (Figure 3.3).

![Figure 3.3: NOSEY correlation of dimer (±)-314b](image)

With the required framework of pestalospirane B ((±)-3) fully assembled, attention then turned to deprotection of the isopropyl ether.

### 3.6 Attempted Synthesis of Racemic Pestalospirane B

The final step in the total synthesis of pestalospirane B ((±)-3) involved the cleavage of the isopropyl ether protecting group (Table 3.17). From previous experiences within our research group, the deprotection step was expected to be facile. The most common methods for deprotection of alkyl ethers are dominated by the use of borane-based reagents. In particular BCl₃ has been established as an effective reagent for isopropyl protecting group
Accordingly, dimers \((\pm)-314a\) and \((\pm)-314b\) were treated with BCl\(_3\) in dichloromethane at -78 °C (Table 3.17, entry 1). Unfortunately the reaction resulted in rapid degradation as detected by TLC and NMR analysis. Coe \(\textit{et al.}\),\(^{213}\) reported a mild, selective aryl alkyl ether deprotection protocol using a combination of BCl\(_3\) and TBAI.\(^{213}\) However, when this procedure was applied to dimers \((\pm)-314a\) and \((\pm)-314b\), rapid degradation of the starting material was observed again (Table 3.17, entry 2). Subsequently, BBr\(_3\) was employed as a milder borane reagent, but again degradation of starting material was observed by TLC and NMR analysis (Table 3.17, entry 3). As alcohol \((\pm)-313\) and dimers \((\pm)-314a\) and \((\pm)-314b\) were found to survive dimerisation condition in the presence of TFA, it was postulated that TFA might be able to effect cleavage of the isopropyl ether protecting group while leaving the sensitive spiroketal ring system unaffected (Table 3.17, entry 4). Unfortunately prolonged exposure to TFA led to degradation of the starting material and none of the desired pestalospirane B ((±)-3) was observed by TLC or NMR analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (eq)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BCl(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>BCl(_3), TBAI</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>BBr(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>AlCl(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>Complex mixture(^a)</td>
</tr>
<tr>
<td>6</td>
<td>AlCl(_3)</td>
<td>CH(_2)Cl(_2)</td>
<td>-78</td>
<td>Complex mixture(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Trace amounts of 332 observed

Table 3.17: Conditions Screened for isopropyl deprotection of dimers \((\pm)-314a\) and \((\pm)-314b\)

In 1998, Banwell \(\textit{et al.}\),\(^{215}\) reported an isopropyl cleavage protocol using aluminium trichloride. Additionally, aluminium trichloride has been successfully employed within our group, where
traditional borane reagents have failed. When dimer (+)-314 was exposed to these conditions, the reaction resulted in a complex mixture of products, as assessed by TLC and NMR analysis (Table 3.17, entries 5 and 6). Attempts to isolate products from the complex mixture provided evidence for formation of ketone 332 in the $^1$H NMR spectrum (Table 3.17). The $^1$H NMR spectrum of the isolated product contained the similar resonances to those described above for previously isolated ketal 326 (Table 3.17, Scheme 3.39) although no methoxy resonance group was observed. Unfortunately, only trace amounts of ketone 332 were obtained, precluding structure determination. It is postulated that the 1,4-dioxane ring is unstable under these conditions and facilitates the breakdown of the central 1,4-dioxane ring via Lewis acid mediated lysis to give ketone 332, leaving the isopropyl group intact.

Unfortunately late-stage isopropyl cleavage was not as facile as expected and in most cases led to degradation of starting material. The protecting group strategy was therefore once again in need of revision.

3.6.1 Summary of attempted total synthesis of pestalospirane B

The revised protecting group strategy began with the preparation of the isopropyl ether protected alkyne 315 which was achieved in 5 steps from commercially available 2,3-dihydroxybenzoic acid (382) (Scheme 3.40). The organolithium mediated coupling of alkyne 311 and previously synthesised Weinreb amide 264b successfully afforded 317, which underwent hydrogenation using the H-cube® to furnish the desired alkene 312. Alternatively, alkene 312 was also synthesised via coupling of vinyl bromide 322 to Weinreb amide 264b. Interestingly, subsequent acid-catalysed cyclisation unexpectedly delivered ketal 326, which was accompanied by complete loss of chirality established previously. Ketal 326 was also obtained when the saturated acetal 328 was subjected to dehydrogenation conditions. Racemic borohydride reduction was next undertaken to access the desired dimerisation precursor (+)-313, which underwent dimerisation under acidic conditions to furnish isopropyl protected pestalospirane B (+)-314a along with unnatural dimer (+)-314b. Disappointingly, deprotection of the isopropyl group resulted in degradation of the starting material (+)-314.
Scheme 3.40: Reagents and conditions: i. TBSCl, imidazole, DMAP, CH₂Cl₂, r.t., 16 h, quant; ii. HN(OMe)Me·HCl, i-PrMgCl, THF, 0 °C, 2 h, 99%; iii. K₂CO₃, isopropyl bromide, DMF, r.t., 16 h, 96%; iv. LiAlH₄, THF, 0 °C, 2 h, 95%; v. TBSCI, imidazole, DMAP, CH₂Cl₂, r.t., 16 h, 99%; vi. LiHMDS, THF, -78 °C→r.t., 2 h, 79%; vii. H-cube® (10 bar), hexanes, quinoline, 20 °C, 80%; viii. p-TsOH, CH(OMe)₂, MeOH, 7 h, r.t., 50%; ix. NBS, AgNO₃, acetone, 0 °C, 2 h, quant.; x. p-TsNH₂, NaOAc, quinoline, MeOH, reflux, 12 h, 93%; xi. t-BuLi, Et₂O, 30 seconds, then 264b, 1 hr, -78 °C→r.t., 40%; xii. Pd/C, EtOAc, r.t., 1 h, 95%; xiii. p-TsOH, CH(OMe)₂, MeOH, r.t., 6 h, 328a 44%, 328b 36%. xiv. DDQ, toluene, 100 °C, 4 h, 60%; xv. NaBH₄, CeCl₃·7H₂O, MeOH, 10 mins, 90%; xvi. TFA, CH₂Cl₂, -78 °C, 1 h, 60% (±)-314a and 15% of (±)-314b.
3.7 EOM Ether Protecting Group Strategy

The previous approach towards the synthesis of pestalospiranes A (2) and B (3) relied on isopropyl ether cleavage in the final step, however, upon exposure to a range of deprotection conditions, degradation of starting material occurred (Section 3.6). To circumvent this undesired outcome, the use of a more labile protecting group was examined. It was decided that use of an ethoxymethyl ether (EOM) would be more appropriate as it can be readily removed under mildly acidic conditions and/or under benign conditions using TMSBr,\textsuperscript{216} or CBr\textsubscript{4} in conjunction with PPh\textsubscript{3}.\textsuperscript{217} The revised protecting group strategy incorporates two key changes; firstly, the alkyne coupling partner 333 would be protected as the ethoxymethyl ether (Scheme 3.41). Secondly, the unsaturated EOM protected ketone 334 was expected to undergo cyclisation to give EOM protected ketal 335, which could then be subjected to borohydride reduction to give racemic alcohol (±)-336. Racemic alcohol (±)-336 would in turn be subjected to dimerisation, followed by late-stage deprotection to deliver racemic pestalospirane B ((±)-3). Upon successful completion of the synthesis of racemic pestalospirane B ((±)-3), investigation into chiral HPLC for determination of enantiomeric excess (e.e.) and subsequent asymmetric reduction of ketal 335 could then be explored, thus enabling the total synthesis of pestalospirane B (3).\textsuperscript{18}

Scheme 3.41: Revised proposed protecting group strategy using an EOM ether
With a suitable protecting group strategy in mind, alkyne 339 was then prepared using a route analogous to that used to prepare isopropyl protected alkyne 316 (Scheme 3.16). The free phenol of 300 was protected as an EOM ether using chloromethyl ethyl ether and diisopropylethylamine in dichloromethane affording ester 338 in 90% yield (Scheme 3.42). Ester 338 was then converted to the corresponding alcohol 333 via lithium aluminium hydride reduction, followed by TBS protection of the resultant benzylic alcohol using tert-butyldimethylsilyl chloride, imidazole, and DMAP in dichloromethane to give alkyne 339 in excellent yield. Pleasingly, ketone 310 was generated in 80% yield by the coupling of alkyne 339 with Weinreb amide 264b using LiHMDS to generate the lithium acetylide.

Reagents and Conditions:  

- i. TBAI, DIPEA, EOMCl, CH₂Cl₂, r.t., 16 h, 90%;  
- ii. LiAlH₄, THF, 0 °C, 3 h, 90%;  
- iii. TBSCI, DMAP (0.2 eq), imidazole, CH₂Cl₂, 0 °C, 16 h, quant.;  
- iv. LiHMDS, THF, -78 °C→r.t., 2 h, 80%.

Scheme 3.42: Synthesis of EOM protected ketone 340
3.8 Racemic Synthesis of Pestalospirane A (±)-2 and B (±)-3

3.8.1 Synthesis of unsaturated ketone 334

Following the successful alkynylation procedure, attention then turned to the selective \( \text{cis} \)-reduction of EOM protected ketone 340. Again, the best results obtained involved the use of the H-cube\(^\circ\) flow reactor, furnishing the desired alkene 334 in 80% yield along with trace quantities of alkane 341. As mentioned previously (Section 3.4.2), this step remained troublesome due to poor reproducibility, rendering scale-up difficult especially when working on quantities larger than 300 mg. However, performing the reaction in parallel on a scale of 200 mg of ketone 340 enabled generation of sufficient quantities of alkene 334, thus this approach was continued.

\[
\begin{align*}
\text{340} & \xrightarrow{\text{H-cube\(^\circ\), Lindlar’s catalyst, quinoline (4-5 eq), hexanes, 10 bar, 20 °C, 1 min/mL,}} \text{80% (9:1 334:341).} \\
\text{Scheme 3.43: Synthesis of alkene 334}
\end{align*}
\]

With alkene 334 in hand, attention then focused on the key intramolecular acid-catalysed cyclisation. Following the previously established cyclisation conditions (Section 3.5), alkene 334 was treated with \( p \)-toluenesulfonic acid and trimethyl orthoformate in methanol. Disconcertingly, the reaction resulted in multiple spots as observed by TLC analysis. Attempts to isolate the desired product from the complex mixture, resulted only in the recovery of starting material, EOM protected ketal 335 and EOM deprotected ketal 342 (Table 3.18, entry 1). Repeating the acid-catalysed cyclisation using 10-camphorsulfonic acid in place of \( p \)-toluenesulfonic acid also resulted in formation of a complex mixture, with EOM ketal 335 isolated predominantly.
In comparison to the cyclisation of isopropyl alkene 312 (Section 3.5), the acid-catalysed cyclisation of EOM protected alkene 334 resulted in multiple spots by TLC analysis, making purification of the pure products challenging without contamination by unidentifiable side-products (Table 3.18, entry 2). Furthermore, allowing the reaction to go to completion was detrimental due to increased by-product formation as observed by TLC and NMR analysis.

![Image of chemical structures]

Table 3.18: Conditions screened for acid-catalysed cyclisation of alkene 334

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Yield % (335:342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH/CH(OMe)3</td>
<td>MeOH</td>
<td>20 (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>CSA/CH(OMe)3</td>
<td>MeOH</td>
<td>20 (1:0)</td>
</tr>
<tr>
<td>3</td>
<td>Dowex 50w/CH(OMe)3</td>
<td>MeOH</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

A preliminary investigation into DDQ dehydrogenation/oxidation of isopropyl acetal 328 proved to be a viable alternative method to access ketals 335 and 342 (Section 3.5.1). It was therefore decided to investigate the DDQ dehydrogenation/oxidation strategy for the EOM-protected analogue series in order to increase the yield of the desired ketal 335 and 342 thereby avoid production of by-products (Scheme 3.44).
For the preparation of the alkane cyclisation precursor 341, hydrogenation of alkynyl ketone 340 was required. Subjecting alkynyl ketone 340 to hydrogenation using Pd/C (10% w/w) under an atmosphere of hydrogen for 1 hour provided alkane 341 in 95% yield (Scheme 3.45). Alkane 341 was then treated with acid and trimethyl orthoformate in methanol for 1 hr. The TLC analysis initially showed that the starting material 341 transformed into a mixture of EOM-protected acetal diastereomers 343a and 343b and EOM-deprotected acetal diastereomers 344a and 344b. Use of prolonged reaction times resulted in complete conversion to the deprotected acetals 344a and 344b in ca. 1:1 diastereomeric mixture which were separable by column chromatography. It was found that the outcome of the reaction could be manipulated by adjusting the water content of the reaction solvent. The use of anhydrous methanol resulted in the formation of predominantly EOM-protected acetals 343a and 343b, whereas use of wet methanol resulted in the formation of predominantly EOM-deprotected acetals 344a and 344b (Scheme 3.45).

The structure of acetals 344a and 344b were confirmed by NMR analysis. The $^1$H NMR spectrum revealed that both silyl protecting groups ($\delta$ 0.88-0.05 ppm) and the EOM ether group ($\delta$ 5.22, 3.72 and 1.26-1.21 ppm) had been cleaved from the starting material 341 (Scheme 3.45). The benzylic OCH$_2$ of starting material 341, previously resonating at 4.79 ppm as a singlet, was resolved into two doublets resonating at $\delta$ 4.92 ppm ($J = 13.8$ Hz) and $\delta$ 4.76 ppm ($J = 13.9$ Hz) for the less polar diastereomer 344a and $\delta$ 4.99 ppm ($J = 13.9$ Hz) and $\delta$ 4.76 ppm ($J = 13.4$ Hz) for the more polar diastereomer 344b indicating successful cyclisation. Similar nOe correlations from previously synthesised intermediates were observed in the
NOESY spectrum of the desired diastereomers 336 and 343, thus enabling the elucidation and confirmation of the stereochemistry (Section 2.5 and Appendix).

\[ \text{Reagents and Conditions:} \]
\[ \text{i. } \text{Pd/C (10% w/w), } H_2, \text{ EtOAc, r.t., 1 h, } 95\%; \text{ ii. } p-\text{TsOH, MeOH (AR grade), CH(O\text{Me})}, 24 \text{ h, EOM deprotected alcohols } 344a \text{ and } 344b \text{ (69% 1:1) or } p-\text{TsOH, anhydrous MeOH, CH(O\text{Me})}, 30 \text{ h, EOM protected alcohols } 343a \text{ and } 343b \text{ (65% 1:1)} \]

Scheme 3.45: Acid-catalysed cyclisation of alkane 341

Regrettably, when the cyclisation was repeated on gram quantities using the conditions established above, degradation of the starting material 341 was observed by TLC and NMR analysis (Table 3.19, entries 1 and 2). Gratifyingly, it was found that use of milder 10-camphorsulfonic acid to perform the acid-catalysed cyclisation furnished the deprotected acetals 344a and 344b in modest yields. The reaction could also be scaled up without further complications (Table 3.19, entry 3).
With access to both EOM-protected acetals 343a and 343b and EOM-deprotected acetals 344a and 344b now established, attention shifted to the DDQ dehydrogenation/oxidation conditions previously described for the isopropyl analogue 328 (Section 3.5.1). DDQ oxidation of EOM-protected acetals 343a and 343b in toluene as solvent with heating to 100 °C, generated the desired ketal 335 in 50% yield (Scheme 3.46, A). In parallel, the deprotected acetals 344a and 344b, were also subjected to DDQ oxidation. However, the reaction afforded EOM deprotected ketal 342 in an extremely low yield of 10% (Scheme 3.46, B). Changing the solvent to acetonitrile and decreasing the temperature to 57 °C resulted in an increase in yield to 30%.

Despite observation of complete consumption of starting materials 343 and 344 and no apparent side product formation as observed by TLC and NMR analysis, the yield for the deprotected ketal 342 remained relatively low. Nevertheless, the DDQ oxidation method provided a more facile route to this intermediate over the acid-catalysed cyclisation of alkene 334, and thus was the preferred method for the synthesis of ketals 335 and 342.


Chapter 3: Discussion

Reagents and conditions: i. DDQ, CH$_3$CN or toluene, 100 °C, 1 h, 50%; ii. DDQ, CH$_3$CN, 57 °C, 4 h, 30%.

Scheme 3.46: Synthesis of ketal 343 and 344 using DDQ oxidation

3.8.2 Synthesis of racemic (±)-pestalospirane B ((±)-3)

With a view to avoid late stage deprotection, deprotected ketal 342 was initially employed for dimerisation studies. With ketal 342 in hand, attention focused on the racemic synthesis of pestalospirane A ((±)-2) and B ((±)-3). Formation of racemic material would then lay the foundation for a chiral HPLC system to be developed to determine the enantiomeric excess of either alcohol (±)-345 or dimer ((±)-3). Accordingly, ketal 342 was reduced to a mixture of racemic alcohols (±)-345 under Luche reduction conditions using sodium borohydride and cerium(III) chloride heptahydrate in methanol at 0 °C (Scheme 3.47). The reaction resulted in an inseparable diastereomeric mixture of racemic alcohol (±)-345 for which it was difficult to establish the diastereoselectivity of the reaction. However, upon subjecting the crude mixture to TFA, the dimerisation proceeded as planned giving an inseparable mixture of (±)-pestalospirane B ((±)-3) along with trace amounts of (±)-pestalospirane A ((±)-2) and (±)-3,13-syn,3',13'-syn-dimer 3a (where the double bond and methyl group are anti to each other). (±)-Pestalospirane B ((±)-3) was clearly identified as the major component of the mixture by $^1$H NMR, $^{13}$C NMR and NOESY spectra analysis, which were in full agreement with those reported, thereby confirming the relative anti-configuration of the natural product.  

18
Reagents and conditions: i. NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 10 min, quant.; ii. TFA, CH₂Cl₂, -78 °C, 1 h, 80\% (±)-pestalospirane B ((±)-3), (±)-pestalospirane A ((±)-2) and (±)-3,13-syn,3’,13’-syn-dimer (±)-3a.

Scheme 3.47: Synthesis of pestalospirane B ((±)-3), pestalospirane A ((±)-2) and 2,12-syn,2’,12’-syn-dimer (±)-3a

With the successful racemic synthesis of pestalospirane B ((±)-3) in hand, attention now shifted towards investigation into chiral HPLC conditions that would enable separation of the enantiomers of pestalospirane B ((±)-3) for determination of the enantiomeric excess (e.e). The HPLC conditions identified to separate the enantiomers would then be used to analyse the enantiomeric excess of the asymmetric reduction. Unfortunately, despite numerous attempts at separation by chiral HPLC analysis (Chiralpak® AD-H, Chiralpak® IA, Chiralpak® IC, Chiralpak® OD-H), no separation of the two enantiomers of pestalospirane B ((±)-3) was achieved.

Given that we could readily access the EOM ketal 335 and thus subsequent dimers 346a and 346b, we considered investigation of chiral HPLC separation of these EOM-protected substrates instead (Scheme 3.48). Accordingly, the Luche reduction was repeated using EOM-protected ketal 335 to furnish alcohol (±)-336a and (±)-336b as a pair of diastereomers that were separable by flash column chromatography. Gratifyingly, upon treatment of a mixture of alcohols (±)-336a and (±)-336b with TFA in dichloromethane at -78 °C for 1 hour,
2,12-anti,2',12'-anti-dimer (±)-346a and 2,12-syn,2',12'-syn-dimer (±)-346b were obtained in 60% and 10% yields respectively, which were separable by flash column chromatography.

**Reagents and conditions:**

i. NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 10 min, (±)-336a 51% and (±)-336b 30%;

ii. TFA, CH₂Cl₂, -78 °C, 1 h, (±)-346a 60% and (±)-346b 10%.

**Scheme 3.48: Synthesis of dimers 346a and 346b**

Pleasingly, it was found that both enantiomers of 2,12-anti,2',12'-anti-dimer (±)-346a were readily identifiable by chiral HPLC (HPLC, Chiralpak® AD-H, hexanes/isopropanol (1:10), t₁ (R,S,S,R) = 8.47 min, t₂ (S,R,R,S) = 9.23 min, Figure 3.4). Having accomplished separation of these two enantiomers by chiral HPLC, all that remained was to effect deprotection of the phenolic EOM ether protecting groups on dimers (±)-346a and (±)-346b to give (±)-pestalospirane B ((±)-3) and 2,12-syn,2',12'-syn-dimer (±)-3a.
Ethoxymethyl ethers are known to be labile under similar reaction conditions used for methoxymethyl (MOM) ethers, notably using Brønsted and Lewis acidic reagents. Other benign deprotection methods have also been developed, enabling reaction for acid-sensitive substrates such as 346, and thereby avoiding isomerisation/decomposition of the spirocentre. A survey of deprotection conditions was therefore undertaken towards the synthesis of (±)-pestalospirane B ((±)-3) and dimer (±)-3a.

The use of sodium bisulfate on silica is known to be a relatively mild method for the deprotection of both EOM and MOM ethers and has previously proven successful in our group where other methods have failed. These conditions were therefore initially employed for our investigations. Unfortunately, application of these conditions to dimer (±)-346 resulted only in decomposition of starting material as assessed by both TLC and NMR analysis (Table 3.20, entry 1).

Another relatively mild deprotection procedure previously used in our group for acid-sensitive substrates was the use of catalytic pyridinium p-toluenesulfonate in tert-butanol under
reflux.\textsuperscript{220} However, exposure of dimer (±)-346 to these conditions also led to the decomposition of starting materials (Table 3.20, entry 2).

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Reagents (eq) & Solvent & Temp (°C) & Result (%) \\
\hline
1 & NaHSO\textsubscript{4}-SiO\textsubscript{2} (2) & CH\textsubscript{2}Cl\textsubscript{2} & 0 & Decomposition \\
2 & PPTS (0.2-4) & t-BuOH & 90 & Decomposition \\
3 & CSA (0.2-2) & MeOH & r.t. & Decomposition \\
4 & Amberlyst-15 & CH\textsubscript{2}Cl\textsubscript{2} & r.t. & Decomposition \\
5 & TsOH (2-4) & MeOH/CH\textsubscript{2}Cl\textsubscript{2} (1:1) & r.t. \rightarrow 50 & SM recovered \\
6 & Dowex 50W & MeOH/CH\textsubscript{2}Cl\textsubscript{2} (1:1) & r.t. \rightarrow 50 & SM recovered \\
7 & Acetyl chloride & MeOH/CH\textsubscript{2}Cl\textsubscript{2} (1:1) & 0 & Ketone 335 (30) \\
8 & TMSCl (5), TBABr (5) & CH\textsubscript{2}Cl\textsubscript{2} & -30 \rightarrow 0 & Decomposition \\
9 & CBr\textsubscript{4} (1.5), PPh\textsubscript{3} (1.5) & DCE & 40 & Complex mixture \\
\hline
\end{tabular}
\caption{Conditions screened for deprotection of dimer (±)-346}
\end{table}

The use of either 10-camphorsulfonic acid in methanol or Amberlyst\textsuperscript{®}-15 in dichloromethane also resulted in rapid decomposition of starting material (Table 3.20, entries 3 and 4), whereas treatment with p-toluenesulfonic acid or Dowex 50w in dichloromethane/methanol (1:1) resulted in recovery of mostly starting material (Table 3.20, entries 5 and 6).\textsuperscript{165} Attempts to push the reaction to completion using either prolonged reaction times or an increase in the equivalents of acid eventually led to decomposition of starting material.

Interestingly, upon treatment of dimer (±)-346 with acetyl chloride in dichloromethane/methanol (1:1), ketal 335 was once again isolated (Table 3.20, entry 7). This result served to highlight the lability of the spirocentre under acidic conditions. The undesired formation of ketal 335 via breakdown of the spirocenter was not unexpected, considering the ease of decomposition of the 1,4-dioxane central ring as previously observed in the isopropyl analogue series (Section 3.6).
In view of the disappointing results obtained thus far, alternative non-acidic conditions were sought. Hanessian et al.,\textsuperscript{216} reported a mild method for cleavage of a methoxymethyl ether using bromotrimethylsilane in dichloromethane at -30 °C. Following an adaption of the procedure used by Maier et al.,\textsuperscript{223} dimer (±)-346 and tetrabutylammonium bromide in dichloromethane were treated with trimethylsilyl chloride at 0 °C and the reaction was stirred for an hour. Disappointingly, rapid decomposition of starting materials was again observed by TLC and NMR analysis (Table 3.18, entry 8).

Carbon tetrabromide (CBr\textsubscript{4}) in isopropyl alcohol under reflux has been reported as an efficient method for deprotection of MOM ethers, however this procedure relies on \textit{in situ} formation of HBr, which provides an anhydrous acidic reaction condition.\textsuperscript{218} Pleasingly, HBr production can be avoided when CBr\textsubscript{4} is used in conjunction with triphenylphosphine (PPh\textsubscript{3}) in aprotic solvents.\textsuperscript{217,218} The use of CBr\textsubscript{4} and PPh\textsubscript{3} in 1,2-dichloroethane at 40 °C resulted in a complex mixture, where none of the by-products could be accurately identified by \textit{1}H NMR analysis.

Unfortunately, all attempts at late stage deprotection of EOM protected dimers (±)-346 failed to give the corresponding deprotected dimer (±)-3, as the reaction predominantly resulted in decomposition of starting materials. Upon consideration of the problems encountered with EOM-deprotection and chiral HPLC of the unprotected pestalospirane B ((±)-3), it was decided to investigate enantioselective reduction of the EOM-deprotected ketal 342 and then subsequent dimerisation to deliver the natural product ((+)-3). Derivatisation of (+)-pestalospirane B ((+)-3) to the EOM-protected dimer (+)-346a would be required to examine the enantiomeric excess of the reaction (Scheme 3.49).

![Scheme 3.49: Proposed alternative approach for the determination of enantiomeric excess of dimerisation using chiral HPLC](image-url)
3.9 Asymmetric reduction of ketal 342

3.9.1 Corey-Bakshi-Shibata reduction

With a method for the synthesis of (+)-pestalospirane B ((+)3) in hand, and the determination of the enantiomeric excess established, attention then shifted towards the asymmetric reduction of ketal 342 followed by dimerisation to afford pestalospirane B (3).18

![Scheme 3.50: Proposed synthesis of pestalospirane B (3)](image)

In 1981, Hirao et al.224 reported that stoichiometric mixtures of chiral amino alcohols, such as (S)-valine (347), and borane-THF complexes had the potential to reduce achiral ketones 348 to their corresponding chiral secondary alcohols 349 enantioselectivity and in high yields (Scheme 3.51). The enantioselectivity obtained using this procedure depended on the ratio of the BH₃ and amino alcohol, the quantity of hydride present in the reagent and the steric bulk of the ketone substituents, however no mechanistic rationale was proposed at the time.224

![Scheme 3.51: First example of enantioselective ketone reduction reported by Hirao et al.224](image)

Later in 1987, Corey et al.225 further investigated the scope and application of this transformation and showed that the reaction between various tertiary amino alcohols and
borane led to the formation of an oxazaborolidine 351, which in conjunction with the borane reagent effected the asymmetric reduction of achiral ketones 350 (Scheme 3.52). Mechanistically, the first step involves the coordination of BH$_3$ (Lewis acid) to the tertiary nitrogen atom (Lewis base) of the CBS catalyst from the $\alpha$-face 351A. This coordination enhances the Lewis acidity of the endocyclic boron atom and activates BH$_3$ to become a strong hydride donor. Consequently, the CBS-borane complex binds to the ketone at the more sterically accessible lone pair via the endocyclic boron atom 351B. The face-selective hydride transfer occurs via a six-membered transition state. Lastly, the regeneration of the catalyst may take place by two different pathways (I or II) (Scheme 3.52). Since it was first reported in the 1980s, a wide range of catalysts and modifications have been developed, making this methodology a good starting point when attempting a chiral reduction.

![Scheme 3.52: Proposed mechanism for CBS-catalysed enantioselective reduction of ketones.](image)

### 3.9.2 First attempt at enantioselective reduction of ketal 342

A literature survey revealed the most popular catalysts for CBS reduction were (S)- and (R)-methyl-Corey-Bakshi-Shibata catalysts, that are commercially available as 1 M solutions, hence they were the first catalysts to be screened. The stereochemistry resulting from each catalyst can be predicted using the above mechanism (Scheme 3.52). The general consensus is that the stereochemistry of the complex is controlled by steric effects with the ketone preferring...
to adopt an orientation where the larger substituent is directed away from the oxazaborolidine moiety. Using the model above, it was determined that the (S)-Me-CBS 352 should afford the desired (R)-alcohol (R)-345. Subsequent dimerisation of alcohol (R)-345 should provide pestalospirane B (3) as reported in the literature (Scheme 3.53).\(^{18}\) Borane dimethylsulfide (BH\(_3\)-DMS) was initially employed as the borane reagent due to its vast precedence for achieving high enantioselectivity.\(^{96,227,228}\)

Subjecting ketal 342 to standard reduction conditions using (S)-Me-CBS (S)-352 and BH\(_3\)-DMS in THF at 0 °C, resulted in over-reduction (Table 3.21).\(^{226,228}\) Not only did the ketone functionality get reduced, this was unfortunately accompanied by the reduction of the acetal centre, affording exclusively alcohol (R)-353 (Table 3.21, entry 1). It was found that temperature and reaction times were extremely crucial in order to favour formation of the desired alcohol (R)-345. An increase in either temperature or reaction times resulted predominantly in the formation of undesired alcohol (R)-353. Consequently, an increase in catalyst loading from 0.3 to 0.6 was required as reaction times exceeding 30 mins resulted in an increase in reduction of the acetal centre to give alcohol (R)-353. Additionally, the optimal temperature was found to be between -20→0 °C, as an increase in temperature also resulted in reduction of the acetal centre, whereas a decrease in temperature below -20 °C resulted in no reaction (Table 3.21, entry 2). When the reaction was repeated with an increase in catalyst...
loading while maintaining a temperature of -10 °C, TLC analysis revealed complete consumption of starting material after 30 min and appearance of a single product spot. Upon isolation of the product it was revealed by \(^1\)H NMR analysis that an inseparable mixture of alcohols \((R)-345\) and \((R)-353\) (4:1) was obtained (Table 3.21, entry 3).

Table 3.21: Conditions screened for CBS-reduction of ketal 342

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (eq)</th>
<th>Borane (eq)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (^b) ((%)) (345:353)</th>
<th>Yield (^b) of dimers ((\pm))-3:2:3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((S))-Me-CBS (0.3)</td>
<td>BH(_3) DMS (1)</td>
<td>0</td>
<td>2</td>
<td>0:80 (0:1)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>((S))-Me-CBS (0.3-0.6)</td>
<td>BH(_3) DMS (1)</td>
<td>-78</td>
<td>2</td>
<td>No reaction</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>((S))-Me-CBS (0.6)</td>
<td>BH(_3) DMS (1)</td>
<td>-10</td>
<td>0.5</td>
<td>75 (4:1)</td>
<td>80 (10:1:1)</td>
</tr>
<tr>
<td>4(^a)</td>
<td>((S))-Me-CBS (0.6)</td>
<td>BH(_3) DMS (1)</td>
<td>-10</td>
<td>0.5</td>
<td>75 (7:3)</td>
<td>80 (10:1:1)</td>
</tr>
</tbody>
</table>

\(^a\)Borane reagent was added slowly to a premixed solution of CBS catalyst and ketal 342. \(^b\)Yields were calculated based on \(^1\)H NMR analysis.

The order of addition of the ketal 342 and borane reagent was next investigated, in order to decrease the time that ketal 342 was exposed to the borane reagent, which was postulated to increase the yield of the desired alcohol \((R)-347\).\(^{229}\) When BH\(_3\) DMS was slowly added to a pre-mixed solution of ketal 342 and \((S)\)-Me-CBS \((S)\)-352, no significant difference was
observed with respect to the yield, however the ratio of (R)-345:353 (4:1 vs. 7:3) was marginally impaired using these conditions (Table 3.21, entries 3 vs. 4).

Furthermore, due to the instability of alcohol (R)-345, a crude mixture of alcohols (R)-345 and (R)-353 was immediately subjected to dimerisation conditions, following a quick filtration through silica to separate CBS-borane reagents from the products. Gratifyingly, when the 4:1 mixture of alcohols (R)-345 and (R)-353 were treated with TFA in dichloromethane at -78 °C for 1 h, dimerisation proceeded as expected affording pestalospirane B ((+)-3) as the major isomer along with trace quantities of pestalospirane A ((+)-2), 3,13-syn,3’,13’-syn-dimer (+)-3a in 80% (10:1:1) yield, and recovered unreactive alcohol (R)-353. Despite best efforts, the dimers were inseparable by column chromatography using a wide range of eluents. Pestalospirane B ((+)-3) was clearly identified as the major component of the mixture by 1H NMR, 13C NMR, NOESY spectra and mass spectra analysis, which were in full agreement with those reported, thereby confirming the relative configuration of the natural product (Table 3.22). The mass spectrum of the dimer mixture exhibited a molecular ion at m/z at 431.1479 consistent with that of the natural product. 1H NMR and 13C NMR spectra showed the absence of the methoxy moiety at 3.30 ppm and 50.0 ppm respectively from the starting material 342, confirming dimerisation had occurred. Analysis of the NOESY spectrum was conducted for determination of relative configuration. Synthetic pestalospirane B ((+)-3) exhibited a diagnostic NOESY correlation between the olefinic protons (H-4/H-4’) and the methyl group (H-13/H-13’), confirming a syn-relationship between these two substituents, consistent with the natural product (Figure 3.5). Additionally a correction between the methine proton (H-12/H-12’) and benzylic protons (H-1/H-1’) was also observed further confirming the 3,12-anti, 3’, 12’-anti relative configuration of synthetic pestalospirane B ((+)-3).
Figure 3.5: nOe correlations of synthetic pestalospirane B (\((+)-3\))
Chapter 3: Discussion

(+)-Pestalospirane B

![Diagram of (+)-Pestalospirane B]

<table>
<thead>
<tr>
<th>δH/C*</th>
<th>¹H NMR CD₃CN</th>
<th>¹³C NMR CD₃CN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lit. m (J [Hz])</td>
<td>Synthetic m (J [Hz])</td>
</tr>
<tr>
<td>1</td>
<td>a 4.52, d (13.8)</td>
<td>a 4.51, d (13.8)</td>
</tr>
<tr>
<td></td>
<td>b 4.97, d, (13.8)</td>
<td>b 4.97, d, (13.8)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5.92, d (12.5)</td>
<td>5.92, d (12.5)</td>
</tr>
<tr>
<td>5</td>
<td>6.67, d (12.5)</td>
<td>6.67, d (12.5)</td>
</tr>
<tr>
<td>6</td>
<td>6.89, d (7.6)</td>
<td>6.89, d (7.9)</td>
</tr>
<tr>
<td>7</td>
<td>7.13, dd (7.6, 8.1)</td>
<td>7.13, t (7.4)</td>
</tr>
<tr>
<td>8</td>
<td>6.78, d (8.1)</td>
<td>6.78, d (8.1)</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>4.03, q (6.5)</td>
<td>4.03, q (6.5)</td>
</tr>
<tr>
<td>13</td>
<td>0.94, d (6.5)</td>
<td>0.94, d (6.5)</td>
</tr>
<tr>
<td>OH</td>
<td>7.08, br</td>
<td>7.07, br</td>
</tr>
</tbody>
</table>

Table 3.22: Comparison of ¹H and ¹³C NMR data for natural pestalospirane B and synthetic pestalospirane B ((+)-3).¹⁸ *Carbon atoms assigned according to natural product numbering.

3.9.3 Determination of enantiomeric excess of EOM-protected dimer (+)-346a

Determination of the enantiomeric excess of the free alcohol (R)-345 and natural products ((±)-3) was not possible due to inseparable mixture of alcohols (R)-345 with undesired alcohol
(R)-353 and ((±)-3) could not be separated by chiral HPLC as previously discussed (Section 3.8.2), dimer (+)-3 was converted to its EOM protected derivative (+)-346a. Accordingly, the mixture of dimers 3:2:3a (10:1:1) was treated with EOMCI and DIPEA in dichloromethane to afford EOM protected dimer (+)-346a in 40% yield (Scheme 3.54). Attempts to increase the yield of (+)-346a by addition of excess reagents offered no significant improvements and the use of prolonged reaction times led to degradation of EOM-protected dimer (+)-346a. Disappointingly, when chiral HPLC [HPLC, Chiralpak® AD-H, hexanes/isopropanol (1:10), flow rate: 0.5 min/mL] analysis was performed, it was established that an enantiomeric excess for (+)-346a of only 20% was achieved.

Reagents and conditions: i. EOMCI, DIPEA, CH₂Cl₂, 0 °C, 16 h, (+)-346a 40%, 20 % e.e.

Scheme 3.54: EOM protection of dimer (+)-346a for chiral HPLC analysis

3.9.4 Optimisation of enantioselective reduction of ketal 342

In an effort to further optimise the enantiomeric excess obtained from the key chiral reduction step, it was decided to investigate the influence of the catalyst on the enantiomeric excess. The optimised reaction sequence was repeated using either (S)-butyl-CBS (S)-354 or (S)-tolyl-CBS (S)-355 as the catalyst (Figure 3.6). Unfortunately, altering the catalyst proved ineffective and only a slight increase in enantioselective excess of EOM-protected dimer (+)-346a was observed from 20% to 25% (Table 3.23, entries 1 and 2).


**Figure 3.6: Structure of (S)-butyl-CBS (S)-354 and (S)-tolyl-CBS (S)-355**

**Reagents and conditions:** i. TFA, CH₂Cl₂, -78 °C, 1 h, 80% (10:1:1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Borane (eq)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield₆ (%) 345:353</th>
<th>Yield₆ of dimers (+)-3:2:3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S-Tolyl-CBS</td>
<td>BH₃·DMS (1)</td>
<td>-10</td>
<td>0.5</td>
<td>75 (4:1)</td>
<td>80 (10:1:1)</td>
</tr>
<tr>
<td>2</td>
<td>S-Butyl-CBS</td>
<td>BH₃·DMS (1)</td>
<td>-10</td>
<td>0.5</td>
<td>75 (4:1)</td>
<td>80 (10:1:1)</td>
</tr>
<tr>
<td>3</td>
<td>S-Me-CBS</td>
<td>Catecholborane (2)</td>
<td>-78</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>S-Me-CBSᵇ</td>
<td>BH₃ diethylaniline (1)</td>
<td>-20→0</td>
<td>1</td>
<td>75 (7:3)</td>
<td>80 (10:1:1)</td>
</tr>
<tr>
<td>5</td>
<td>S-Me-CBS</td>
<td>BH₃ diethylaniline (1)</td>
<td>-20→0</td>
<td>0.5</td>
<td>75 (4:1)</td>
<td>80 (10:1:1)</td>
</tr>
</tbody>
</table>

ᵃCatalyst loading of 0.6 eq. ᵇBorane reagent was added slowly to a premixed solution of CBS catalyst and ketal 342. ᶠYields were calculated based on ¹H NMR analysis.

Table 3.23: Conditions screened for CBS-reduction for ketal 342
Attempts to improve the enantiomeric excess of EOM-protected dimer (+)-346 by altering the catalyst proved unsuccessful, therefore investigation of changing the nature of the borane reagent was next attempted. Catecholborane was initially employed as the reaction could be performed at lower temperatures, with the hope of increasing the enantioselectivity. When a solution of ketal 342 was added to a premixed solution of (S)-Me-CBS (S)-352 and catecholborane in THF at -78 ºC, the reaction resulted in a complex mixture of unidentifiable products by NMR analysis (Table 3.23, entry 3). Gratifyingly, changing the borane reagent to BH₃-diethylaniline was found to result in a desirable enantiomeric excess of EOM-protected dimer (+)-346a of 97% [HPLC, Chiralpak® AD-H, hexanes/isopropanol (4:40), flow rate: 0.5 min/mL: t₁ (R,S,S,R) = 8.87 min, t₂ (S,R,R,S) = 9.63 min; [α]D²₇.₅ +25.2 (c 0.25, CHCl₃) (Figure 3.7)

Reagents and conditions: i. TFA, CH₂Cl₂, -78 ºC, 1 h, 80%; ii. EOMCl, DIPEA, CH₂Cl₂, 0 ºC, 16 h, (+)-346a 40%, 97% e.e.
Chapter 3: Discussion

HPLC conditions: Chiralpak® AD-H, hexanes/isopropanol (1:10), flow rate: 0.5 min/mL; t₁ (R,S,S,R) = 9.21 min, t₂ (S,R,R,S) = 9.63 min

Figure 3.7: Chiral HPLC chromatogram of EOM-dimer (+)-346a

Having successfully achieved the synthesis of (+)-pestalospirane B ((+)-3) with high enantioselectivity, attention then focused on confirming the absolute stereochemistry of the reported natural product. Kesting et al.,\textsuperscript{18} assigned the absolute stereochemistry by comparing time-dependent density functional theory (TDDFT) calculations and calculated electronic circula dichroism (ECD) spectra with experimental data. Kesting et al.,\textsuperscript{18} did not provide any α\textsubscript{0} data, preventing direct comparison of the α\textsubscript{0} obtained for our synthetic material (+)-pestalospirane B ((+)-3) with the natural product. Consequently, in order to confirm the absolute stereochemistry of synthetic (+)-pestalospirane B ((+)-3), ECD analysis was conducted (Figure 3.9). It is important to note that trace quantities of other dimers were present by \textsuperscript{1}H NMR and therefore might have an influence on the magnitude of the ECD spectra. Interestingly, the measured ECD of synthetic (+)-pestalospirane B ((+)-3) was in disagreement with the reported spectra. Synthetic (+)-pestalospirane B ((+)-3) displayed a negative short-
wavelength Cotton effect (\(\lambda_{\text{max}} 250\) nm) (Figure 3.8), whereas Kesting et al.\(^{18}\) observed a positive short-wavelength Cotton effect (\(\lambda_{\text{max}} 250\) nm) (Figure 3.9).

![Molar CD vs Wavelength](image1)

**Figure 3.8:** ECD spectra of synthetic (+)-pestalospirane B ((+)-3) and (-)-pestalospirane B ((-)-3) (c 0.00036, acetonitrile)

![Circle diagram](image2)

**Figure 3.9:** ECD spectra of pestalospirane B (3) reported by Kesting et al.\(^{18}\)

Consequently, preparation of the opposite enantiomer of (+)-pestalospirane B ((+)-3) was achieved using the optimised reaction sequence summarised in Table 3.21 using (R)-Me-CBS catalyst instead (Scheme 3.55). This procedure furnished (-)-pestalospirane B ((-)-3) with an enantiomeric excess of (-)-EOM-protected dimer (-)-346a of 98\% [HPLC, Chiralpak\(^\text{®}\) AD-H, hexanes/isopropanol (1:10), flow rate: 0.5 min/mL: \(t_1 (R,S,S,R) = 8.53\) min, \(t_2 (S,R,R,S) = 9.23\) min; \([\alpha]_D^{22} -24.1\) (c 0.25, CHCl\(_3\))] (Figure 3.10). In this case the measured ECD of
(-)-pestalospirane B (-)-346a and reported ECD of pestalospirane B (3) were in full agreement (Figure 3.8 and Figure 3.9).

Reagents and conditions: i. (R)-Me-CBS, BH3 diethylaniline, THF, -20 → 0 °C, 0.5 h, 75% (S)-245:253 (4:1); ii. TFA, CH2Cl2, -78 °C, 1 h, 80%.

Scheme 3.55: Synthesis of (-)-pestalospirane B ((-)-3)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time</th>
<th>Peak Name</th>
<th>Height</th>
<th>Area</th>
<th>Rel.Area</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.53</td>
<td>n.a.</td>
<td>617.157</td>
<td>124.629</td>
<td>98.64</td>
<td>n.a.</td>
<td>BMB²</td>
</tr>
<tr>
<td>2</td>
<td>9.23</td>
<td>n.a.</td>
<td>8.622</td>
<td>1.718</td>
<td>1.36</td>
<td>n.a.</td>
<td>BMB²</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>625.979</td>
<td>128.346</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.10: HPLC trace of (-)-EOM-dimer (-)-346a
Given the discrepancy between the reported ECD data and synthetic (+)-pestalospirane B ((+)-3), the original stereochemical assignment postulated by Kesting et al.\textsuperscript{18} was brought into question. In addition, the CBS-reduction model was used to determine the stereochemistry of the asymmetric reduction (Section 3.9.1) and was expected to give the desired stereochemistry of pestalospirane B 3. Accordingly, to determine the stereochemistry of the natural product and asymmetric reduction, conversion of (-)-pestalospirane B ((-)-3) to its p-bromobenzoyl derivative (-)-356 for X-ray analysis was next carried out (Scheme 3.56).

![Scheme 3.56: Proposed synthesis of (-)-p-bromobenzoyl dimer (-)-356](image)

### 3.9.5 Determination of the absolute stereochemistry of pestalospirane B

In order to unambiguously confirm the absolute stereochemistry of (-)-pestalospirane B ((-)-3), dibromobenzoyl derivatisation of (-)-356 was required to enable single X-ray crystallography (Scheme 3.57). Gratifyingly, (-)-dibromobenzoyl dimer (-)-356 was successfully synthesised in 80% yield from ((-)-3) using p-bromobenzoyl chloride and DMAP in dichloromethane at 0 °C for 15 hours. Preparation of a single crystal for X-ray crystallography analysis was achieved using a solvent mixture of dichloromethane-methanol-hexanes (1:1:1) at -4 °C using the slow evaporation technique to give (-)-p-bromobenzoyl dimer (-)-356 as colourless needles.
**Chapter 3: Discussion**

**Reagents and conditions**: i. \( p \)-BrBzCl, DMAP, CH\(_2\)Cl\(_2\), 0 °C, 1.5 h, 80%.

Scheme 3.57: Synthesis of \((-\)p\)-bromobenzoyl dimer \((-\)356)

From the X-ray structure we were able to unambiguously assign the stereochemistry of \((-\)p\)-pestalospirane B \((-\)3\) (Figure 3.11). The structure was solved in space group \( P2_1 \) and contained one molecule of compound \((-\)356\) and half a molecule of \( n \)-hexane; crystal symmetry produced a chain of \( n \)-hexane solvent that extends through the crystal in a confined channel. The final round of refinement gave an \( R_1 \) value of 0.0661 for 6437 \( F_0 > 4 \) sig \( (F_0) \). To determine the absolute configuration of the molecule unambiguously, two Br atoms were introduced into the molecule to produce an anomalous dispersion signal. The C3 and C3' atoms display an \( R \) configuration, and the C12 and C12' atoms are found in the \( S \) configuration (Scheme 3.57). The refined Flack parameter for this structure is 0.035(11).\(^{230}\) The inverted structure when refined gives an \( R_1 \) value of 0.0899 and Flack parameter of 0.976(17) confirming we have determined the correct absolute configuration.

**Figure 3.11**: Ortep diagram of bromo-dimer \((-\)356)
3.9.6 Overall summary and conclusion

In summary, the first total synthesis of the proposed structure of pestalospirane B \((+)-3\) has been accomplished in 14 steps (longest linear sequence) from commercially available 2,6-dihydroxybenzoic acid \((282)\) (Scheme 3.58). The key feature of the synthesis was the bioinspired dimerisation of alcohol \(245\) to furnish synthetic pestalospirane B \((+)-3\). The key acid cyclisation of alkene \(334\) provided ketal \(342\), however with the EOM-protected series isolation of pure material was difficult and was low yielding. Consequently, DDQ oxidation of saturated alcohols \(344a\) and \(344b\) was the preferred method to obtain ketal \(342\). Ketal \(342\) underwent enantioselective reduction using \((S)\)-Me-CBS catalyst and \(\text{BH}_3\cdot\text{diethylaniline}\) to furnish alcohol \((R)-345\), which was then subjected to TFA to give pestalospirane B \((+)-3\) as the major isomer. Comparison of \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectroscopic data of synthetic and natural pestalospirane B \((3)\) were in complete agreement (Table 3.22), however ECD data suggested a discrepancy with the original structure assignment and consequently the other enantiomer of pestalospirane B \((-)-3\) was prepared using \((R)\)-Me-CBS catalyst instead. In order to unequivocally assign the natural product and stereochemical outcome of the CBS reduction of ketal \(342\), derivatisation of \((-)\)-pestalospirane B \((-)-3\) for single X-ray crystal structure analysis was conducted. The X-ray crystal structure obtained enabled unambiguous assignment of the absolute stereochemistry. Accordingly, the structure was revised and absolute stereochemistry confirmed by total synthesis. The successful synthetic route to \((-)\)-pestalospirane B \((-)-3\) is summarised in Scheme 3.58 and Scheme 3.59.
Scheme 3.58: Reagents and conditions: i. TBSCI, imidazole, DMAP, CH$_2$Cl$_2$, r.t., 16 h, quant; ii. HN(OMe)Me·HCl, i-PrMgCl, THF, 0 °C, 2 h, 99%; iii. SOCl$_2$, acetone, DMAP, DCE, 0 °C, 24 h, 70%; iv. NaH, DMAP, PhNTf$_2$, DMF, 0 °C, 2 h, 90%; v. PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N/NMP, then trimethylsilylacetylene, r.t., 2 h, 80%; vi. K$_2$CO$_3$, MeOH, 40 °C, 3 h, 80%; vii. TBAI, DIPEA, EOMCl, CH$_2$Cl$_2$, r.t., 16 h, 90%; viii. LiAlH$_4$, THF, 0 °C, 3 h, 90%; ix. TBSCI, DMAP, imidazole, 0 ºC, 16 h, quant.; x. LiHMDS, THF, -78 ºC → r.t., 2 h, 80%; xi. H-cube®, Lindlar’s catalyst, quinoline (4-5 eq), hexanes, 10 bar, 20 ºC, 1 min/mL, 80% (9:1 334:341); xii. p-TsOH, CH(OMe)$_3$, MeOH, 16 h, 20%; xiii. Pd/C, EtOAc, r.t., 1 h, 95%; xiv. CSA, MeOH (AR bottle), CH(OMe)$_3$, 24 h, 69% (1:1, 344a:344b); xv. DDQ, CH$_2$CN, 57 ºC, 2 h, 30%; xvi. (S)-Me-CBS, BH$_3$-diethylaniline, THF, -20 ºC, 75% (4:1 345:353); xvii. TFA, CH$_2$Cl$_2$,-78 ºC, 80% (10:1:1).
Chapter 3: Discussion

Scheme 3.59: i. Pd/C, EtOAc, r.t., 1 h, 95%; ii. p-TsOH, MeOH (AR bottle), CH(OMe)₃, 24 h, 69% 1:1; iii. (R)-Me-CBS, BH₃-diethylaniline, THF, -20 °C, 75% (4:1 345:353); iv. TFA, CH₂Cl₂, -78 °C, 80%.

3.9.7 Future work

After evaluating the above described synthetic approach towards (-)-pestalospirane B (−)-3, we recognised a major drawback in the synthesis; the loss of stereochemistry of the alcohol group during the acid-catalysed cyclisation of unsaturated ketone 334 to give ketal 342 instead of the desired unsaturated alcohol 345 (Scheme 3.60, route A). In order to circumvent this problem dehydrogenation of saturated alcohol 344 was attempted to obtain the unsaturated alcohol 344. However when alcohol 344 was treated with DDQ, ketal 342 was once again isolated (Scheme 3.60, route B).

More in-depth study and investigation into this reaction is required to test our mechanistic hypothesis (Scheme 3.30, Section 3.5). A complete temperature and solvent screen could first be attempted in order to investigate the possibility of trapping the desired alcohol 345, thus avoiding ketal 342 formation. In addition, deuterium labelling studies of the acid-catalysed cyclisation step using deuterated methanol as the solvent could also be examined in order to
probe the hydride shift/loss step (Section 3.5, Table 3.18). By avoiding loss of stereochemistry of the alcohol group the total synthesis would be far more streamlined.

Future work for this project will also involve biological testing of pestalospiranes A (2) and B (3) and intermediates to assess any biological activity.
Chapter Four: Experimentals
4.1 General Details

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon. Tetrahydrofuran and diethyl ether were freshly distilled over sodium/benzophenone ketyl. Dichloromethane, acetonitrile, methanol and dimethylsulfoxide were freshly distilled from calcium hydride. Toluene was freshly distilled over sodium. Triethylamine and diisopropylamine were freshly distilled from calcium hydride and stored over potassium hydroxide. All other reagents were used as received unless otherwise noted.

Yields refer to chromatographically and spectroscopically (\(^1\)H NMR) homogeneous materials, unless otherwise stated. Reactions performed at low temperature were cooled either with an acetone/dry ice bath to reach −78 °C or an ice/water bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel was used for flash chromatography. Preparatory TLC was carried out on 500 μm, 20 × 20 cm UniplateTM (Analtech) silica gel thin layer chromatography plates.

NMR spectra were recorded at room temperature in CDCl\(_3\), CD\(_3\)OD, (CD\(_3\))\(_3\)CO, C\(_6\)D\(_6\) or (CD\(_3\))SO solutions on either a Bruker DRX300 spectrometer operating at 300 MHz for \(^1\)H nuclei and 75 MHz for \(^{13}\)C nuclei or using a Bruker DRX-400 spectrometer operating at 400 MHz for \(^1\)H nuclei and 100 MHz for \(^{13}\)C nuclei. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (\(\delta = 0\)) and were measured relative to the solvent in which the sample was analysed. Coupling constants, \(J\), are reported in hertz (Hz). Multiplicities are reported as “s” (singlet), “br s” (broad singlet), “d” (doublet), “dd” (doublet of doublets), “ddd” (doublet of doublets of doublets), “t” (triplet) and “m” (multiplets). Where distinguishable from those due to a major rotamer or diastereomer, resonances due to minor rotamers or diastereomers are denoted by an asterix. Optical rotations were measured with an Autopol® IV automatic polarimeter, using the sodium-D line (589 nm), with the concentration measured in grams per 100 mL. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained using a VG70SE spectrometer or on a micrOTOF-Q II mass spectrometer.
4.2 Experimental Procedures

L-Diethyltartrate (152)

To a stirred solution of L-tartaric acid 151 (20.0 g, 0.13 mol) in ethanol (202 mL, 3.30 mmol) was added thionyl chloride (19.4 mL, 0.26 mol) dropwise at room temperature and stirred at this temperature for 18 h. The reaction mixture was concentrated in vacuo and then dichloromethane (50 mL) was added. The combined organic layers were washed with sat. aq. NaHCO₃ (3 × 50 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:1) gave the title compound (25.0 g, 94%) as a colourless oil.

[α]_{D}^{20.0} \text{ -9.1 (c 1.04, EtOH) [lit.,}^{231,232} \text{ -9.4 (c 1.04, EtOH)];}

Rf: 0.3 (2:3 ethyl acetate/hexanes);

¹H NMR (400 MHz, CDCl₃): δ 4.54 (2H, d, J = 5.0 Hz, H-2 and H-3), 4.24 (4H, q, J = 7.0 Hz, OCH₂CH₃), 3.46 (2H, brs, OH), 1.28 (6H, t, J = 6.8 Hz, OCH₂CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 171.6 (2 × C=O), 72.2 (2 × CH, C-2 and C-3), 62.3 (2 × CH₂, OCH₂CH₃), 14.1 (2 × CH₃, OCH₂CH₃);

Spectroscopic data are consistent with reported literature.²³¹,²³²
1-Dimethyl 2,3-O-isopropylidenetartrate (153)

To a stirred solution of L-diethyltartrate 152 (25.0 g, 0.12 mol) in toluene (50 mL) was added p-toluenesulfonic acid (231 mg, 1.20 mmol) and 2,2-dimethylpropane (22.0 mL, 0.18 mol) at room temperature and refluxed for 16 h. Sat. aq. NaHCO₃ (40 mL) was then added and the aqueous layer was separated and extracted with ethyl acetate (2 × 30 mL). The combined organic layer was dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:2) as eluent gave the title compound (17.1 g, 90%) as a colourless oil.

[α]²².⁵D -2.1 (c 1.0, CHCl₃) [lit.³³⁻².1 (c 1.7, CHCl₃)];

Rf: 0.3 (1:2 ethyl acetate/hexanes);

¹H NMR (400 MHz, CDCl₃): δ 4.77 (2H, s, H-2 and H-3), 4.27 (4H, q, J = 7.1 Hz, OCH₂CH₃), 1.49 (6 H, s, C(CH₃)₂), 1.32 (6H, t, J = 7.5 Hz, OCH₂CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 170.0 (2 x C=O), 113.9 (Cq, C(CH₃)₂), 76.9 (2 × CH, C-2 and C-3), 52.7 (2 × CH₂, OCH₂CH₃), 26.2 (2 × CH₃, C(CH₃)₂), 14.1 (2 × CH₃, OCH₂CH₃);

Spectroscopic data are consistent with reported literature.³³
2,3-O-Isopropylidene-l-threitol (154)

A suspension of LiAlH$_4$ (6.80 g, 0.18 mol) in THF (100 mL) at 0 °C was added dicarboxylate 153 (11.0 g, 0.04 mol) dropwise and stirred for 2 h. The reaction was quenched with brine (30 mL) and the resulting suspension was stirred for a further 1 h, then filtered through a pad of Celite® and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:1) gave the title compound (7.20 g, quant) as a colourless oil.

$\left[\alpha\right]_{D}^{22.5}$ -4.3 (c 1.0, CHCl$_3$) [lit.,$^{234}$ -4.3 (c 1.4, CHCl$_3$)];

$\text{Rf}$: 0.3 (1:2 ethyl acetate/hexanes);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.02-3.98 (2H, m, OH), 3.80-3.78 (2H, m, H-2 and H-3), 3.69-3.67 (2H, m, CH$_2$OH), 1.44 (6 H, s, C(CH$_3$)$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 109.4 (C$_q$, C(CH$_3$)$_2$), 78.1 (2 × CH, C-2 and C-3), 62.1 (2 × CH$_2$, CH$_2$OH), 27.1 (2 × CH$_3$, C(CH$_3$)$_2$);

Spectroscopic data are consistent with reported literature.$^{234}$
[(4R,5R)-5-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (155)

To a stirred solution of diol 154 (3.50 g, 21.5 mmol) in DMSO (10 mL) was added a solution of sodium hydroxide (1.50 g, 38.8 mmol) in DMSO (10 mL) at room temperature and stirred for 1 h. A solution of benzyl chloride (3 mL, 25.9 mmol) in DMSO (10 mL) was then added and stirred for a further 2 h. The reaction mixture was poured over ice-water (15 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 3:2) gave the title compound (5.40 g, 80%) as a colourless oil.

$[\alpha]_D^{20.5} +7.9$ (c 1.0, CHCl₃) [lit.,²³⁴,²³⁵ +7.3 (c 3.14, CHCl₃)];

Rf: 0.3 (3:2 ethyl acetate/hexanes);

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.24 (5H, m, Ar-H), 4.58 (2H, s, H-7), 4.08-4.02 (1H, m, H-5), 3.96-3.92 (1H, m, H-4), 3.78-3.73 (1H, m, OHCH₂ab), 3.68-3.63 (2H, m, OHCH₂ab and H-6αβ), 3.57-3.54 (1H, m, H-6αβ), 2.42 (1H, brs, OH), 1.42 (6H, s, C(CH₃)₂);

¹³C NMR (100 MHz, CDCl₃): δ 137.5 (C₉, Ar-C), 128.7 (2 × CH, Ar-C), 128.1 (2 × CH, Ar-C), 128.0 (CH, Ar-C), 109.1 (C₉, C(CH₃)₂), 79.9 (CH, C-2), 76.8 (CH, C-3), 73.9 (CH₂, C-7), 70.2 (CH₂, C-6), 62.2 (CH₂, OHCH₂), 27.1 (2 × CH₃, C(CH₃)₃);

Spectroscopic data are consistent with reported literature.²³⁶
(4R,5R)-4-[(Benzyloxy)methyl]-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (156)

To a stirred solution of alcohol 155 (1.0 g, 3.96 mmol) in carbon tetrachloride (40 mL) was added triphenylphosphine at room temperature before being refluxed for 20 h. The reaction mixture was cooled to room temperature then filtered through a pad of Celite® and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound (1.10 g, quant) as a colourless oil.

\[ [\alpha]_D^{20.5} +1.5 \text{ (c 1.0, CHCl}_3) \text{ [lit.,}^{237} +2.09 \text{ (c 1.05, CHCl}_3)]; \]

**Rr**: 0.4 (1:4 ethyl acetate/hexanes);

**\( ^1H \) NMR** (400 MHz, CDCl\(_3\)): \( \delta \) 7.35-7.27 (5H, m, Ar-H), 4.57 (2H, s, CH\(_2\)OCH\(_2\)Ph), 4.11-4.07 (2H, m, H-4 and H-5), 3.67-3.59 (4H, m, CH\(_2\)OCH\(_2\)Ph and ClCH\(_2\)), 1.43 (6H, s, C(CH\(_3\))\(_2\));

**\( ^{13}C \) NMR** (100 MHz, CDCl\(_3\)): \( \delta \) 137.5 (C\(_q\), Ar-C), 128.5 (2 × CH, Ar-C), 127.7 (CH, Ar-C) 127.7 (2 × CH, Ar-C), 110.1 (C\(_q\), C(CH\(_3\))\(_2\)), 78.2 (CH, C-5), 77.9 (CH, C-4), 73.6 (CH\(_2\), CH\(_2\)OCH\(_2\)Ph), 70.5 (CH\(_2\), ClCH\(_2\)), 44.5 (CH\(_2\), CH\(_2\)OCH\(_2\)Ph), 27.2 (CH\(_3\), C(CH\(_3\))\(_2\)), 27.2 (CH\(_3\), C(CH\(_3\))\(_2\)).

Spectroscopic data are consistent with reported literature.\(^{237}\)
(R)-1-(Benzyloxy)but-3-yn-2-ol (157)

Method A

To a stirred solution of chloride 156 (130 mg, 0.74 mmol) in THF (2 mL) was added n-BuLi (2.50 M in THF, 3.70 mL, 5.94 mmol) and DMPU (8.80 mL, 5.94 mmol) at -30 °C and stirred at room temperature for 16 h. The reaction mixture was quenched with NaHCO$_3$ (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (52.0 mg, 40%) as a yellow oil and recovered starting material (119 mg, 60%).

Method B

To a stirred solution of chloride 156 (200 mg, 0.74 mmol) in THF (2 mL) was added to freshly prepared LDA (i-Pr$_2$NH (0.73 mL, 5.20 mmol) and n-BuLi (2.5 M in THF, 2 mL, 5.0 mmol) in THF (5mL)) at -78 °C and stirred at 2 h then warmed to -40 °C for 1 h. The reaction mixture was quenched with NaHCO$_3$ (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (150 mg, 90%) as a yellow oil.

$[\alpha]_{D}^{20.5} -6.5$ (c 1.0, CHCl$_3$) [lit.,$^87$ -8.54 (c 2.68, CHCl$_3$)];

Rr: 0.2 (1:4 ethyl acetate\hexanes);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35-7.27 (5H, m, Ar-H), 4.61 (2H, ABq, $J = 12.1$ Hz, OCH$_2$Ph), 4.56-4.53 (1H, m, H-2), 3.66-3.62 (1H, m, H-1αb), 3.59-3.55 (1H, m, H-1αb), 2.75 (1H, brs, OH), 2.45 (1H, s, H-4);
\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 137.6 \ (C_q, \text{Ar-C}), \ 128.6 \ (2 \times \text{CH, Ar-C}), \ 128.0 \ (\text{CH, Ar-C}) \]

\[127.9 \ (2 \times \text{CH, Ar-C}), \ 81.8 \ (C_q, \text{C-3}), \ 73.8 \ (\text{CH, C-4}), \ 73.6 \ (\text{CH}_2, \text{OCH}_2\text{Ph}), \ 73.4 \ (\text{CH}_2, \text{C-1}), \ 60.6 \ (\text{CH, C-2}); \]

Spectroscopic data are consistent with reported literature.\(^{87}\)

\[1,2:5,6-\text{Di-O-isopropylidene-D-mannitol (159)}\]

To a stirred solution of D-mannitol (158) (30.0 g, 0.16 mol) in DMSO (56 ml) was added \(p\)-toluenesulfonic acid (282 mg, 1.67 mmol) and 2,2-dimethoxypropane (42.9 mL, 0.41 mol) at room temperature and stirred for 48 h. Sat. aq. NaHCO\(_3\) (50 mL) was added and extracted with ethyl acetate (3 \times 30 mL). The combined organic layers were washed with brine (3 \times 30 mL), dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to afford the \textit{title compound} (38.0 g, 90%).

\[ [\alpha]_{D}^{20.5} +6.5 \ (c \ 1.0, \text{EtOH}) \ [\text{lit.,} \ ^{238} +6.2 \ (c \ 1.00, \text{EtOH})]; \]

\textbf{Rf}: 0.2 (1:4 ethyl acetate\textbackslash hexanes);

\[ ^{1} \text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 4.21-4.15 \ (2\text{H, m, H-2 and H-5}), \ 4.13 \ (2\text{H, dd, } J = 6.3, 8.3 \text{ Hz, H-1ab and H-6ab}), \ 3.99 \ (2\text{H, dd, } J = 5.5, 8.6 \text{ Hz, H-1ab and H-6ab}), \ 3.77 \ (2\text{H, t, } J = 6.5 \text{ Hz, H-3 and H-4}), \ 1.43 \ (6\text{H, s, C(CH}_3)_3), \ 1.36 \ (6\text{H, s, C(CH}_3)_3); \]

\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 109.4 \ (2 \times C_q, \text{C(CH}_3)_3), \ 76.3 \ (2 \times \text{CH, C-2 and C-5}), \ 71.2 \ (2 \times \text{CH, C-3 and C-4}), \ 66.7 \ (2 \times \text{CH}_2, \text{C1 and C-6}), \ 26.7 \ (2 \times \text{CH}_3, \text{C(CH}_3)_3), \ 25.2 \ (2 \times \text{CH}_3, \text{C(CH}_3)_3); \]

Spectroscopic data are consistent with reported literature.\(^{238}\)
Experimental

(R)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (160)

To a stirred solution of acetonide 159 (10.0 g, 18.0 mmol) in dichloromethane (45 mL) was added a solution of sat. aq. NaHCO₃ (4.20 mL). NaIO₄ (5.80 g, 27.2 mmol) was added slowly and the resulting suspension was stirred vigorously for 2 h. Anhydrous MgSO₄ was added and the reaction mixture was filtered. Purification by distillation (bp: 77-80 °C/40 torr) to afford title compound (7.10 g, 75%) as a colourless oil. The aldehyde was unstable and polymerised upon standing.

**Rf:** 0.2 (1:1 ethyl acetate/hexanes);

**¹H NMR** (400 MHz, CDCl₃): δ 9.72 (1H, s, CHO), 4.41-4.36 (1H, m, CHCHO), 4.20-4.08 (2H, m, CH₂O), 1.48 (3H, s, C(CH₃)₃), 1.42 (3H, s, C(CH₃)₃);

**¹³C NMR** (100 MHz, CDCl₃): δ 201.8 (C=O), 111.2 (C₆, C(CH₃)₃), 79.7 (CH, CHCHO), 65.6 (CH₂, CH₂O), 26.2 (CH₃, C(CH₃)₃), 25.1 (CH₃, C(CH₃)₃);

Spectroscopic data are consistent with reported literature.²³⁹
Experimentals

Dimethyl (2-oxopropyl)phosphonate (169)

To a stirred suspension of KI (89.6 g, 0.54 mmol) in acetone/acetonitrile (1:1.25, 225 mL) was added chloroacetone (44 mL, 0.54 mmol). Stirring was continued for 1 h at r.t. before trimethyl phosphite (63.7 mL, 0.54 mmol) was added dropwise. After 12 h at r.t., the mixture was heated to 50 °C to ensure complete conversion. After cooling to room temperature the reaction mixture was filtered through a pad of Celite® and concentrated in vacuo yielding the crude residue. Distillation of the crude residue furnished the phosphonate (89.0 g, 54%) as a colourless liquid.

\textbf{B.p:} 69–70 °C/0.47 mbar (Lit.11b 85–88 °C/0.67 mbar).
Bestmann-Ohira Reagent (168)

\[
\begin{array}{c}
\text{Sulfuryl chloride (16.2 mL, 0.20 mol) was added dropwise to an ice-cooled suspension of NaN}_3 \\
(13.0 g, 0.20 mol) in anhydrous acetonitrile (200 mL) and the mixture was stirred overnight allowing reaction mixture to slowly warm to room temperature. Imidazole (27.2 g, 0.40 mol) was added portion-wise at 0 °C and the slurry was stirred for 5 h. The mixture was diluted by ethyl acetate (400 mL) and 400 mL of water was added. The organic layer was washed with water (2 × 400 mL), sat. NaHCO}_3 solution (2 × 400 mL) and brine (400 mL). The organic layer was separated and dried over Na}_2SO}_4. Purification by flash chromatography using ethyl acetate/hexanes (1:2) as eluent gave the azide (25.0 g, 73 %) as a yellow oil.
\end{array}
\]

Phosphonate 169 (20.0 g, 0.11 mol) in toluene (22 mL) was added to a solution of sodium hyride (17.2 g, 0.11 mol) in toluene/THF (1:1, 100 mL) and stirred at room temperature for 1 h. A solution of azide 357 in toluene (22 mL) was added dropwise and stirred for 3 h. Reaction was then diluted with ethyl acetate (100 mL) and filtered through a pad of Celite®. Purification by flash chromatography using ethyl acetate/hexanes (1:1) as eluent gave the title compound (15.0 g, 77 %) as a yellow oil.

\[1H \text{ NMR (400 MHz, CDCl}_3): \delta 3.81 (6H, d, } J = 11.9 \text{ Hz, OCH}_3), 2.24 (3H, s, CH}_3);\]

\[13C \text{ NMR (100 MHz, CDCl}_3): \delta 190.0 (C=O), 54.0 (2 \times \text{OCH}_3), 27.5 (\text{CH}_3);\]

Spectroscopic data are consistent with reported literature.\textsuperscript{95}
(R)-But-3-yne-1,2-diol (149)

Method A

To a stirred solution of D-glyceraldehyde 160 (3.01 g, 23.1 mmol) and the Bestmann-Ohira reagent 168 (6.60 g, 34.6 mmol) in methanol (40 mL) was cooled to 0 °C. Anhydrous potassium carbonate (6.40 g, 46.1 mmol) was added portion-wise over 30 min and the reaction mixture was stirred for 12 h, allowing it to warm to room temperature. Sat. aq. NH₄Cl (50 mL) was added and the aqueous solution was extracted with diethyl ether (50 mL). Dowex 50W (5.01 g) and methanol (40 mL) were added to the combined organic layers at room temperature and stirred at 35 °C for 40 h. Dowex 50W was filtered off and the filtrate was concentrated in vacuo. Purification by flash chromatography using ethyl acetate\hexanes (3:2) as eluent gave the title compound (1.30 g, 66% over 2 steps) as a colourless solids.

Method B

A stirred solution of triphenylphosphine (40.0 g, 0.15 mol) in dichloromethane was cooled 0 °C and carbon tetrabromide (25.5 g, 0.77 mol) was slowly added over 10 min. The reaction was allowed to warm to room temperature and stirred for 30 min. The solution was re-cooled to 0 °C and before a solution of aldehyde 160 (5.00 g, 38.5 mmol) in dichloromethane (10 mL). Reaction was warmed to room temperature and stirred for 2.5 h. The reaction mixture was then poured onto hexanes (50 ml) and filtered through a pad of Celite®. The solids were washed with diethyl ether (3 × 20 mL) and filterate was concentrated in vacuo to afford crude dibromo 161 (7.20 g, 65%).

To a stirred solution of dibromo 161 (7.20 g, 25.1 mmol) in THF (40 ml) was cooled to -78 °C and was added n-BuLi (2 M in THF, 25.1 mL, 50.2 mmol) before the solution was allowed to warm to room temperature for 1 h. Diethyl ether (50 mL) and water (50 mL) were added and
stirring was continued for 15 min. The aqueous layer was extracted with ether. Dowex 50W (5.0 g) and methanol (40 mL) were added to the combined organic layers at room temperature and stirred at 35 °C for 40 h. Dowex 50W was filtered off and the filtrate was concentrated in vacuo. Purification by flash chromatography using ethyl acetate\hexanes (3:2) as eluent gave the title compound (1.70 g, 80%) as a colourless solid.

\[\alpha\]_D^{20.5} + 20.1 (c 1.0, CHCl_3) [lit.,^100 + 35.5 (c 1.07, CHCl_3)];

M.p: 35.3-37.4 °C (lit.,^100 34-35 °C);

Rf: 0.2 (3:2 ethyl acetate\hexanes);

\textbf{^1H NMR} (400 MHz, CDCl_3): \(\delta\) 4.47 (1H, s, H-2), 3.76-3.68 (2H, m, H-1), 3.02 (1H, brs, OH), 2.67 (1H, brs, OH), 2.51 (1H, d, \(J = 1.8\) Hz, H-4);

\textbf{^13C NMR} (100 MHz, CDCl_3): \(\delta\) 81.7 (C_q, C-3), 74.6 (CH, C-2), 66.4 (CH_2, C-1), 63.1 (CH, C-4);

Spectroscopic data are consistent with reported literature.^100
(R)-But-3-yne-1,2-diyl bis(4-methylbenzenesulfonate) (177)

To a stirred solution of diol 149 (2.00 g, 23.2 mmol) in dichloromethane (60 mL) at 0 °C was added DMAP (562 mg, 4.60 mmol), trimethylamine (9.0 mL, 69.7 mmol) and tosyl chloride (13.1 g, 69.6 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. Water (5 mL) was added and the separated organic layer was washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:1) gave the title compound (5.50 g, 80%) as a colourless oil.

[α]D²⁰.⁵ +40.3 (c 1.0, CHCl₃);

Rf: 0.2 (1:2 ethyl acetate/hexanes);

IR νmax (neat): 3279, 1732, 1597, 1362, 1190, 1174, 981, 998, 900, 811, 765, 663 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.78 (2H, J = 8.4 Hz, Ar-H), 7.74 (2H, d, J = 8.3 Hz, Ar-H), 7.35-7.32 (4H, m, Ar-H), 5.23-5.19 (1H, m, H-2), 4.20-4.12 (2H, m, H-1), 2.49 (1H, s, H-3), 2.46 (6H, brs, CH₃-OTs);

¹³C NMR (100 MHz, CDCl₃): δ 145.5 (2 × C q, Ar-C), 133.1 (C q, Ar-C), 132.3 (C q, Ar-C), 130.1 (2 × CH, Ar-C), 129.9 (2 × CH, Ar-C), 128.3 (2 × CH, Ar-C), 128.2 (2 × CH, Ar-C), 78.5 (CH, C-4), 74.9 (C q, C-3), 68.8 (CH, C-2), 67.5 (CH₂, C-2), 21.8 (CH₃, CH₃-OTs);

(R)-2-[(tert-Butyldimethylsilyl)oxy]but-3-yn-1-ol (185) and (R)-5-Ethynyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (188)

**Method A**

To a stirred solution of diol 149 (100 mg, 1.10 mmol) in dichloromethane (8 mL) at 0 °C was added imidazole (80 mg, 1.10 mmol), tert-butylidemethylsilyl chloride (175 mg, 1.10 mmol) and stirred for 2 h. The reaction mixture was quenched with water (10 mL) and the separated organic layer was washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:2) gave the *title compound* 185 (77.0 mg, 36%) as a colourless oil and *title compound* 188 (43.0 mg, 12%) as a colourless oil.

**Method B**

A stirred solution of diol 149 (110 mg, 1.20 mmol) in methanol (5 mL) was added dibutyltin oxide (318 mg, 1.20 mmol) was refluxed until the solution became clear. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting white solid was dissolved in dichloromethane (10 mL) and *tert*-butylidemethylsilyl chloride (217 mg, 1.40 mmol) was added and the solution was stirred for 24 h. The reaction mixture was quenched with water (10 mL), the organic layer was washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:2) gave the *title compound* 185 (216 mg, 90%) as a colourless oil

\[ [\alpha]_D^{22.4} +15.0 \text{ (c 1.0, CHCl}_3) \text{ [lit.,}^{240}+16.0 \text{ (c 1.1, CHCl}_3)] \]

**Rr**: 0.3 (1:2 ethyl acetate/hexanes);

**IR \( \nu_{\text{max}} \) (neat)**: 3307, 3671, 2942, 2867, 2252, 1463, 1385, 1246, 1104, 1068, 1014, 985, 908, 883, 801, 736, 685, 651 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 4.44-4.39 (1H, m, H-2), 3.81 (1H, dd, J = 10.1, 3.4 Hz, H-1αb), 3.69 (1H, dd, J = 10.6, 6.6 Hz, H-1αb), 2.60 (1H, brd, J = 5.3 Hz, OH), 2.42 (1H, d, J = 2.5 Hz, H-4), 0.91 (9H, s, SiMe₂'Bu), 0.11 (3H, s, SiMe₂'Bu), 0.09 (3H, s, SiMe₂'Bu);
\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 82.0 \ (C_\text{q}, C-3), 73.6 \ (\text{CH}, C-4), 66.9 \ (\text{CH}_2, C-1), 63.1 \ (\text{CH}, C-2), 25.9 \ (3 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}), 18.5 \ (C_\text{q}, \text{SiMe}_2'\text{Bu}), -5.2 \ (2 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}); \]

Spectroscopic data are consistent with reported literature. \cite{240}

\[ [\alpha]^{20.5}_D + 30.2 \ (c 1.0, \text{CHCl}_3); \]

\textbf{Rr}: 0.4 (1:2 ethyl acetate\hexanes);

\textbf{IR} \ \nu_{\text{max}} \ (\text{neat}): 2928, 2254, 1464, 1383, 1077, 905, 730, 650 cm\(^{-1}\);

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 4.40-4.37 \ (1\text{H}, \text{m}, \text{H}-1), 3.67 \ (2\text{H}, \text{dd}, J = 6.6, 1.2 \text{ Hz, H-2}), 2.36 \ (1\text{H}, \text{d}, J = 1.9 \text{ Hz, H-4}), 0.91 \ (9\text{H}, \text{s, SiMe}_2'\text{Bu}), 0.90 \ (9\text{H}, \text{s, SiMe}_2'\text{Bu}), 0.14 \ (3\text{H}, \text{s, SiMe}_2'\text{Bu}), 0.12 \ (3\text{H}, \text{s, SiMe}_2'\text{Bu}), 0.08 \ (3\text{H}, \text{s, SiMe}_2'\text{Bu}), 0.07 \ (3\text{H}, \text{s, SiMe}_2'\text{Bu}); \]

\[ ^{13} \text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 83.7 \ (C_\text{q}, C-3), 72.9 \ (\text{CH}, C-4), 68.1 \ (\text{CH}_2, C-2), 64.7 \ (\text{CH}, C-1), 26.1 \ (3 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}), 25.9 \ (3 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}), 18.6 \ (C_\text{q}, \text{SiMe}_2'\text{Bu}), 18.5 \ (C_\text{q}, \text{SiMe}_2'\text{Bu}), -4.6 \ (2 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}), -4.7 \ (2 \times \text{CH}_3, \text{SiMe}_2'\text{Bu}); \]

\textbf{HRMS}: found [M + Na]\(^+\) 337.1986, [C\(_{16}\)H\(_{34}\)O\(_2\)Si\(_2\) + Na]\(^+\) requires 337.1990.
2-(2-tert-Butyldimethylsiloxethoxy)ethanol (203)

To a stirred solution of tert-butyldimethylsilyl chloride (14.2 g, 0.94 mol) and imidazole (25.6 g, 0.37 mol) in dichloromethane (200 mL) was added diethylene glycol 202 (20.0 g, 0.18 mol) at room temperature and stirred for 16 h. The reaction mixture was quenched with water (100 mL), and the organic layer was separated and washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:3) gave the title compound (130 g, 65% based on TBSCI) as a colourless oil.

Rr: 0.20 (1:2 ethyl acetate\hexanes);

$^1$H NMR (400 MHz, CDCl₃): δ 3.79 (2H, t, $J = 5.4$ Hz, H-2'), 3.72 (2H, brs, H-1), 3.62-3.59 (4H, m, H-2 and H-1'), 2.40 (1H, brs, OH), 0.91 (9H, s, SiMe₂'Bu), 0.08 (6H, s, SiMe₂'Bu);

$^{13}$C NMR (100 MHz, CDCl₃): δ 72.7 (CH₂, C-2), 72.5 (CH₂, C-3), 63.0 (CH₂, C-1), 62.1 (CH₂, C-4), 26.0 (3 × CH₃, SiMe₂'Bu), 18.5 (C₉, SiMe₂'Bu), -5.2 (2 × CH₃, SiMe₂'Bu);

Spectroscopic data are consistent with reported literature.¹⁰⁹
(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)ethanal (201)

Method A

To a stirred solution of oxalyl chloride (0.43 mL, 4.90 mmol) in dichloromethane (6 mL) at -78 °C was added a solution of DMSO (0.71 mL, 9.90 mmol) in dichloromethane (2 mL) and stirred for 30 min. A solution of alcohol 203 (1.00 g, 4.50 mmol) in dichloromethane (3 mL) was added dropwise and stirred for 1 h. Triethylamine (3.10 mL, 22.0 mmol) was then added and stirred at this temperature for 15 min before warming up to room temperature for 1 h. The reaction mixture was quenched with water (10 mL) and the organic layer was separated washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo to afford the title compound (942 mg, 96%) as a pale yellow oil.

Method B

To a stirred solution of alcohol 203 (500 mg, 2.30 mmol) in ethyl acetate (10 mL) was added IBX (1.90 g, 6.80 mmol) and heated to reflux for 2 h. The reaction mixture was cooled to room temperature and filtered through a pad of silica. The filtrate was concentrated in vacuo to afford the title compound (350 mg, 70%)

Rf: 0.60 (1:2 ethyl acetate\hexanes);


Spectroscopic data are consistent with reported literature.¹¹₀
1-{2-[((tert-Butyldimethylsilyl)oxy)ethoxy]but-3-yn-2-ol (204)

A solution of ethynylmagnesium bromide (0.5M in THF, 45.0 mL, 22.9 mmol) was added dropwise to a stirred solution of aldehyde 201 (1.00 g, 4.50 mmol) in THF (5 mL). Ethyl acetate (30 mL) and sat. aq. NH₄Cl (30 mL) were then added and the aqueous layer was separated and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:1) gave the title compound (748 mg, 67 %) as a yellow oil.

Rf: 0.50 (1:1 ethyl acetate\hexanes);

IR νmax (neat): 3407, 3304, 2953, 2929, 2857, 2884, 1737, 1472, 1426, 1389, 1361, 1253, 1100, 1006, 944, 834, 812, 778, 716, 660 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 4.53 (1H, m, H-2), 3.79-3.59 (6H, m, H-1, H-1’ and H-2’), 3.17 (1H brs, OH), 2.44 (1H, d, J = 2.0 Hz, H-4), 0.91 (3 × CH₃, SiMe₂^tBu), 0.08 (2 × CH₃, SiMe₂^tBu);

¹³C NMR (100 MHz, CDCl₃): δ 81.8 (C₁, C-3), 75.0 (CH₂, C-1), 73.7 (CH, C-4), 73.3 (CH₂, C-1’), 63.0 (CH₂, C-2’), 61.8 (CH, C-1’), 26.1 (3 × CH₃, SiMe₂^tBu), 18.5 (C₁, SiMe₂^tBu), -5.2 (2 × CH₃, SiMe₂^tBu);

To a stirred solution of alcohol 204 (200 mg, 0.81 mmol), DMAP (20.0 mg, 0.16 mg), and trimethylamine (0.14 mL, 0.81 mmol) in dichloromethane (30 mL) was added tosyl chloride (203 mg, 1.10 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. Sat. aq. NH₄Cl (30 mL) was added and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (229 mg, 71%) as a colourless oil.

Rf: 0.2 (1:4 ethyl acetate\hexanes);

IR νₘₐₓ(neat): 3304, 2953, 2929, 2857, 2884, 1737, 1472, 1426, 1389, 1361, 1253, 1100, 944, 834, 812, 778, 716, 660 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.83 (2H, d, J = 8.3 Hz, Ar-H), 7.32 (2H, d, J = 8.2 Hz, Ar-H), 5.21-5.17 (1H, m, H-2), 3.76 (2H, dd, J = 2.0, 6.2 Hz, H-1), 3.69 (2H, t, J = 4.7 Hz, H-2'), 3.55 (2H, t, J = 5.2 Hz, H-1'), 2.44 (4H, s, H-1 and TsCH₃), 0.88 (3 × CH₃, s, SiMe₂Bu), 0.05 (2 × CH₃, SiMe₂Bu);

¹³C NMR (100 MHz, CDCl₃): δ 144.9 (Cq, Ar-C), 133.9 (Cq, Ar-C), 129.7 (2 × CH, Ar-C), 128.3 (2 × CH, Ar-C), 77.3 (Cq, C-3), 77.9 (CH, C-2'), 73.3 (CH₂, C-2), 72.9 (CH₂, C-3), 69.9 (CH, C-1'), 62.9 (CH₂, C-4), 26.1 (3 × CH₃, SiMe₂Bu), 21.8 (CH₃, TsCH₃), 18.4 (Cq, SiMe₂Bu), -5.2 (2 × CH₃, SiMe₂Bu);

HRMS: found [M + Na]⁺ 421.1479, [C₁₉H₃₆O₅Si⁺ Na⁺ requires 421.1475.
2-((2-[(4-Methylbenzenesulfonyloxy)but-3-yn-1-yl]oxy)ethan-1-ol (205)

![Chemical structure](image)

To a stirred solution of alkyne 200 (200 mg, 0.44 mmol) in THF (8 mL) was added slowly TBAF(acetic acid (0.5M in THF, 0.44 mL, 0.88 mmol) at 0 °C and stirred for 12 h. Water (10 mL) and ethyl acetate (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated \textit{in vacuo}. Purification by flash chromatography (ethyl acetate\hexanes, 1:1) gave the title compound (94.0 mg, 75%) as a colourless oil.

**Rf**: 0.1 (1:1 ethyl acetate\hexanes);

**IR v_{max} (neat)**: 3532, 3276, 2908, 2126, 1759, 1597, 1453, 1400, 1360, 1308, 1293, 1213, 1190, 1133, 1095, 1065, 1021, 952, 902, 838, 815, 775, 704 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.85 (2H, d, J = 8.3 Hz, Ar-H), 7.35 (2H, d, J = 7.9 Hz, Ar-H), 5.27-5.23 (1H, m, H-2'), 3.76-3.57 (2H, m, H-1'), 3.69-3.55 (4H, m, H-1 and H-2), 2.48 (1H, d, J = 2.1 H-4'), 2.45 (CH₃, s, TsCH₃);

**¹³C NMR** (100 MHz, CDCl₃): δ 145.2 (C₀, Ar-C), 133.8 (C₀, Ar-C), 129.8 (2 × CH, Ar-C), 128.2 (2 × CH, Ar-C), 77.4 (CH, C-4'), 76.6 (CH, C-3'), 73.1 (CH₂, C-1'), 72.5 (CH₂, C-2), 69.7 (CH, C-2'), 61.8 (CH₂, C-1), 21.8 (CH₃, TsCH₃);

1-(2-hydroxyethoxy)but-3-yn-2-ol (206)

To a stirred solution of alcohol 204 (144 mg, 0.59 mmol) in THF (15 mL) was added TBAF (1.0 M, 0.59 mL, 0.59 mmol) at 0 °C and stirred for 5 min. Water (10 mL) and ethyl acetate (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (neat ethyl acetate) gave the title compound (50.0 mg, 65%) as a yellow oil.

Rf: 0.2 (ethyl acetate);

IR νmax (neat): 3307, 3243, 2927, 2892, 2874, 2116, 1473, 1449, 1435, 1351, 1322, 1307, 1260, 1126, 1078, 1058, 1045, 1013, 963, 890, 707, 678 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 4.59-4.55 (1H, m, H-2), 3.78-3.61 (6H, m, H-1, H-1', H-2'); 2.47 (1H, d, J = 2.1 Hz, H-4);

¹³C NMR (100 MHz, CDCl₃): δ 81.8 (C₉, C-3), 74.7 (CH₂, C-1), 74.0 (CH, C-4), 72.9 (CH₂, C-2'), 61.7 (CH₂, C-1'), 61.6 (CH, C-2);

(2-Iodophenyl)methanol (212)

To stirred solution of 2-iodobenzoic acid 211 (5.00 g, 20.2 mmol) in THF (40 mL) at 0 °C and was slowly added borane-dimethylsulfane complex (2.30 mL, 24.1 mmol) over 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with methanol (1.0 mL) and sat. aq. potassium carbonate (30 mL) was added and aqueous layer was separated and extracted with ether (3 × 30 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude residue was recrystallised from ethyl acetate\hexanes to afford *title compound* (4.20 g, 90%) as colourless solid.

**Rf:** 0.50 (1:1 ethyl acetate\hexanes);

**M.p:** 90-92 °C (lit., 90-95 °C²⁴¹);

**IR** ν<sub>max</sub>(neat): 3406, 3286, 2949, 2253, 2119, 1729, 1376, 1239, 1042, 913, 733, 701, 676, 646 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.83 (1H, dd, J = 1.1, 7.9 Hz, H-3), 7.47 (1H, dd, J = 2.1, 7.9 Hz, H-6), 7.39 (1H, td, J = 1.1, 7.5 Hz, H-5), 7.02 (1H, td, J = 1.8, 7.5 Hz, H-4), 4.69 (2H, d, J = 6.3 Hz, H-7), 1.98 (1H, t, J = 6.3 Hz, OH);

**¹³C NMR** (100 MHz, CDCl₃): δ 142.9 (C₆, C-1), 139.4 (CH, C-3), 129.5 (CH, C-6), 128.7 (2 × CH, C-4 and C-5), 97.6 (C₆, C-2), 69.5 (CH₂, C-7);

Spectroscopic data are consistent with reported literature.²⁴¹
1-[(Ethoxymethoxy)methyl]-2-iodobenzene (210)

Method A

To a stirred solution of alcohol 212 (1.00 g, 4.30 mmol) in THF (13 mL) was added N,N-diisopropylethylamine (2.20 mL, 12.8 mmol) and stirred for 10 min at 0 °C. Chloromethyl ethyl ether (0.86 mL, 9.20 mmol) was then added and the mixture was warmed and stirred at room temperature for 18 h. Water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound (250 mg, 20%) as a colourless oil.

Method B

To a stirred solution of alcohol 212 (1.00 g, 4.30 mmol) in DMF (10 mL) at 0 °C was added sodium hydride (154.1 mg, 6.50 mmol) and stirred for 10 min. Chloromethyl ethyl ether (0.86 mL, 9.20 mmol) was added and the mixture was stirred at room temperature for 18 h. Water (10 mL) was added and aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound (1.13 g, 90%) as a colourless oil.

Rf: 0.2 (1:4 ethyl acetate/hexanes);

IR νmax (neat): 2365, 2253, 1038, 906, 730, 695, 686, 679, 669, 660, 650, 640, 632, 625, 620, 614, 605 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.82 (1H, dd, J = 1.4, 8.0 Hz, H-3), 7.46 (1H, dd, J = 1.4, 7.6 Hz, H-6), 7.36 (1H, td, J = 1.4, 7.6 Hz, H-5), 7.00 (1H, td, J = 1.4, 7.6 Hz, H-4), 4.82 (2H, s, H-8), 4.60 (2H, s, H-7), 3.70 (2H, q, J = 7.5 Hz, OCH₂OCH₂CH₃), 1.26 (3H, t, J = 7.1 Hz, OCH₂OCH₂CH₃);
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.6 (C$_q$, C-1) 139.4 (CH, C-3), 129.4 (CH, C-6), 129.1 (CH, C-5), 128.4 (CH, C-4), 98.1 (C$_q$, C-2), 95.0 (CH$_2$, OCH$_2$OCH$_2$CH$_3$), 73.5 (CH$_2$, C-7), 63.8 (CH$_2$, OCH$_2$OCH$_2$CH$_3$), 15.3 (CH$_3$, OCH$_2$OCH$_2$CH$_3$);

HRMS: found [M + Na]$^+$ 314.9852, [C$_{10}$H$_{13}$O$_2$I + Na]$^+$ requires 314.9858.
1-{2-[(tert-Butyldimethylsilyl)oxy]ethoxy}-4-{2-[(ethoxymethoxy)methyl]phenyl}but-3-yn-2-ol (213)

Method A

Iodine 210 (42.0 mg, 0.15 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (1.20 mg, 0.03 mmol) and CuI (0.60 mg, 0.03 mmol) were purged with argon for 1 h. Pre purged trimethylamine/DMF (3 mL, 1:1) was added and stirred at room temperature for 10 min, followed by the addition of alkyne 204 (40 mg, 0.16 mmol) in triethylamine/DMF (0.5 mL, 1:1) and stirred for 16 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (20 mL). The organic layer was washed with sat. aq. NH$_4$Cl (3 × 5 mL), brine (3 × 5 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:1) gave the title compound (18.4 mg, 30%) as a yellow oil.

Method B

Iodine 210 (42.0 mg, 0.15 mmol), Pd(OAc)$_2$ (1.70 mg, 0.01 mmol), X-phos (14.0 mg, 0.03 mmol) and CuI (1.40 mg, 0.01 mmol) were purged with argon for 1 h. Pre purged trimethylamine (3 mL) was added and stirred at room temperature for 10 min, followed by the addition of alkyne 204 (40.0 mg, 0.16 mmol) in triethylamine (0.5 mL) and stirred for 28 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (20 mL). The filterate was washed with sat. aq. NH$_4$Cl (3 × 5 mL), brine (3 × 5 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:1) gave the title compound (30.6 mg, 50%) as a yellow oil.

Method C

Iodine 210 (100 mg, 0.42 mmol), Pd(OAc)$_2$ (5.00 mg, 0.021 mmol), X-phos (19.0 mg, 0.04 mmol), K$_2$CO$_3$ (275.1 mg, 2.05 mmol) in NMP (7 mL) was purged with argon for 1 h. A solution of alkyne 204 (143 mg, 0.49 mmol) in NMP (1 mL) was added and stirred for 18 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (20
The organic layer was washed with sat. aq. NH₄Cl (3 × 5 mL), brine (3 × 5 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography using ethyl acetate/hexanes (1:1) as eluent gave the title compound (106.3 mg, 62%) as a yellow oil.

**Rf:** 0.30 (1:1 ethyl acetate/hexanes);

**IR v_{max}** (neat): 3430, 2928, 2882, 2857, 2229, 1598, 1486, 1471, 1365, 1253, 1189, 1176, 1119, 1097, 1044, 895, 835, 814, 767, 666 cm⁻¹;

**^1H NMR** (400 MHz, CDCl₃): δ 7.42 (2H, t, J = 7.6 Hz, H-3 and H-6), 7.35 (1H, td, J = 1.4, 7.7 Hz, H-4), 7.25 (1H, td, J = 1.5, 7.6 Hz, H-5), 4.79 (2H, s, OCH₂OCH₂CH₃), 4.79-4.77 (1H, m, H-2'), 4.75 (2H, s, CH₂O), 3.82-3.79 (3H, m, C₂H₂), 3.71-3.65 (5H, m, CH₂), 1.26 (3H, t, J = 7.1 Hz, OCH₂OCH₂CH₃), 0.91 (9H, s, SiMe₂Bu), 0.09 (2 × CH₃, SiMe₂Bu);

**^13C NMR** (100 MHz, CDCl₃): δ 140.1 (C₆, C-2), 132.4 (CH, C-6), 128.8 (CH, C-3), 128.0 (CH, C-5), 127.5 (CH, C-4), 121.4 (C₆, C-1), 94.7 (CH₂, OCH₂OCH₂CH₃), 91.5 (C₆, C-3'), 83.3 (C₆, C-4'), 75.2 (CH₂), 73.2 (CH₂), 67.5 (CH₂), 63.6 (CH₂), 63.0 (CH₂), 62.5 (CH, C-2'), 26.0 (3 × CH₃, SiMe₂Bu), 18.5 (C₆, SiMe₂Bu), 15.3 (CH₃, OCH₂OCH₂CH₃), -5.17 (2 × CH₃, SiMe₂Bu);

To a stirred solution of alcohol 213 (500 mg, 1.20 mmol) in dichloromethane (70 mL) at 0 °C was added DMAP (29.0 mg, 0.24 mmol), trimethylamine (0.17 mL, 1.40 mmol) and tosyl chloride (266 mg, 1.10 mmol). The reaction mixture was warmed to room temperature and stirred for 18 h. Sat. aq. NH₄Cl (40 mL) was added and the aqueous layer was separated and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:2) gave the title compound (451 mg, 67%) as a colourless oil.

**Rr:** 0.3 (1:2 ethyl acetate/hexanes);

**IR vₘₐₓ** (neat): 2929, 2858, 2251, 1468, 1255, 1103, 1045, 907, 733 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.85 (2H, d, J = 8.4 Hz, Ts-H), 7.44 (1H, d, J = 7.2 Hz, H-6), 7.35 (1H, td, J = 2.0, 6.9 Hz, H-3), 7.27 (2H, d, J = 8.1 Hz, Ts-H), 7.19-7.17 (2H, m, H-4 and H-5), 5.36 (1H, dd, J = 4.4, 6.1 Hz, H-2'), 4.76 (2H, s, OC₃H₂OCH₂CH₃), 4.57 (2H, s, H-7), 3.85 (2H, dd, J = 4.4, 6.4, H-1'), 3.73 (2H, t, J = 4.8 Hz, H-2''), 3.67 (2H, q, J = 6.9 Hz, OC₃H₂OC₂H₃), 2.33 (3H, s, Ts-C₃H₃), 1.25 (3H, t, J = 6.9 Hz, OCH₂OCH₂CH₃), 0.89 (9H, s, SiMe₂'Bu), 0.06 (2 × CH₃, SiMe₂'Bu);

**¹³C NMR** (100 MHz, CDCl₃): δ 144.9 (C₉, C-2), 140.5 (C₉, Ts-C), 134.4 (C₉, Ts-C), 132.6 (CH, C-3), 129.7 (2 × CH, Ts-C), 129.4 (CH, C-6), 128.3 (2 × CH, Ts-C), 127.7 (CH, C-5), 127.3 (CH, C-4), 120.1 (C₉, C-1), 95.1 (CH₂, C-7), 86.6 (C₉, C-3'), 86.4 (C₉, C-4'), 73.4 (CH₂, C-1'), 73.1 (CH₂, C-2'), 71.2 (CH, C-2'), 67.4 (CH₂, OCH₂OCH₂CH₃), 63.6 (CH₂, C-1'), 62.9 (CH₂, OCH₂OCH₂CH₃), 26.1 (3 × SiMe₂'Bu), 21.7 (CH₃, Ts-CH₃), 18.5 (C₉, SiMe₂'Bu), 15.3 (CH₃, OCH₂OCH₂CH₃), -5.2 (2 × SiMe₂'Bu);

**HRMS:** mass not found.
**Experimentals**

2-(2-[2-[(Ethoxymethoxy)methyl]phenyl]ethynyl)-1,4-dioxane (214)

![Chemical structure](image)

To a stirred solution of tosylate 209 (230 mg, 0.41 mmol) in THF (5 mL) at 0 °C was added TBAF (1.0 M in THF, 0.61 mL, 0.61 mmol). The reaction mixture was heated to 50 °C and stirred for 6 h. The reaction mixture was cooled to room temperature and sat. aq. NH₄Cl (40 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:8) gave the title compound (85.0 mg, 75%) as a colourless oil.

**Rf:** 0.25 (1:8 ethyl acetate-toluene);

**IR v_max (neat):** 2254, 1465, 1381, 1096, 1045, 904, 727 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.47 (2H, d, J = 7.1 Hz, H-3 and H-6), 7.36 (1H, t, J= 8.1 Hz, H-5), 7.26 (1H, t, J = 7.7 Hz, H-4), 4.81 (2H, s, OCH₂OCH₂CH₃), 4.75 (2H, s, H-13), 4.61 (1H, dd, J = 3.0, 8.6 Hz, H-9), 3.95 (2H, m, H-10), 3.74-3.64 (6H, m, H-11, H-12, OCH₂OCH₂CH₃), 1.28 (3H, t, J = 6.7 Hz, OCH₂OCH₂CH₃);

**¹³C NMR** (100 MHz, CDCl₃): δ 140.3 (C₆, C-2), 132.7 (CH, C-6), 129.1 (CH, C-3), 127.8 (CH, C-5), 127.5 (CH, C-4), 120.9 (C₆, C-1), 95.1 (CH₂, OCH₂OCH₂CH₃), 89.1 (C₆, C-8), 84.3 (C₆, C-7), 70.6 (CH₂, C-10), 67.7 (CH₂, C-13), 66.62 (CH₂, C-11), 66.60 (CH, C-9), 65.8 (CH₂, C-12), 63.6 (CH₂, OCH₂OCH₂CH₃), 15.3 (CH₃, OCH₂OCH₂CH₃);

**HRMS:** found [M + Na]⁺ 299.1254, [C₁₆H₂₀O₄+ Na]⁺ requires 299.1254.
2-(2-[(Ethoxymethoxy)methyl]phenyl)ethyl)-1,4-dioxane (228)

To a stirred solution of alkyne 214 (75.0 mg, 0.30 mmol) in ethyl acetate (15 mL) was added Pd/C (30.0 mg) and then the reaction mixture was placed under an atmosphere of H₂ (1 atm) and stirred for 1 h. The reaction mixture was filtered through a pad of silica and concentrated in vacuo to afford the title compound (75.0 mg, 90%), which was used in the next step without further purification.

Rf: 0.25 (1:8 ethyl acetate-toluene);

IR v_max (neat): 2907, 2250, 1569, 1489, 1378, 1314, 1264, 115, 1037, 905, 728, 649 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.36 (1H, d, J = 7.1 Hz, Ar-H), 7.27-7.17 (3H, m, Ar-H), 4.76 (2H, s, OCH₂OCH₂CH₃), 4.63 (2H, s, H-13), 3.79-3.33 (8H, m, H-9 and 4 × CH₂), 3.32 (1H, td, J = 10.1 Hz, CH₂), 2.90-2.82 (1H, m, CH₂), 2.74-2.66 (1H, m, CH₂), 1.75-1.58 (2H, m, CH₂), 1.26 (3H, t, J = 6.3 Hz, OCH₂OCH₂CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 140.6 (C₄, C-2), 135.7 (C₄, C-1), 129.6 (CH, C-3), 129.5 (CH, C-6), 128.3 (CH, C-5), 126.3 (CH, C-4), 94.6 (CH₂, OCH₂OCH₂CH₃), 74.9 (CH, C-9), 71.4 (CH₂), 67.3 (CH₂), 66.9 (CH₂), 66.7 (CH₂), 63.6 (CH₂), 33.1 (CH₂), 27.8 (CH₂), 15.4 (CH₃, OCH₂OCH₂CH₃);

(2-(2-(1,4-dioxan-2-yl)ethyl)phenyl)methanol (226)

To a stirred solution of dioxane 228 (100 mg, 0.36 mmol) in methanol (20 mL) was added p-toluenesulfonic acid (13.7 mg, 0.072 mmol) and heated to 55 °C for 5 h. The reaction mixture was cooled to room temperature and sat. aq. NaHCO₃ (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave the title compound (60.0 mg, 75%) as a colourless oil.

Rf: 0.25 (1:1 ethyl acetate/hexanes);

IR ν max (neat): 3403, 2955, 2913, 2853, 1489, 1450, 1361, 1275, 1113, 1075, 1008, 896, 873, 753 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.36 (1H, d, J = 7.1 Hz, Ar-H), 7.26-7.19 (3H, m, Ar-H), 4.73-4.69 (2H, m, H₁₃), 3.81-3.53 (6H, m, CH₂), 3.33 (1H, m, CH₂), 2.91-2.84 (1H, m, CH₂), 2.80-2.72 (1H, m, CH₂), 2.04 (1H, t, J = 6.1 Hz, H-9), 1.78-1.61 (2H, m, CH₂);

¹³C NMR (100 MHz, CDCl₃): δ 140.1 (Cq, C-2), 138.7 (Cq, C-1), 129.5 (CH, C-3), 129.0 (CH, C-6), 128.3 (CH, C-5), 126.6 (CH, C-4), 74.6 (CH, C-9), 71.4 (CH₂), 66.8 (CH₂), 66.6 (CH₂), 63.5 (CH₂), 32.9 (CH₂), 27.4 (CH₂);

4,5-Dihydro-1H-spiro[2-benzoexepine-3,2'-[1,4]dioxane] (227) and 2-(2-(1,4-dioxan-2-yl)ethyl)benzaldehyde (229)

To a stirred solution of alcohol 226 (18.0 mg, 0.08 mmol) in cyclohexane (4 mL) was added iodine (41.0 mg, 0.16 mmol) and iodobenzene diacetate (52.0 mg, 0.16 mmol) and stirred at room temperature for 2 h. Sat. aq. Na$_2$S$_2$O$_3$ (4 mL) and ethyl acetate (5 mL) was added. The organic layer was separated and washed with brine (3 × 5 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave a mixture of title compound 227 (7.00 mg, 40%) as a yellow oil and title compound 229 (7.20 mg, 41%) as a yellow oil.

Rr: 0.20 (1:19 ethyl acetate\hexanes);

IR $\nu_{\text{max}}$ (neat): 2924, 2850, 1717, 1451, 1276, 1235, 1148, 1117, 1089, 1066, 1032, 1018, 946, 878, 840, 823, 759, 723 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.22-7.13 (4H, m, Ar-H), 5.19 (1H, d, $J = 13.6$ Hz, H-1a$b$), 4.40 (1H, d, $J = 13.6$ Hz, H-1a$b$), 4.17 (1H, td, $J = 2.9, 11.4$ Hz, CH$_2$), 3.84-3.57 (4H, m, CH$_2$ and CH), 3.38-3.31 (2H, m, CH$_2$), 2.64 (1H, ddd, $J = 1.9, 8.0, 15.1$ Hz, CH$_2$), 1.95 (1H, ddd, $J = 1.9, 8.0, 14.5$ Hz, CH$_2$), 1.64 (1H, dt, $J = 1.7, 14.0$ Hz, CH$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 141.9 (C$_q$, C-2), 139.5 (C$_q$, C-3), 128.9 (CH, Ar-C), 128.3 (CH, Ar-C), 128.0 (CH, Ar-C), 126.4 (Ar-C), 96.4 (C$_q$, C-6), 73.0 (CH), 66.2 (CH$_2$), 63.7 (CH$_2$, C-1), 60.0 (CH$_2$), 34.8 (CH$_2$), 28.0 (CH$_2$);

**Experimentals**

**Rf:** 0.25 (1:19 ethyl acetate/hexanes);

**IR** $\nu_{\text{max}}$ (neat): 2959, 2918, 2851, 1765, 1599, 1573, 1450, 1285, 1198, 1116, 1018, 1003, 954, 897, 875, 802, 752 cm$^{-1}$;

**$^1$H NMR** (400 MHz, CDCl$_3$): 10.26 (1H, s, H-1), 7.83 (1H, dd, $J = 7.4$, 1.5 Hz, Ar-H), 7.51 (1H, td, $J = 7.1$, 1.8 Hz, Ar-H), 7.41 (1H, td, $J = 7.5$, 1.1 Hz, Ar-H), 7.30 (1H, d, $J = 7.70$, Ar-H), 3.81-3.50 (6H, m, CH$_2$ and H-6), 3.38-3.29 (1H, m, CH$_2$), 3.18-3.06 (2H, m, CH$_2$), 1.74-1.60 (2H, m, CH$_2$);

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 192.7 (C-1), 144.6 (C$_q$, Ar-C), 134.0 (CH, Ar-C), 132.5 (CH, Ar-C), 131.3 (CH, Ar-C), 129.2 (C$_q$, Ar-C), 126.9 (Ar-C), 74.5 (CH, C-6), 71.3 (CH$_2$), 66.9 (CH$_2$), 66.7 (CH$_2$), 33.6 (CH$_2$), 28.1 (CH$_2$);

**HRMS:** found [M + Na]$^+$ 243.0992, [C$_{13}$H$_{16}$O$_6$+ Na]$^+$ requires 243.0996.
(Z)-(2-(2-(1,4-dioxan-2-yl)vinyl)phenyl)methanol (208)

To a stirred solution of alkyne 214 (100 mg, 0.36 mmol) in ethyl acetate (10 mL) was added quinoline (90.0 μL, 0.09 mmol), Lindlar’s catalyst (30 mg). The reaction mixture was then placed under an atmosphere of hydrogen (1 atm) and stirred at room temperature for 1 h. The reaction mixture was then filtered through a plug of Celite® and the filtrate was concentrated in vacuo to afford crude alkene (100 mg, quant) as a yellow oil which was subjected to the next step immediately.

To a stirred solution of alkene 212 (50.0 mg, 0.18 mmol) in methanol-ethanol (1:1, 10 mL) was added p-toluenesulfonic acid (11.0 mg, 0.05 mmol) and heated to 50 °C for 14 h. The reaction mixture was cooled to room temperature and sat. aq. NaHCO₃ (5 mL) was added and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 × 5 mL), brine (3 × 5 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound (41.0 mg, quant.) as a yellow oil.

Rᵣ: 0.25 (1:4 ethyl acetate/hexanes);

IR ν_max (neat): 3407, 2880, 2252, 1458, 1116, 907, 732, 650, 608 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): 7.44 (1H, d, J = 7.0 Hz, Ar-H), 7.34-7.26 (2H, m, Ar-H), 7.20 (1H, d, J = 7.4 Hz, Ar-H), 6.88 (1H, d, J = 11.5 Hz, H-7), 5.71 (1H, dd, J = 11.5, 8.9 Hz, H-8), 4.67 (2H, ABq, J =13.4 Hz, H-13), 4.20 (1H, td, J = 9.6, 2.4 Hz, H-9), 3.75-3.59 (5H, m, CH₂), 3.47 (1H, t, J = 10.8 Hz, CH₂), 2.16 (1H, brs, OH);

¹³C NMR (100 MHz, CDCl₃): δ 138.8 (C₉, Ar-C), 135.2 (C₉, Ar-C), 133.2 (CH, C-7), 129.1 (CH, Ar-C), 129.0 (CH, Ar-C), 128.4 (CH, Ar-C), 128.2 (CH, Ar-C), 127.9 (CH, C-8), 72.1 (CH, C-9), 70.3 (CH₂), 66.3 (CH₂), 66.2 (CH₂), 63.4 (CH₂);

**1H-spiro[2-benzoxepine-3,2’-[1,4]dioxane] (207)**

To a stirred solution of dioxane 227 (40.0 mg, 0.18 mmol) in toluene (2 mL) was added activated MnO$_2$ (200 mg, 3.6 mmol) and refluxed for 48 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated. Purification by flash chromatography using ethyl acetate\hexanes (1:19) as eluent gave the title compound (2.00 mg, 5%) as a colourless oil.

**Rr:** 0.25 (1:4 ethyl acetate\hexanes);

**IR** $\nu_{\text{max}}$ (neat): 2919, 2852, 1460, 1377, 1258, 1066, 1010, 786 cm$^{-1}$;

**$^1$H NMR** (400 MHz, CDCl$_3$): 7.33-7.31 (2H, m, Ar-H), 7.27-7.25 (2H, m, Ar-H), 6.68 (1H, d, $J = 12.4$ Hz, H-4), 5.75 (1H, d, $J = 12.5$, H-3), 4.90 (1H, d, $J = 13.2$ Hz, H-1gb), 4.59 (1H, d, $J = 13.2$ Hz, H-1ab), 4.26 (1H, td, $J = 11.7$, 3.4 Hz, CH$_2$), 3.79 (1H, dd, $J = 11.7$, 3.3 Hz, CH$_2$), 3.71 (1H, dd, $J = 11.5$, 2.7 Hz, CH$_2$), 3.63-3.54 (3H, m, CH$_2$);

**$^{13}$C NMR** (80 MHz, CDCl$_3$): $\delta$ 132.8 (CH), 131.0 (CH, Ar-C), 130.3 (CH, Ar-C), 127.99, 127.96 (CH, Ar-C), 127.6 (C$_q$, Ar-C), 127.5 (CH), 126.4 (C$_q$, Ar-C), 109.5 (C$_q$, C-2), 72.0 (CH$_2$), 66.0 (CH$_2$), 65.4 (CH$_2$), 59.2 (CH$_2$);

**HRMS:** found [M + Na]$^+$ 241.0839, [C$_{13}$H$_{14}$O$_3$+ Na]$^+$ requires 241.0835.
Iodine 212 (1.00 g, 4.3 mmol), Pd(PPh₃)₂Cl₂ (270 mg, 0.38 mmol), and CuI (114 mg, 0.59 mmol) was purged with argon for 1 h. Pre purged trimethylamine (7 mL) was then added and the mixture was stirred at room temperature for 10 min, followed by the addition of ethynyltrimethylsilane (0.90 mL, 6.40 mmol) and stirred for 15 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (30 mL). The organic layer was washed with sat. aq. NH₄Cl (3 × 10 mL), brine (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\|hexanes, 2:3) gave the title compound (837 mg, 95%) as a yellow oil.

Rf: 0.30 (2:3 ethyl acetate\|hexanes);

¹H NMR (400 MHz, CDCl₃): δ 7.47 (1 H, d, J = 7.5 Hz, H-3) 7.42 (1 H, d, J = 7.5 Hz, H-5), 7.33 (1 H, td, J = 7.1, 1.1 Hz, H-6), 7.23 (1 H, td, J = 7.4, 1.5 Hz, H-4), 4.82 (2 H, s, CH₂OH), 2.70 (1H, brs, OH), 0.29 (9H, s, SiMe₃);

¹³C NMR (100 MHz, CDCl₃): δ 143.8 (Cq, C-1), 132.6 (CH, C-3), 129.2 (CH, C-5), 127.9 (CH, C-6), 127.8 (CH, C-4), 121.2 (Cq, C-2), 102.3 (Cq, C-8), 99.9 (Cq, C-7), 63.9 (CH₂, CH₂OH), 0.03 (CH₃, SiMe₃);

Spectroscopic data consistent with literature.²⁴²,²⁴³
**Experimentals**

(2-Ethynylphenyl)methanol (259)

![](image)

To a solution of alkyne 258 (871 mg, 4.27 mmol) in methanol (30 mL) was added K$_2$CO$_3$ (236 mg, 1.7 mmol) and stirred at room temperature for 1.5 h. The reaction was diluted with brine (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:20) gave the *title compound* (507 mg, 90%) as an orange solid.

**M.p.:** 63.1-65.2 °C (lit.,$^{244}$ 59-61 °C);

**Rf:** 0.20 (1:4 ethyl acetate/hexanes);

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.51 (1 H, dd, $J = 7.5, 1.1$ Hz, H-3) 7.44 (1 H, d, $J = 7.7$ Hz, H-5), 7.37 (1 H, td, $J = 7.4, 1.2$ Hz, H-6), 7.28 (1 H, td, $J = 7.8, 1.5$ Hz, H-4), 4.84 (2 H, s, CH$_2$OH), 3.34 (1H, s, H-8), 2.09 (1H, brs, OH);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.5 (C$_q$, C-1), 133.1 (CH, C-3), 129.5 (CH, C-5), 127.6 (CH, C-6), 127.5 (CH, C-4), 120.4 (C$_q$, C-2), 81.9 (C$_q$, C-7), 82.2 (CH, C-8), 63.9 (CH$_2$, CH$_2$OH);

Spectroscopic data consistent with literature.$^{244}$
tert-Butyl((2-ethynylbenzyl)oxy)diphenylsilane (260)

To a stirred solution of alcohol 259 (500 mg, 3.80 mmol) in dichloromethane (40 mL) was added 4-dimethylaminopyridine (46.4 mg, 0.38 mmol), imidazole (519 mg, 7.56 mmol) and stirred at room temperature for 10 min. tert-Butyldiphenylchlorosilane (1.20 mL, 4.50 mmol) was added and stirred at this temperature for 16 h. Water (30 mL) was added and layers separated. The organic layer was washed with brine (3 × 30 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography using ethyl acetate\hexanes (1:1) as eluent gave the title compound (1.30 g, 90%) as an orange oil.

Rf: 0.20 (1:1 ethyl acetate\hexanes);

IR ν max (neat): 3287, 2857, 1110, 1007, 1072, 998, 821, 759, 738, 699, 505 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.73-7.69 (5H, m, Ar-H), 7.45-7.36 (9H, m Ar-H), 7.23 (1H, t, J = 7.8 Hz, Ar-H), 4.96 (2H, s, CH₂OH), 3.14 (1H, s, H-8), 1.12 (9H, s, SiMe₃);

¹³C NMR (100 MHz, CDCl₃): δ 143.6 (Cq, C-1), 135.7 (4 × CH, Ar-C), 133.6 (2 × Cq, Ar-C) 132.5 (CH, Ar-C), 129.8 (2 × CH, Ar-C), 129.2 (CH, Ar-C), 127.9 (4 × CH, Ar-C), 126.6 (CH, Ar-C), 126.0 (CH, Ar-C), 119.1 (Cq, C-2), 82.2 (CH, C-8), 81.0 (Cq, C-7), 64.0 (CH₂, CH₂OSi), 27.0 (3 × CH₃, SiPh₂Bu), 19.5 (Cq, SiPh₂Bu);

Methyl (S)-2-[(tert-butyldimethylsilyl)oxy]propanoate (263a)

To a stirred solution of (S)-ester 261a (10.0 g, 96.1 mmol) in dichloromethane (500 mL) at room temperature was added DMAP (585 mg, 4.80 mmol), imidazole (9.80 g, 144 mmol) and tert-butyldimethylsilyl chloride (21.7 g, 144 mmol). The mixture stirred for 16 h at this temperature. Sat. aq. NH₄Cl (100 mL) was added and the aqueous layer was separated, and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (3 × 100 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:9) gave the *title compound* (21.0 g, quant) as a colourless oil.

\[ [\alpha]_{D}^{20} = 25.0 \text{ (c 1.00, CHCl}_3), \text{[lit.,}^{245} = 26.9 \text{ (c 1.06, CHCl}_3)\];

\[ \text{Rr: 0.30 (1:9 ethyl acetate/hexanes)}; \]

\[ \text{IR } \nu_{\text{max}} \text{ (neat): 2953, 2930, 2857, 2887, 1759, 1741, 1463, 1253, 1146, 1062, 1004, 836, 778}; \]

\[ ^1\text{H NMR (400 MHz, CDCl}_3): \delta 4.27 \text{ (1H, q, J = 6.5 Hz, H-2), 3.62 (3H, s, OCH}_3), 1.29 \text{ (3H, d, J = 6.8, H-3), 0.81 (9H, s, SiMe}_2\text{Bu), 0.09 (3H, s, SiMe}_2\text{Bu), 0.07 (3H, s, SiMe}_2\text{Bu});} \]

\[ ^13\text{C NMR (125 MHz, CDCl}_3): \delta 174.8 \text{ (C=O), 68.2 (CH, C-2), 25.8 (2 × CH}_3, \text{SiMe}_2\text{Bu), 21.3 (CH}_3, \text{C-3), 18.3 (C}_q, \text{SiMe}_2\text{Bu), -4.5 (CH}_3, \text{SiMe}_2\text{Bu), -4.8 (CH}_3, \text{SiMe}_2\text{Bu).} \]

Spectroscopic data are consistent with reported literature.\(^{245}\)

Methyl (R)-2-[(tert-butyldimethylsilyl)oxy]propanoate (263b)

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Using the same procedure described above for 261b gave the title compound (21.0 g, quant) as a colourless oil. All spectroscopic data were in agreement to those previously described for 263a.

\[
\left[\alpha\right]^{20}_D + 26.0 \text{ (c 1.00, CHCl}_3\text{), [lit.,}^{245} + 26.9 \text{ (c 1.06, CHCl}_3\text{)}];
\]

(S)-2-[(tert-Butyldimethylsilyl)oxy]-\(N\)-methoxy-\(N\)-methylpropanamide (264a)

To a stirred solution of (S)-ester 263a (2.00 g, 9.20 mmol) in anhydrous THF (80 mL) was added \(N,O\)-dimethylhydroxylamine hydrochloride (1.70 g, 18.3 mmol). The solution was cooled to 0 °C and \(i\)-PrMgCl (18.3 mL, 2.0 M in THF, 36.7 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 2 h, then quenched with saturated aqueous \(\text{NH}_4\text{Cl}\) (40 mL). Ethyl acetate (50 mL) was then added and the mixture was stirred for 30 minutes. The aqueous layer was separated and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (3 x 50 mL), dried (\(\text{MgSO}_4\)), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\(\times\)hexanes, 1:4) gave the title compound (2.24 g, 99 %) as a colourless oil.

\[
\left[\alpha\right]^{20}_D -20.9 \text{ (c 1.00, CHCl}_3\text{)[lit., -23.9 (c 1.1, CHCl}_3\text{)];}
\]

\textbf{Rr:} 0.20 (ethyl acetate\(\times\)hexanes 1:4)

\textbf{IR} \(\nu\text{max (neat):} 2930, 1682, 1462, 1387, 1250, 1153, 1103, 1054, 986, 813, 776, 611, 509, 505;\)

\emph{\textbf{\textsuperscript{1}H NMR}} (400 MHz, CDCl\(_3\)): \(\delta 4.67 \text{ (1H, br s, H-2), 3.70 \text{ (3H, s, OCH}_3\text{), 3.20 \text{ (3H, s, NCH}_3\text{),}}\) 1.35 (3H, d, \(J = 6.6 \text{ Hz, H-3}), 0.89 \text{ (9H, s, SiMe}_2^\text{tBu}), 0.09 \text{ (3H, s, SiMe}_2^\text{tBu}), 0.06 \text{ (3H, s, SiMe}_2^\text{tBu});\)

\emph{\textbf{\textsuperscript{13}C NMR}} (100 MHz, CDCl\(_3\)): \(\delta 174.7 \text{ (C=O), 68.4 \text{ (CH, C-2) 61.3 \text{ (CH}_3\text{, OCH}_3\text{), 51.8 \text{ (CH}_3\text{, NCH}_3\text{), 25.8 \text{ (CH}_3\text{, SiMe}_2^\text{tBu), 21.5 \text{ (CH}_3\text{, C-3,}} 18.4 \text{ (C_q, SiMe}_2^\text{tBu), -4.6 \text{ (CH}_3\text{, SiMe}_2^\text{tBu), -4.9 \text{ (CH}_3\text{, SiMe}_2^\text{tBu).}}\)

Spectroscopic data are consistent with reported literature.\(^{149}\)
\((R)\)-2-[(tert-Butyldimethylsilyl)oxy]-N-methoxy-N-methylpropanamide (264b)

Using the same procedure described above for 263b gave the title compound (2.24 g, 99 %) as a colourless oil. All spectroscopic data were in agreement to those previously described for 264a.

\([\alpha]_{D}^{20} +25.0 \text{ (c 1.00, CHCl}_3\)
Experimental

(S)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[[tert-butyldiphenylsilyl]oxy]methyl)phenyl)pent-1-yn-3-one (265)

Method A

To a stirred solution of alkyne 260 (424 mg, 1.20 mmol) in anhydrous THF (15 mL) at -78 °C was added n-BuLi (1.6 M in THF, 1.1 mL, 1.80 mmol) and stirred at this temperature for 1 h. A solution of Weinreb amide 264b (283 mg, 1.20 mmol) in anhydrous THF (3 mL) was then added dropwise and the mixture was warmed to 0 °C and stirred at this temperature for 1 h. Sat. aq. NH₄Cl (10 mL) was then added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NH₄Cl (3 × 10 mL), brine (3 × 10 mL), dried (NaSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (400 mg, 60%) as a yellow oil.

Method B

To a stirred solution of alkyne 260 (424 mg, 1.20 mmol) in anhydrous THF (15 mL) at -78 °C was added LiHDMS (1.0 M in THF, 1.8 mL, 1.80 mmol) and stirred at this temperature for 1 h. A solution of Weinreb amide 264b (283 mg, 1.20 mmol) in anhydrous THF (3 mL) was then added dropwise and the mixture was warmed to 0 °C and stirred at this temperature for 1 h. Sat. aq. NH₄Cl (10 mL) was then added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NH₄Cl (3 × 10 mL), brine (3 × 10 mL), dried (NaSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (467 mg, 70%) as a yellow oil.

[α]D²⁰ -18.9 (c 1.0, CHCl₃);

Rr: 0.15 (1:9 ethyl acetate/hexanes);
**Experimentals**

**IR** $\nu_{\text{max}}$ (neat): 2955, 2930, 2857, 2194, 1677, 1111, 1072, 941, 828, 778, 739, 730, 701, 671 cm$^{-1}$.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.75 (1H, d, $J = 7.9$ Hz, Ar-H), 7.68-7.66 (4H, m, Ar-H), 7.41-7.34 (6H, m, Ar-H), 7.29 (2H, d, $J = 7.7$ Hz, Ar-H), 4.96 (2H, s, CH$_2$OH), 4.22 (1H, q, $J = 6.6$ Hz, H-4'), 1.26 (3H, d, $J = 7.2$ Hz, H-5'), 1.12 (9H, s, SiMe$_2$Bu) 0.86 (9H, s, SiPh$_2$Bu), 0.04 (3H, s, SiMe$_2$Bu), 0.02 (3H, s, SiMe$_2$Bu);

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 189.6 (C=O), 144.8 (C$_q$, C-2), 135.6 (4 × CH, SiPh$_2$Bu), 133.4 (CH, Ar-C), 133.3 (C$_q$, Ar-C), 131.1 (CH, Ar-C), 129.9 (2 × CH, Ar-C), 127.9 (4 × CH, SiPh$_2$Bu), 127.0 (CH, Ar-C), 126.4 (CH, Ar-C), 117.1 (C$_q$, Ar-C), 110.1 (C$_q$, Ar-C), 91.2 (C$_q$, C-1'), 90.8 (C$_q$, C-2'), 75.4 (CH, C-4'), 63.9 (CH$_2$, CH$_2$Si), 27.0 (3 × CH$_3$, SiPh$_2$Bu), 25.9 (3 × SiMe$_2$Bu), 20.6 (CH$_3$, C-5'), 19.5 (C$_q$, SiPh$_2$Bu), 18.4 (C$_q$, SiMe$_2$Bu), -4.6 (CH$_3$, SiMe$_2$Bu), -4.9 (CH$_3$, SiMe$_2$Bu);

**HRMS**: found [M + Na]$^+$ 579.2720, [C$_{25}$H$_{26}$O$_3$Si Na]$^+$ requires 579.2721.
(S)-5-(2-[[tert-Butyldiphenylsilyl]oxy]methyl)phenyl)-3,3-dimethoxypent-4-yn-2-ol (266)

To a stirred solution of ketone 265 (20.0 mg, 0.035 mmol) in methanol (5 mL) was added trimethylorthoformate (4.00 μL, 0.04 mmol) and p-toluenesulfonic acid (3.00 mg, 0.015 mmol) and the mixture was stirred for 16 h. Sat. aq. NaHCO₃ (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (3 × 10 mL), brine (3 × 10 mL), dried (NaSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (10.2 mg, 60%) as a yellow oil.

Rf: 0.20 (1:19 ethyl acetate/hexanes);

IR ν_{max} (neat): 3452, 2928, 2855, 1668, 1462, 1428, 1258, 1109, 1081, 840, 755, 701 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.75-7.66 (5H, m, Ar-H), 7.45-7.32 (8H, m, Ar-H), 7.24 (1H, t, J = 8.1 Hz, Ar-H), 4.93 (2H, s, CH₂OTBDPS), 3.38 (1H, q, J = 6.5 Hz, H-5'), 3.29 (3H, s, OCH₃), 3.25 (3H, s, OCH₃); 2.06 (1H, brs, OH), 1.16 (3H, d, J = 6.6 Hz, H-6'), 1.12 (9H, s, SiPh₂Bu);

¹³C NMR (100 MHz, CDCl₃): δ 143.5 (C₉, Ar-C), 135.7 (4 × CH, SiPh₂Bu), 132.2 (CH, Ar-C), 129.9 (2 × CH, Ar-C), 129.5 (CH, Ar-C), 128.9 (C₉, Ar-C), 127.9 (4 × CH, SiPh₂Bu), 126.7 (CH, Ar-C), 125.8 (CH, Ar-C), 121.1 (C₉, Ar-C), 119.9 (C₉, Ar-C), 102.2 (C₉, C-3'), 87.6 (C₉, C-2'), 85.6 (C₉, C-4'), 70.2 (CH, C-5'), 64.3 (CH₂, CH₂OSi), 51.9 (CH₃, OCH₃), 51.8 (CH₃, OCH₃), 27.0 (3 × CH₃, SiPh₂Bu), 19.5 (C₉, SiPh₂Bu), 17.2 (CH₃, C-6');

(S)-1-(2-[(tert-Butyldiphenylsilyl)oxy]methyl)phenyl)-4-hydroxypentan-3-one (267)

To a stirred solution of alkyne 265 (500 mg, 0.89 mmol) in ethyl acetate (50 mL) was added Pd/C (50 mg) and then the reaction was placed under an atmosphere of hydrogen and stirred at room temperature for 1 h. The reaction mixture was then filtered through a plug of Celite® and the filtrate was concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound (448 mg, 90%) as colourless oil

\[ \alpha \] \text{D}^22 \cdot 20.2 (c 1.0, CHCl₃);

Rf: 0.25 (1:19 ethyl acetate\hexanes);

IR \nu\text{max} (neat): 2955, 2930, 2857, 2890, 1718, 1462, 1428, 1111, 1073, 930, 832, 776, 739, 700 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.69 (4H, d, \( J = 7.2 \text{ Hz}, \text{SiPh}_2\text{Bu} \)), 7.50 (1H, t, \( J = 4.1 \text{ Hz}, \text{H-3} \)), 7.44-7.35 (6H, m, \text{SiPh}_2\text{Bu} ), 7.22-7.21 (2H, m, H-4 and H-5), 7.13 (1H, t, \( J = 5.6 \text{ Hz}, \text{H-6} \)), 4.72 (2H, s, \text{CH}_2\text{OTBDPS}), 4.10 (1H, q, \( J = 6.3 \text{ Hz}, \text{H-4'} \)), 2.86-2.75 (4H, m, H-2' and H-1'), 1.19 (3H, d, \( J = 6.8 \text{ Hz}, \text{H-5'} \)), 1.07 (9H, s, \text{SiPh}_2\text{Bu} ), 0.88 (9H, s, \text{SiMe}_2\text{Bu} ), 0.02 (6H, d, \( J = 5.9 \text{ Hz}, \text{SiMe}_2\text{Bu} \));

¹³C NMR (100 MHz, CDCl₃): δ 213.0 (C=O), 138.6 (C₄, C-2), 138.5 (C₄, C-1), 135.7 (4 \times CH, \text{SiPh}_2\text{Bu} ), 133.6 (C₄, \text{SiPh}_2\text{Bu} ), 129.6 (2 \times CH, \text{SiPh}_2\text{Bu} ), 128.6 (CH, C-3), 127.9 (4 \times CH, \text{SiPh}_2\text{Bu} ), 127.4 (2 \times CH, C-5 and C-6), 126.3 (CH, C-4), 75.1 (CH, C-4'), 63.7 (CH₂, CH₂OSi), 37.5 (CH₂, C-2'), 27.0 (3 \times CH₃, \text{SiPh}_2\text{Bu} ), 25.9 (3 \times CH₃, \text{SiMe}_2\text{Bu} ), 25.4 (CH₂ C-1'), 20.9 (CH₃, C-5'), 19.5 (2 \times C₄, \text{SiPh}_2\text{Bu} ), 18.2 (C₄, \text{SiMe}_2\text{Bu} ), -4.6 (CH₃, \text{SiMe}_2\text{Bu} ), -4.9 (CH₃, \text{SiMe}_2\text{Bu} );

(S)-5-[(tert-Butyldiphenylsilyl)oxy]methyl]phenyl)-3,3-dimethoxypentan-2-ol (268)

![Chemical Structure](image)

To a stirred solution of ketone 267 (50.0 mg, 0.089 mmol) in methanol (5 mL) was added trimethyloorthoformate (10.0 μL, 0.11 mmol) and p-toluenesulfonic acid (6.00 mg, 0.036 mmol) and stirred at room temperature for 1 h. sat. aq. NaHCO₃ (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with Sat. aq. NaHCO₃ (3 × 10 mL), brine (3 × 10 mL), dried (NaSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave the title compound (35.0 mg, 80%) as a colourless oil.

\[\alpha\]^22.4_D +4.7 (c 1.4, CHCl₃);

Rf: 0.20 (1:9 ethyl acetate\hexanes);

IR \(\nu_{\text{max}}\) (neat): 3487, 2894, 2930, 2856, 1471, 1461, 1427, 1362, 1266, 1111, 1059, 1040, 1007, 822, 739, 700, 621, 616 cm⁻¹;

\(^1\)H NMR (400 MHz, CDCl₃): δ 7.71 (4H, dd, \(J = 7.8, 1.5 \text{ Hz, SiPh}_2^tBu\)), 7.57-7.55 (1H, m, H-3), 7.45-7.35 (6H, m, SiPh₂Bu), 7.24-7.22 (2H, m, H-4 and H-5), 7.14-7.12 (1H, m, H-6), 4.79 (2H, s, CH₂OTBDPS), 3.22 (CH₃, s, OCH₃), 3.15 (CH₃, s, OCH₃), 2.73 (1H, td, \(J = 13.9, 5.6 \text{ Hz, H-3}^{'ab}\)), 2.50 (1H, td, \(J = 13.3, 5.1 \text{ Hz, H-3}^{'ab}\)), 2.21 (1H, s, OH), 1.91-1.72 (2H, m, H-2'), 1.13 (3H, d, \(J = 6.5 \text{ Hz, H-6}^{'}\)), 1.09 (9H, s, SiPh₂Bu);

\(^{13}\)C NMR (100 MHz, CDCl₃): δ 139.1 (C₉, C-2), 138.5 (C₉, C-1), 135.7 (4 × CH, SiPh₂Bu), 133.6 (C₉, SiPh₂Bu), 129.8 (2 × CH, SiPh₂Bu), 128.7 (CH, C-3), 127.9 (4 × CH, SiPh₂Bu), 127.3 (CH, C-5), 127.0 (CH, C-6), 126.3 (CH, C-4), 102.0 (C₉, C-4'), 69.6 (CH, C-5'), 63.6 (CH₂, CH₂OSi), 49.5 (CH₃, OCH₃), 49.0 (CH₃, OCH₃), 33.0 (CH₂, C-3'), 27.0 (3 × CH₃, SiPh₂Bu), 26.6 (CH₂, C-2'), 19.5 (2 × C₉, SiPh₂Bu), 16.7 (CH₃, C-1);

(S)-1-(2-[[tert-Butyldiphenylsilyl]oxy]methyl)phenyl)-4-hydroxypentan-3-one (269)

To a stirred solution of ketone 267 (100 mg, 0.18 mmol) in methanol (8 mL) was added p-toluenesulfonic acid (10.5 mg, 0.054 mmol) and stirred at room temperature for 1 h. Sat. aq. NaHCO₃ (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (3 × 10 mL), brine (3 × 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:9) gave the title compound (35.0 mg, 80%) as a colourless oil.

\[ \alpha \]D²²⁺ -5.8 (c 1.0, CHCl₃);

Rr: 0.15 (1:9 ethyl acetate/hexanes);

IR \( \nu_{max} \) (neat): 3472, 2928, 2855 1713, 1455, 1427, 1361, 1112, 1075, 998, 824, 739, 703 cm⁻¹;

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.70 (4H, dd, \( J = 7.9, 1.2 \) Hz, SiPh₂Bu), 7.46-7.36 (7H, m, SiPh₂Bu and H-3), 7.23-7.22 (2H, m, H-4 and H-5), 7.13-7.11 (1H, m, H-6), 4.75 (2H, s, CH₂OTBDPS), 4.10 (1H, m, H-1'), 3.43 (1H, d, \( J = 4.5 \) Hz, OH), 2.91-2.82 (2H, m, H-5'), 2.76-2.58 (2H, m, H-4'), 1.26 (3H, d, \( J = 7.1 \) Hz, H-2'), 1.08 (9H, s, SiPh₂Bu);

\(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \) 211.7 (C=O), 138.4 (C₉, C-2), 138.1 (C₉, C-1), 135.8 (4 × CH, SiPh₂Bu), 133.5 (C₉, SiPh₂Bu), 129.9 (2 × CH, SiPh₂Bu), 129.0 (CH, C-3), 128.1 (CH, C-5), 127.9 (4 × CH, SiPh₂Bu), 127.7 (CH, C-6), 126.7 (CH, C-4), 72.8 (CH, C-1'), 64.0 (CH₂, CH₂OSi), 38.8 (CH₂, C-4'), 27.0 (3 × CH₃, SiPh₂Bu), 26.1 (CH₂, C-5'), 19.7 (CH₃, C-2'), 19.4 (2 × C₉, SiPh₂Bu);

HRMS: found [M + Na]⁺ 469.2161, [C₂₈H₃₄O₃Si₂ + Na]⁺ requires 469.2169.
(S)-1-[(S)-3-Methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (273a) and (S)-1-[(R)-3-Methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (273b)

To a stirred solution of ketone 267 (154 mg, 0.27 mmol) in methanol (8 mL) was added p-toluenesulfonic acid (20.0 mg, 0.11 mmol) and stirred at room temperature for 5 h. Sat. aq. NaHCO$_3$ (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with sat. aq. NaHCO$_3$ (3 x 10 mL), brine (3 x 10 mL), dried (NaSO$_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound 273a (22.0 mg, 37%) as a colourless solid and title compound 273b (18.0 mg, 30%) as a colourless oil.

[α]$^D_{93}^{\circ}$ -77.6 (c 1.0, CHCl$_3$);

Mp: 78.3 - 81.0 °C;

Rf: 0.30 (1:4 ethyl acetate/hexanes);

IR $\nu_{\text{max}}$ (neat): 3413, 2945, 2160, 1455, 1432, 1367, 1242, 1106, 1094, 1059, 1036, 1011, 974, 865, 834, 761, 730, 622 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.22-7.15 (4H, m, Ar-H), 5.09 (1H, d, $J = 14.0$ Hz, H-1'ab), 4.33 (1H, d, $J = 14.0$ Hz, H-1'ab), 3.90 (1H, q, $J = 6.5$ Hz, H-1), 3.44 (3H, s, OCH$_3$), 3.37 (1H, t, $J = 13.7$ Hz, H-5'ab), 2.66 (1H, ddd, $J = 15.7$, 7.7, 1.6 Hz, H-5'ab), 2.30 (1H, brs, OH), 2.07 (1H, ddd, $J = 14.8$, 7.9, 1.7 Hz, H-4'ab), 1.71(1H, td, $J = 13.4$, 1.7 Hz, H-4'ab), 1.17 (3H, d, $J = 6.5$ Hz, H-2);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.0 (C$_q$, C-11'), 138.9 (C$_q$, C-10'), 128.7 (CH, C-9'), 128.3 (CH, C-7'), 128.1 (CH, C-6'), 126.2 (CH, C-8'), 102.8 (C$_q$, C-3), 69.7 (CH, C-1), 64.5 (CH$_2$, C-1'), 49.0 (CH$_3$, OCH$_3$), 31.9 (CH$_2$, C-4'), 28.5 (CH$_2$, C-5'), 16.6 (CH$_3$, C-2);
**Experimental**

**HRMS:** found [M + Na]⁺ 245.1154, [C₁₃H₁₈O₃ + Na]⁺ requires 245.1148.

\[\alpha\]D²¹.⁴ +43.4 (c 1.0, CHCl₃);

**Rr:** 0.20 (1:4 ethyl acetate\hexanes);

**IR vₚₚₚₚₚ.MM (neat):** 3468, 2940, 1494, 1455, 1373, 1266, 1244, 1174, 1097, 1038, 1021, 991, 896, 884, 860, 757, 731 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.22-7.15 (4H, m, Ar-H), 5.09 (1H, d, J = 14.0 Hz, H-1'ab), 4.27 (1H, d, J = 14.0 Hz, H-1'ab), 4.01 (1H, q, J = 6.5 Hz, H-1), 3.39-3.31 (1H, m, H-5'ab), 3.34 (3H, s, OC₃H₃), 2.68 (1H, ddd, J = 14.7, 6.5, 2.2 Hz, H-5'ab), 2.10 (1H, brs, OH), 1.98-1.85 (2H, m, H-4'ab), 1.14 (3H, d, J = 6.5 Hz, H-2);

**¹³C NMR** (100 MHz, CDCl₃): δ 143.1 (C₉, C-11'), 139.1 (C₉, C-10'), 128.7 (CH, C-9'), 128.3 (CH, C-7'), 128.2 (CH, C-6'), 126.1 (CH, C-8'), 103.4 (C₉, C-3'), 69.3 (CH, C-1), 64.1 (CH₂, C-1'), 48.3 (CH₃, OCH₃), 29.7 (CH₂, C-4'), 28.3 (CH₂, C-5'), 15.8 (CH₂, C-2);

**HRMS:** found [M + Na]⁺ 245.1151, [C₁₃H₁₈O₃ + Na]⁺ requires 245.1148.
(3R,3'S,5'R,6'S)-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (275a) and (3R,3'R,5'S,6'R)-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (275b)

To a stirred solution of alcohol 273 (17.0 mg, 0.07 mmol) in dichloromethane (1 mL) at -78 °C was added trifluoromethanesulfonic acid (8.00 μL, 0.09 mmol) and the reaction mixture was stirred for 1 h. Triethylamine (0.5 mL) was then added and then mixture was warmed to room temperature then concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound 275a (10.0 mg, 37%) as a colourless solid and title compound 275b (8.00 mg, 30%) as a colourless solid.

[α]_D^{21.4} -52.4 (c 0.5, CHCl₃);

Mp: 178.6–181.4 °C;

Rf: 0.20 (1:19 ethyl acetate\hexanes);

IR ν_max (neat): 2948, 2872, 2160, 2027, 1976, 1454, 1237, 1111, 1128, 1099, 1050, 1020, 1001, 861, 756, 744, 637, 620, 612 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.22-7.12 (8H, m, Ar-H), 5.38 (2H, d, J = 13.9 Hz, H-1αb and H-1'αb), 4.22 (2H, d, J = 13.9 Hz, H-1αb and H-1'αb), 3.96 (2H, q, J = 6.6 Hz, H-3 and H-3'), 3.45 (2H, t, J = 13.2 Hz, H-5αb and H-5'αb), 2.65 (2H, dd, J = 14.7, 7.1 Hz, H-5αb and H-5'αb),
2.05 (2H, ddd, J = 13.6, 7.5, 1.3 Hz, H-4'ab and H-4'ab), 1.76 (2H, dt, J = 13.1, 1.5 Hz, H-4'ab and H-4'ab), 1.20 (6H, d, J = 7.0 Hz, H-12 and H-12');

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 143.3 (2 × C\(_q\), C-11 and C-11'), 139.6 (2 × C\(_q\), C-10 and C-10'), 128.5 (2 × CH, C-9 and C-9'), 128.4 (2 × CH, C-7 and C-7'), 127.7 (2 × CH, C-6 and C-6'), 125.9 (2 × CH, C-8 and C-8'), 101.4 (2 × C\(_q\), C-2 and C-2'), 68.9 (2 × CH, C-3 and C-3'), 63.9 (2 × CH\(_2\), C-1 and C-1'), 32.9 (2 × CH\(_2\), C-4 and C-4'), 28.4 (2 × CH\(_2\), C-5 and C-5'), 15.5 (CH\(_3\), C-12 and C-12');

HRMS: found [M + Na]\(^+\) 403.1866, [C\(_{24}\)H\(_{28}\)O\(_4\) + Na]\(^+\) requires 403.1880.

[α]\(^{21}\)\(_D\) -52.4 (c 0.5, CHCl\(_3\));

Mp: 185.6 – 187.6 °C;

Rr: 0.13 (1:19 ethyl acetate\(|\)hexanes);

IR \(\nu\)\(_{\max}\) (neat): 2941, 2873, 2161, 2030, 1977, 1466, 1454, 1428, 1375, 1258, 1223, 1207, 1166, 1113, 1086, 1069, 1047, 1022, 1010, 985, 945, 887, 859, 761, 747, 621 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.20-7.17 (8H, m, Ar-H), 5.35 (1H, d, J = 13.5 Hz, H-1'ab), 5.11 (1H, d, J = 13.5 Hz, H-1'ab), 4.32 (1H, d, J = 13.5 Hz, H-1'ab) 4.22 (1H, d, J = 13.5 Hz, H-1'ab), 3.92 (1H, q, J = 6.6 Hz, H-3), 3.83 (1H, q, J = 6.9 Hz, H-3'), 3.49 (2H, AB\(_q\), J = 13.5 Hz, H-5'ab and H-5'ab), 2.66 (2H, m, H-5'ab and H-5'ab), 2.12 (1H, ddd, J = 14.0, 7.5, 1.3 Hz, H-4'ab) 1.96 (1H, ddd, J = 14.0, 7.4, 1.6 Hz H-4'ab), 1.71 (2H, m, H-4'ab), 1.47 (3H, d, J = 7.0 Hz, H-12) 1.20 (3H, d, J = 7.0 Hz, H-12');

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 142.1 (C\(_q\), C-11), 141.5 (C\(_q\), C-11'), 138.8 (C\(_q\), C-10), 138.6 (C\(_q\), C-10'), 127.7 (CH, C-9), 127.5 (CH, C-9'), 127.4 (CH, C-7), 127.2 (CH, C-7'), 127.0 (CH, C-6), 127.0 (CH, C-6'), 125.3 (CH, C-8), 125.2 (CH, C-8'), 98.9 (C\(_q\), C-2), 96.3 (C\(_q\), C-2'), 72.4 (CH, C-3'), 68.8 (CH, C-3), 63.4 (CH\(_2\), C-1), 62.6 (CH\(_2\), C-1'), 34.2 (CH\(_2\), C-4), 33.3 (CH\(_2\), C-4'), 27.4 (CH\(_2\), C-5), 27.2 (CH\(_2\), C-5'), 16.8 (CH\(_3\), C-12), 14.6 (CH\(_3\), C-12');

HRMS: found [M + Na]\(^+\) 403.1866, [C\(_{24}\)H\(_{28}\)O\(_4\) + Na]\(^+\) requires 403.1880.
**Experimental**

5-Hydroxy-2,2-dimethyl-4H-(1,3)benzodioxin-4-one (285)

To a stirred solution of 2,6-dihydroxybenzoic acid (282) (5.00 g, 32.5 mmol) in 1,2-dimethoxyethane (20 mL) at 0 °C was added acetone (3.50 mL, 48.7 mmol) and DMAP (198.3 mg, 1.60 mmol). Thionyl chloride (3.50 mL, 48.7 mmol) was then added over 20 min and the mixture was stirred at 0 °C for 1 h, then warmed to room temperature for 24 h. Sat. aq. NaHCO₃ (80 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave the title compound (3.50 g, 70%) as a colourless solid.

**Mp:** 59-61 °C (lit.,²⁴⁶ 59-61 °C);

**Rr:** 0.20 (ethyl acetate\hexanes 1:9);

**IR ν max (neat):** 3189, 1689, 1631, 1585, 1471, 1385, 1343, 1277, 1205, 1080, 1057, 920, 803, 687, 666 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 10.33 (1H, s, OH) 7.43 (1H, t, J = 8.0 Hz, H-7), 6.64 (1H, dd, J = 8.5, 0.84 Hz, H-6), 6.44 (1H, dd, J = 7.7, 0.96 Hz, H-8), 1.75 (6H, s, 2 × CCH₃);

**¹³C NMR** (100 MHz, CDCl₃): δ 165.5 (C=O), 161.5 (C₆), 155.6 (C₄, C-5), 137.9 (CH, C-7), 110.8 (CH, C-6), 107.3 (CH, C-8), 107.1 (C₄, C-4), 99.4 (C₄, C-2), 25.7 (2 × CH₃, CCH₃).

Spectroscopic data are consistent with reported literature.²⁴⁶,²⁴⁷
2,2-Dimethyl-4-oxo-2,4-dihydro-1,3-benzodioxin-5-yl trifluoromethanesulfonate (284)

Method A:

Anhydrous pyridine (0.80 mL, 0.98 mmol) and trifluoromethanesulfonic anhydride (50.0 µL, 0.33 mmol) were added successively to a solution of alcohol 285 (53.0 mg, 0.27 mmol) in dichloromethane (2 mL) at 0 ºC and stirred at this temperature for 1 h. Sat. aq. NH₄Cl (10 mL) was then added to the reaction mixture and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude compound was recrystallized from hexanes to give title compound (81 mg, 93%) as a colourless solid.

Method B:

To a stirred solution of alcohol 285 (700 mg, 3.88 mmol) in DMF (15 mL) at 0 ºC was added DMAP (94.0 mg, 0.77 mmol) and NaH (102 mg, 4.26 mmol) and stirred for 15 mins. N-phenyl-bis (trifluoromethanesulfonimide) (1.90 g, 3.88 mmol) was then added and stirred for a further 2 h. Water (10 mL) was then added and the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude compound was recrystallized from hexanes to give title compound (1.10 g, 90%) as a colourless solid.

Mp: 114-116 ºC (lit., 246 117-118 ºC);

Rf: 0.20 (ethyl acetate-hexans1:19);

IR vₘₐₓ (neat): 3094, 2997, 2926, 1746, 1622, 1580, 1475, 1439, 1325, 1298, 1217, 1140, 1024 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.62 (1H, t, J = 8.0 Hz, H-7), 7.06 (1H, d, J = 8.4 Hz, H-6), 7.01 (1H, d, J = 8.0 Hz, H-8), 1.76 (6H, s, 2 × CCH₃);
Experimentals

$^{13}\text{C NMR (100 MHz, CDCl}_3):$ $\delta$ 157.5 (C=O), 157.1 (C$_q$, C-1), 148.7 (C$_q$, C-5), 136.2 (CH, C-4), 117.9 (CH, C-7), 116.6 (CH, C-3), 108.4 (C$_q$, COTs), 106.9 (2 $\times$ C$_q$, C-4 and C-2), 25.5 (2 $\times$ CH$_3$, CCH$_3$).

Spectroscopic data are consistent with reported literature.$^{246,247}$
2,2-Dimethyl-5-[2-(trimethylsilyl)ethynyl]-2,4-dihydro-1,3-benzodioxin-4-one (286)

Triflate 284 (1.00 g, 3.07 mmol), PdCl₂(PPh₃)₂ (172 mg, 0.21 mmol), CuI (28.0 mg, 0.15 mmol) were subsequently added to anhydrous triethylamine/NMP (1:5, 8 mL) and stirred for 10 min at room temperature. Trimethylsilylacetylene (0.35 ml, 4.90 mmol) was then slowly added over 15 min and the mixture was stirred for a further 2 h. The reaction mixture was diluted with ethyl acetate (30 mL) and filtered through a pad of Celite®. The filtrate was washed with sat. aq. NH₄Cl (3 x 30 mL), brine (3 x 30 mL), dried (MgSO₄), filtered and the filtrate was concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:100 to 1:20) gave the title compound (0.68 g, 80%) as a yellow oil.

Rf: 0.30 (ethyl acetate/hexanes 1:19);

IR νmax (neat): 3255, 2999, 2104, 1742, 1579, 1438, 1390, 1318, 1284, 1253, 1206, 1168, 1145, 1075, 1045, 1016, 964, 920, 848, 808, 773 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.44 (1H, t, J = 7.8 Hz, H-7), 7.28 (1H, dd, J = 7.9 Hz, 0.9 Hz, H-6), 6.91 (1H, dd, J = 8.4, 1.0 Hz, H-8), 1.70 (6H, s, 2 x CH₃), 0.29 (9H, s, SiMe₃);

¹³C NMR (100 MHz, CDCl₃): δ 158.9 (C=O), 156.7 (Cq, C-1), 135.0 (CH, C-7), 129.5 (CH, C-6), 125.3 (Cq, C-5), 117.7 (CH, C-8), 114.6 (Cq, C-4), 105.9 (Cq, C-9), 102.8 (Cq, C-10), 102.5 (Cq, C-2), 26.0 (2 x CH₃, CCH₃), 0.03 (3 x CH₃, SiMe₃).

Spectroscopic data are consistent with reported literature.²⁴⁸
5-Ethynyl-2,2-dimethyl-2,4-dihydro-1,3-benzodioxin-4-one (287)

To a stirred solution of alkyne 286 (200 mg, 0.73 mmol) in THF (6 mL) was added TBAF (0.87 mL, 1.0 M in THF, 0.87 mmol) at 0 °C and was stirred at this temperature for 15 min. The reaction mixture was diluted with hexanes (50 mL) and filtered through a pad of silica. The filtrate was concentrated in vacuo to afford the title compound (150 mg, 99%) as off white solid, which decomposes slowly upon standing.248

M.p.: 80-82 °C (lit.,248 117-118 °C);

Rr: 0.40 (1:19 ethyl acetate:hexanes);

IR ν max (neat): 3255, 2999, 2104, 1742, 1593, 1579, 1474, 1438, 1390, 1379, 1318, 1284, 1253, 1206, 1168, 1145, 1075, 1045, 1016, 964, 920, 848, 808, 773 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.44 (1H, t, J = 7.6 Hz, H-7), 7.32 (1H, dd, J = 7.5, 1.1 Hz, H-6), 6.98 (1H, dd, J = 8.4, 1.0 Hz, H-8), 3.52 (1H, s, H-10), 1.72 (6H, s, 2 × CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 158.9 (C=O), 156.7 (Cq, C-1), 135.1 (CH, C-7), 129.8 (CH, C-6), 124.2 (Cq, C-5), 118.2 (CH, C-8), 114.7 (Cq, C-4), 105.9 (Cq, C-2), 84.3, (CH, C-10), 81.3 (Cq, C-9), 25.8 (2 × CH₃, CH₃).

Spectroscopic data is consistent with reported literature.248
3-Ethynyl-2-(hydroxymethyl)phenol (288)

To a stirred solution of acetonide 287 (150 mg, 0.99 mmol) in THF (5 mL) was added lithium aluminium hydride (112 mg, 2.90 mmol) at 0 °C and stirred at this temperature for 3 h. The reaction mixture was quenched with HCl (2 mL, 0.5M in MeOH/water, 1:1) and ethyl acetate (20 mL) was added and stirred for 30 min. The reaction mixture was then filtered through a pad of Celite® and the filtrate was washed with brine (3 × 20 mL), dried (MgSO₄) and concentrated in vacuo to afford the title compound (130 mg, 99%) as a colourless oil.

Rf: 0.20 (ethyl acetate/hexanes1:9);  
IR νmax (neat): 3290, 1580, 1463, 993, 792 cm⁻¹;  
¹H NMR (400 MHz, CDCl₃): δ 7.14 (1H, t, J = 7.2 Hz, H-5), 7.05 (1H, d, J = 7.9 Hz, H-4), 6.88 (1H, d, J = 7.9 Hz, H-6), 5.17 (2H, s, H-7), 3.25 (1H, s, H-9).

Spectroscopic data are consistent with reported literature.²⁴⁹
5-Ethynyl-2,2-dimethyl-2,4-dihydro-1,3-benzodioxine (281)

To a stirred solution of diol 288 (500 mg, 3.40 mmol) in acetone (20 mL) was added p-toluenesulfonic acid (0.68 mg, 0.68 mmol) and 2,2-dimethoxypropane (0.63 mL, 5.1 mmol) at room temperature and stirred for 16 h. The reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (0.58 g, 90%) as a colourless oil which decomposes upon standing.

Rf: 0.35 (1:19 ethyl acetate/hexanes);

IR νₘₐₓ (neat): 3849, 2140, 1582, 1465, 1386, 864, 785 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.13 (1H, t, J = 7.5 Hz, H-7), 7.07 (1H, d, J = 7.7 Hz, H-6), 6.83 (1H, d, J = 8.1 Hz, H-8), 4.91 (2H, s, H-3), 3.29 (1H, s, H-10), 1.54 (6H, s, C(CH₃)₂).

Spectroscopic data are consistent with reported literature.²⁴⁹
(R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2,2-dimethyl-2,4-dihydro-1,3-benzodioxin-5-yl)pent-1-yn-3-one hydrate (290)

To a solution of alkyne 281 (400 mg, 2.10 mmol) in anhydrous THF (15 mL) at -78 °C was added LiHMDS (2.70 mL, 1.0 M in THF, 2.70 mmol) and stirred at this temperature for 1 h. A solution of Weinreb amide 264b (0.83 g, 3.40 mmol) in anhydrous THF (3 mL) was then added dropwise and the mixture was warmed to room temperature and stirred for 1 h. sat. aq. NH₄Cl (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with Sat. aq. NH₄Cl (2 × 10 mL), brine (3 × 10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound (628 mg, 80%) as a colourless oil.

\[\alpha\]D\textsubscript{19.6} +38.3 (c 1.0, CHCl₃);

RIR \(v_{\text{max}}\) (neat): 2954, 2930, 2857, 2193, 1673, 1583, 1467, 1386, 1467, 1386, 1374, 1363, 1254, 1195, 1128, 1090, 1045, 854, 779 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl₃): δ 7.18-7.14 (1H, m, H-6 and H-7), 6.93 (1H, dd, J = 7.6, 1.9 Hz, H-8), 4.95 (2H, s, H-3), 4.34 (1H, q, \(J = 6.8\) Hz, H-4\'), 1.54 (6H, s, C(CH₃)₂), 1.45 (3H, d, \(J = 6.8\) Hz, H-5\'), 0.93 (9H, s, SiMe₂'Bu), 0.12 (6H, d, \(J = 8.4\) Hz, SiMe₂'Bu);

\(^{13}\)C NMR (100 MHz, CDCl₃): δ 190.2 (C=O), 151.6 (C₉, C-1) 128.2 (CH, C-7), 125.8 (CH, C-6), 123.1 (C₉, C-5), 120.2 (CH, C-8), 116.5 (C₉, C-4), 100.0 (C₉, C-2), 90.8 (C₉, C-1'), 90.2 (C₉, C-2'), 75.3 (CH, C-4'), 60.4 (CH, C-3), 25.9 (3 × CH₃, SiMe₂'Bu), 24.9 (CH₃, CCH₃), 24.7 (CH₃, CCH₃), 20.9 (CH₃, C-5'), 18.4 (C₉, SiMe₂'Bu), -4.6 (CH₃, SiMe₂'Bu), -4.8 (CH₃, SiMe₂'Bu);

HRMS: found [M + Na\]+, 397.1802. [C\textsubscript{21}H\textsubscript{30}O\textsubscript{4}Si+ Na\]+ requires 387.1806.
(Z,R)-4-[((tert-butyldimethylsilyl)oxy]-1-(2,2-dimethyl-2,4-dihydro-1,3-benzodioxin-5-yl)pent-1-en-3-one (289a) and (E,R)-4-[((tert-butyldimethylsilyl)oxy]-1-(2,2-dimethyl-2,4-dihydro-1,3-benzodioxin-5-yl)pent-1-en-3-one (289b)*

To a solution of alkyne 290 (200 mg, 0.53 mmol) in ethyl acetate (10 mL) was added quinoline (0.01 mL, 0.10 mmol) and Lindlar catalyst (40.0 mg). The reaction mixture was then placed under an atmosphere of hydrogen and stirred for 1 h at room temperature. The reaction mixture was filtered through a pad of Celite® and filtrate was concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound 289a (124 mg, 90%) and a trace amount of the E-isomer 289b as a bright yellow oil.

$[\alpha]_{D}^{22.1}$ –3.9 (c 1.0, CHCl3);

Rr: 0.25 (ethyl acetate\hexanes1:19);

IR $\nu_{\text{max}}$(neat): 2953, 2930, 2857, 1699, 1581, 1472, 1453, 1385, 1374, 1276, 1256, 1204, 1142, 1117, 1089, 1058, 1027, 1004, 934, 898, 865, 850, 777 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl3 *denotes E-isomer): $\delta$ 7.67* (0.1 H, d, $J$ = 16.1 Hz, H-11), 7.22* (0.2, m, H-12 and H-4), 7.13 (1H, t, $J$ = 8.0 Hz, H-4), 6.89 (1H, d, $J$ = 7.6 Hz, H-3), 6.85 (1H, d, $J$ = 12.2 Hz, H-11), 6.78 (1H, d, $J$ = 7.7 Hz, H-5), 6.72 (1H, d, $J$ = 12.4 Hz, H-12), 4.99* (0.2 H, s, H-10), 4.74 (2H, s, H-10), 4.34* (0.2H, q, $J$ = 6.8 Hz, H-14), 4.19 (1H, q, $J$ = 6.7 Hz, H-14), 1.50 (6H, s, H-8 and H-9), 1.36* (0.4H, d, $J$ = 6.8 Hz, H-15), 0.94* (1H, s, SiMe$_2$Bu), 0.92 (9H, s, SiMe$_2$Bu), 0.11* (0.4H, s, SiMe$_2$Bu), 0.09* (0.4H, s, SiMe$_2$Bu), 0.07 (3H, s, SiMe$_2$Bu), 0.06 (3H, s, SiMe$_2$Bu);

$^{13}$C NMR (100 MHz, CDCl3 *denotes E-isomer): $\delta$ 202.7 (C=O), 201.9*, 151.2 (C$_q$, C-6), 138.8 (CH, C-11), 138.7*, 133.1 (C$_q$, C-2), 131.7*, 128.3*, 127.6 (CH, C-4), 126.0 (CH, C-12), 122.3*, 120.6 (CH, C-3), 119.3*, 119.0*, 117.9 (C$_q$, C-1), 117.3 (CH, C-5), 99.3 (C$_q$,
C-7), 75.0 (CH, C-14), 60.0 (CH₂, C-10), 25.9 (3 × CH₃, SiMe₂'Bu), 24.8 (CH₃, C-8 and C-9), 21.3*, 20.9 (CH₃, C-15), 18.3 (C₉, SiMe₂'Bu), -4.6 (Me, SiMe₂'Bu), -4.8 (CH₃, SiMe₂'Bu);

**HRMS:** found [M + Na]⁺ 283.1302, [C₁₆H₂₀O₃Si+ Na]⁺ requires 283.1304.
To a stirred solution of ketone 290 (100 mg, 0.26 mmol) in ethyl acetate (10 mL) was added Pd/C (10.0 mg) and the mixture was then placed under an atmosphere of hydrogen. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then filtered through a plug of Celite® and the filtrate was concentrated in vacuo to afford title compound (91.0 mg, 90%) as colourless oil and used immediately without further purification.

$\alpha^\mathrm{D}_{22} +2.00$ (c 1.0, CHCl$_3$);

$\text{Rr}$: 0.30 (ethyl acetate\hexanes1:19);

IR $\nu$$_{\text{max}}$ (neat): 2930, 2857, 1719, 1588, 1461, 1384, 1372, 1259, 1204, 1144, 1116, 831, 779, cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.12 (1H, t, $J = 7.6$ Hz, H-7), 6.72 (1H, d, $J = 7.4$ Hz, H-6), 6.69 (1H, d, $J = 8.2$ Hz, H-8), 4.86 (2H, s, H-3), 4.18 (1H, q, $J = 7.1$ Hz, H-4), 2.95-2.81 (2H, m, H-2'), 2.70 (2H, t, $J = 7.5$ Hz, H-1'), 1.53 (6H, s, C(CH$_3$)$_2$), 1.26 (3H, d, $J = 6.9$ Hz, H-15), 0.90 (9H, s, SiMe$_2$Bu), 0.07 (6H, s, SiMe$_2$Bu);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.0 (C=O), 151.4 (C$_q$, C-1), 137.4 (C$_q$, C-5), 128.0 (CH, C-7), 120.2 (CH, C-6), 117.8 (C$_q$, C-4), 115.2 (CH, C-8), 98.9 (C$_q$, C-2), 75.1 (CH, C-4'), 59.8 (CH$_2$, C-3), 36.7 (CH$_2$, C-2'), 25.9 (3 $\times$ CH$_3$, SiMe$_2$Bu), 24.8 (CH$_3$, CCH$_3$), 24.7 (CH$_3$, CCH$_3$), 24.6 (CH$_2$, C-1'), 20.9 (CH$_3$, C-5'), 18.2 (C$_q$, SiMe$_2$Bu), -4.6 (CH$_3$, SiMe$_2$Bu), -4.9 (CH$_3$, SiMe$_2$Bu);

HRMS: found [M + Na]$^+$ 401.2115, [C$_{21}$H$_{34}$O$_4$Si+ Na]$^+$ requires 401.2119.
(R)-4-Hydroxy-1-[3-hydroxy-2-(methoxymethyl)phenyl]pentan-3-one (293)

**TsOH**

To a stirred solution of ketone 291 (50.0 mg, 0.13 mmol) in methanol (5 mL) was added trimethyl orthoformate (0.03 mL, 0.19 mmol) and p-toluenesulfonic acid (7.00 mg, 0.04 mmol) and stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. NaHCO$_3$ (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate-toluene, 1:2) gave the *title compound* (12.0 mg, 40%) as a yellow oil.

**Dowex 50W**

To a stirred solution of ketone 291 (50.0 mg, 0.13 mmol) in methanol (5 mL) was added trimethyl orthoformate (0.03 mL, 0.19 mmol) and Dowex 50W (100 mg) and stirred at room temperature for 48 h. The reaction mixture was filtered through cotton wool and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate-toluene, 1:2) gave the *title compound* (15.0 mg, 50%) as a yellow oil.

**HCl**

To a stirred solution of ketone 291 (50.0 mg, 0.13 mmol) in methanol (5 mL) was added trimethyl orthoformate (0.03 mL, 0.19 mmol) and HCl (4.0 M, 0.05 mL, 0.16 mmol) at 0 °C and was stirred at this temperature for 1 h then warmed to room temperature for 5 h. Water (2 mL) was added to the reaction mixture and then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate-toluene, 1:2) gave the *title compound* (15.0 mg, 0.08 mmol, 50%) as a yellow oil.

$\left[\alpha\right]_D^{22.4} -10.4$ (c 1.0, CHCl$_3$);

$R_r$: 0.20 (ethyl acetate/hexanes 1:2);
**Experimentals**

\[ \text{IR } \nu_{\text{max}} \text{(neat): 3338, 2930, 1710, 1587, 1466, 1361, 1273, 1186, 1074, 789, 745 cm}^{-1}; \]

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \( \delta \) 7.74 (1H, brs, OH), 7.14 (1H, t, \( J = 7.6 \), H-5), 6.77 (1H, d, \( J = 8.2 \), H-6), 6.69 (1H, d, \( J = 7.4 \), H-4), 4.73 (2H, s, H-2), 4.21 (1H, m, H-4'), 3.47 (3H, s, OCH\(_3\)), 3.44 (1H, brs, OH), 2.94-2.63 (4H, m, H-1' and H-2'), 1.34 (3H, s, H-5');

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \( \delta \) 211.5 (C=O), 157.1 (C\(_q\), C-3) 139.1 (C\(_q\), C-7), 129.5 (CH, C-5), 120.9 (CH, C-6), 120.2 (C\(_q\), C-2), 115.4 (CH, C-4), 72.9 (CH, C-4'), 69.9 (CH\(_2\), C-2), 58.6 (CH\(_3\), OCH\(_3\)), 39.0 (CH\(_2\), C-1'), 26.6 (CH\(_2\), C-2'), 19.8 (CH\(_3\), C-5');

**HRMS**: found [M + Na]** 261.1090, [C\(_{13}\)H\(_{18}\)O\(_4\)Si + Na]** requires 261.1097.
Experimental

(R)-4-Hydroxy-1-[3-hydroxy-2-(hydroxymethyl)phenyl]pentan-3-one (294)

To a solution of ketone 294 (20.0 mg, 0.08 mmol) in THF/water (1:1, 2 mL) was added p-toluenesulfonic acid (5.00 mg, 0.03 mmol) and stirred for 12 h at room temperature. The reaction mixture was quenched with sat. aq. NaHCO₃ (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by preparative TLC plate (ethyl acetate/hexanes, 1:2) gave the title compound (9.00 mg, 50%) as a yellow oil.

$[\alpha]_D^{22.4} -9.50$ (c 1.0, CHCl₃);

Rr: 0.10 (ethyl acetate/hexanes1:2);

IR $\nu_{max}$ (neat): 3311, 2918, 2850, 1711, 1588, 1497, 1365, 1272, 990, 780 cm⁻¹;

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 7.14 (1H, t, $J = 7.6$, H-5), 6.77 (1H, d, $J = 7.6$, H-6), 6.70 (1H, d, $J = 7.5$, H-4), 4.93 (2H, s, H-2), 4.16 (1H, m, H-4'), 3.35 (1H, brs, OH), 2.97-2.92 (2H, m, H-2'), 2.85-2.67 (2H, m, H-1'), 1.31 (3H, s, H-5');

$^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 212.1 (C=O), 156.8 (C₆, C-3) 138.9 (C₄, C-7), 129.4 (CH, C-5), 123.4 (C₆, C-1), 121.2 (CH, C-6), 115.2 (CH, C-4), 73.0 (CH, C-4'), 59.7 (CH₂, C-2), 39.4 (CH₂, C-2'), 26.4 (CH₂, C-1'), 19.7 (CH₃, C-5');

Methyl 2-ethynyl-6-hydroxybenzoate (300)

To a stirred solution of alkyne 286 (680 mg 2.50 mmol) in methanol (10 mL) was added potassium carbonate (517 mg, 2.75 mmol) at room temperature. The reaction mixture was heated to 40 °C and stirred for 3 h. The reaction was cooled to room temperature then quenched with sat. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:20) gave the title compound (0.68 mg, 80%) as a colourless solid.

Mp: 62.9-66.1 °C;

Rf: 0.40 (ethyl acetate\hexanes1:20);

IR ν_max (neat): 3256, 3017, 2954, 1660, 1599, 1573, 1446, 1351, 1315, 1293, 1244, 1212, 1126, 1067, 945, 811, 742, 693, 559, 520;

¹H NMR (400 MHz, CDCl₃): δ 11.22 (1H, s, OH), 7.35 (1H, t, J = 8.2 Hz, H-4), 7.16 (1H, dd, J = 7.3, 1.2 Hz, H-3), 7.01 (1H, dd, J = 8.6, 1.5 Hz, H-5), 3.97 (3H, s, OCH₃), 3.34 (1H, s, H-9);

¹³C NMR (100 MHz, CDCl₃): δ 170.5 (C=O), 162.2 (Cₚ, C-6), 134.0 (CH, C-4), 127.2 (CH, C-4), 123.4 (Cₚ, C-2), 118.8 (CH, C-5) 113.6 (Cₚ, C-1), 82.9 (Cₚ, C-8), 81.9 (CH, C-9), 52.1 (OCH₃);

Methyl 2-ethynyl-6-[\(4\)-methylbenzenesulfonyloxy]benzoate (301)

To a stirred solution of alkyne 300 (300 mg, 1.70 mmol) in acetone (25 mL) was added potassium carbonate (471 mg, 3.40 mmol) and 4-toluenesulfonyl chloride (487.3 mg, 2.6 mmol) at room temperature and stirred for 16 h. Water (20 mL) was then added and the mixture was extracted with ethyl acetate (\(2 \times 30\) mL). The combined organic phases were washed with brine (\(3 \times 20\) mL), dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (ethyl acetate/hexanes, 2:3) gave the \textit{title compound} (0.68 g, 80\%) as a colourless oil.

\(R_f: 0.20\), (ethyl acetate/hexanes 2:3);

\textbf{IR} \(\nu_{\text{max}}\) (neat): 3299, 1731, 1597, 1455, 1371, 1271, 1221, 1175, 1090, 975, 811, 756, 777, 662 cm\(^{-1}\);

\textbf{\(^1H\text{ NMR}\)} (400 MHz, CDCl\(_3\)): \(\delta\) 7.63 (2H, d, \(J = 8.2\) Hz, H-2' and H-5'), 7.34 (1H, dd, \(J = 7.5, 1.1\) Hz, H-4), 7.23-7.21 (3H, m, H-3', H-5' and H-3), 7.16 (1H, dd, \(J = 8.3, 1.0\) Hz, H-5), 3.66 (3H, s, OCH\(_3\)), 3.12 (1H, s, CCH), 2.34 (3H, s, OTs-CH\(_3\));

\textbf{\(^{13}C\text{ NMR}\)} (100 MHz, CDCl\(_3\)): \(\delta\) 164.8 (C=O), 146.5 (C\(_q\), C-1'), 145.9 (C\(_q\), H-6), 132.4 (C\(_q\), H-4'), 131.8 (CH, H-4), 130.9 (CH, C-3), 130.6 (C\(_q\), C-2), 130.0 (2 \(\times\) CH, C-2' and C-6'), 128.6 (2 \(\times\) CH, C-3' and C-5'), 123.5 (CH, C-5), 122.7 (C\(_q\), C-1), 82.2 (CH, CCH), 79.9 (C\(_q\), CCH), 52.7 (CH\(_3\), OCH\(_3\)), 21.8 (CH\(_3\), OTs-OCH\(_3\));

\textbf{HRMS}: found [M + Na]\(^+\) 353.0463, [C\(_{17}\)H\(_{14}\)O\(_5\)S + Na]\(^+\) requires 353.0454.
3-Ethynyl-2-(hydroxymethyl)phenyl 4-methylbenzene-1-sulfonate (302)

![Chemical Structure]

To a stirred solution of tosylate 301 (100 mg, 0.30 mmol) in dichloromethane (12 mL) at -78 °C and was added diisobutylaluminum hydride (0.75 mL, 1.0 M in toluene, 0.75 mmol) dropwise and stirred at this temperature for 5 h. The reaction mixture was quenched with sat. aq. Rochelle’s salt (20 mL) and stirred for 3 h then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:1) to afford title compound (90 mg, quant) as a colourless oil.

Rf: 0.10 (ethyl acetate\hexanes 1:1);

IR νmax (neat): 3544, 3287, 1597, 1568, 1460, 1368, 1222, 1193, 1168, 1091, 999, 897, 837, 801, 761, 740, 656 cm⁻¹

¹H NMR (300 MHz, CDCl₃): δ 7.82 (2H, d, J = 8.1 Hz, H-2' and H-6'), 7.48 (1H, d, J = 8.1 Hz, H-4), 7.39 (2H, d, J = 7.7 Hz, H-3' and H-5'), 7.21 (1H, t, J = 8.1 Hz, H-5), 6.92 (1H, d, J = 8.1 Hz, H-6), 4.75 (2H, s, CH₂), 3.37 (1H, s, CCH), 2.48 (3H, s, OTs-CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 147.6 (C, C-1), 146.2 (C, C-2), 137.0 (C, C-1'), 132.4 (CH, C-5), 132.1 (C, C-4'), 130.2 (2 × CH₂, H-2' and H-6'), 129.0 (CH, C-4), 128.7 (2 × CH, H-3' and H-5'), 125.0 (C, C-3), 123.7 (CH, C-6), 82.8 (CH, CCH), 80.5 (C, CCH), 57.8 (CH₂, CH₂OH), 21.9 (CH₃, OTs-CH₃);

2-[[{(tert-Butyldimethylsilyl)oxy}methyl]-3-ethynylphenyl 4-methylbenzene-1-sulfonate (303)

To a stirred solution of alcohol 302 (90.0 mg) in dichloromethane (15 mL) was added imidazole (36.0 mg, 0.53 mmol), DMAP (1.83 mg, 0.015 mmol) and tert-butyldimethylsilyl chloride (60.0 mg, 0.39 mmol) at room temperature and stirred for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (99.0 mg, 80%) as a pinkish oil.

Rf: 0.20 (ethyl acetate\hexanes1:4);

IR νmax(neat): 3301, 2955, 2929, 2856, 2886, 1599, 1569, 1461, 1374, 1220, 1252, 1186, 1196, 1175, 1081, 1068, 1028, 911, 835, 802, 775, 754 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.79 (2H, d, J = 8.2 Hz, H-2' and H-6'), 7.42 (1H, dd, J = 7.8, 1.5 Hz, H-4), 7.35 (2H, d, J = 8.1 Hz, H-3' and H-5'), 7.21 (1H, t, J = 8.1 Hz, H-5), 7.12 (1H, dd, J = 8.1, 1.0 Hz, H-6), 7.64 (2H, s, CCH), 3.25 (1H, s, CCH), 2.46 (3H, s, OTs-CH₃), 0.86 (9H, s, SiMe₂Bu), 0.04 (6H, s, SiMe₂Bu);

¹³C NMR (100 MHz, CDCl₃): δ 148.4 (Cₗ, C-1), 145.6 (Cₗ, C-1'), 136.2 (Cₗ, C-2), 133.2 (Cₗ, C-4'), 132.0 (CH, C-5), 130.0 (2 × CH, C-2' and C-6'), 128.7 (CH, C-4), 128.5 (2 × CH, C-3' and C-5'), 124.9 (Cₗ, C-3), 1223.2 (CH, C-6), 81.9 (CH, CCH), 81.2 (Cₗ, CCH), 58.4 (CH₂, CH₂OTBS), 26.0 (3 × CH₃, SiMe₂Bu), 21.8 (CH₃, OTs-CH₃), 18.6 (Cₗ, SiMe₂Bu), -5.3 (2 × CH₃, SiMe₂Bu);

Methyl 2-[(4-methylbenzenesulfonyl)oxy]-6-(trifluoromethanesulfonyloxy)benzoate (308)

To a stirred solution of acetonide 284 (680 mg, 2.08 mmol) in methanol (15 mL) was added potassium carbonate (576 mg, 4.20 mmol) at room temperature. The reaction mixture was heated to 40 °C and stirred for 3 h. The reaction was cooled to room temperature then quenched with sat. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄), filtered and concentrated in vacuo to give the title compound (528 mg, 80%), which was immediately used in the next step.

To a stirred solution of triflate 307 (390 mg, 1.19 mmol) in dichloromethane (25 mL) was added triethylamine (0.22 mL, 1.54 mmol) and 4-toluenesulfonyl chloride (342 mg, 1.79 mmol) at room temperature. The reaction mixture was stirred for 1 h, then water (20 mL) was added and the mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic phases were washed with brine (3 × 20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (486 mg, 90%) as a colourless oil.

Rf: 0.20 (ethyl acetate\hexanes1:4);

IR νₘₐₓ(neat): 1740, 1610, 1598, 1578, 1454, 1426, 1382, 1279, 1251, 1211, 1190, 1177, 1136, 1115, 1092, 1066, 981, 951, 860, 813, 774, 742, 709, 660 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.72 (2H, d, J = 8.2 Hz, H-2’ and H-6’), 7.54 (1H, t, J = 8.4 Hz, H-4), 7.35-7.32 (3H, m, H-5, H-3’ and H-5’), 7.28 (1H, d, J = 8.8 Hz, H-3), 3.71 (3H, s, OC₃H₃), 2.48 (3H, s, OTs-CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 161.5 (C=O), 147.9 (C₉, C-6), 147.0 (C₉, C-2), 146.3 (C₉, C-1’), 132.3 (CH, C-4), 131.9 (C₉, C-4’), 130.1 (2 × CH, C-2’ and C-6’), 128.7 (2 × CH, C-3’
and C-5'), 123.4 (CH, C-5), 122.4 (C_q, C-1), 120.7 (CH, C-3), 120.2 (C_q, OTs), 53.1 (CH_3, OCH_3), 21.9 (CH_3, OTs-CH_3);

HRMS: found [M + Na]^+ 476.9908, [C_{16}H_{13}F_3O_8S_2Na]^+ requires 476.9896.

2-(Hydroxymethyl)-3-(trifluoromethanesulfonyloxy)phenyl 4-methylbenzene-1-sulfonate (305) and 3-Hydroxy-2-(hydroxymethyl)phenyl 4-methylbenzenesulfonate (358)

To a stirred solution of tosylate 308 (200 mg, 0.44 mmol) in dichloromethane (12 mL) at -78 °C was added diisobutyalalminum hydride (0.88 mL, 1.0 M in toluene, 0.88 mmol) was added drop wise and stirred for 5 h. The reaction mixture was quenched with sat. aq. Rochelle salt (20 mL) and stirred for 3 h then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried (MgSO_4), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:1) afforded the title compound 305 (168 mg, 90%) as colourless oil and title compound 358 (13.0 mg, 10%) as a yellow oil.

Rr: 0.30 (ethyl acetate\hexanes1:1);
**Experimentals**

IR \( \nu_{\text{max}} \) (neat): 3565, 1598, 1459, 1377, 1216, 1179, 1138, 1004, 918, 816, 801, 749 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.80 (2H, d, \( J = 8.1 \) Hz, H-2' and H-6'), 7.40 (2H, d, \( J = 8.3 \) Hz, H-3' and H-5'), 7.35 (1H, t, \( J = 7.7 \) Hz, H-5), 7.30 (1H, dd, \( J = 8.1 \), 1.2 Hz, H-4), 7.03 (1H, dd, \( J = 8.3 \), 2.1 Hz, H-6), 4.64 (2H, d, \( J = 6.4 \) Hz, \( CH_2 \)), 2.49 (3H, s, OTs-\( CH_3 \)), 2.36 (1H, brs, OH);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 149.0 (C\(_q\), C-3), 148.6 (C\(_q\), C-1), 146.6 (C\(_q\), C-1'), 131.8 (C\(_q\), C-4'), 130.3 (2 \times CH, C-2' and C-6'), 130.0 (CH, C-5), 128.8 (C\(_q\), C-2), 128.8 (2 \times CH, C-3' and C-5'), 123.1 (CH, C-4), 120.9 (CH, C-6), 120.3 (C\(_q\), OTs), 54.5 (CH\(_2\), CH\(_2\)OH), 22.0 (CH\(_3\), OTs-CH\(_3\));

HRMS: found [M + Na]\(^+\) 439.1362, [C\(_{15}\)H\(_{13}\)F\(_3\)O\(_7\)S\(_2\) + Na]\(^+\) requires 439.1370.

\[
\begin{align*}
&\text{IR } \nu_{\text{max}} \text{ (neat): 3515, 3238, 2921, 1738, 1612, 1595, 1467, 1364, 1217, 1189, 1160, 1009, 923, 815, 801, 793, 658 cm}^{-1}; \\
&\text{\(^1\)H NMR (300 MHz, CDCl\(_3\)): } \delta \text{ 7.73 (2H, d, } J = 8.6 \text{ Hz, H-2' and H-6'), 7.54 (1H, brs, OH), 7.36 (1H, d, } J = 8.1 \text{ Hz, H-3' and H-5'), 7.08 (1H, t, } J = 8.4 \text{ Hz, H-5), 6.83 (1H, t, } J = 7.8 \text{ Hz, H-4), 6.31 (1H, dd, } J = 8.0, 1.1 \text{ Hz, H-6), 4.83 (1H, d, } J = 5.9 \text{ Hz, } CH_2)\text{, 2.47 (3H, s, OTs-CH}_3\); \\
&\text{\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): } \delta \text{ 158.1 (C\(_q\), C-3), 146.7 (C\(_q\), C-1), 145.9 (C\(_q\), C-1'), 132.3 (C\(_q\), C-4'), 130.0 (2 \times CH, C-2' and C-6'), 129.3 (CH, C-5), 128.7 (2 \times CH, C-3' and C-5'), 119.6 (C\(_q\), C-2), 116.0 (CH, C-4), 114.2 (CH, C-6), 58.4 (CH\(_2\), CH\(_2\)OH), 21.9 (CH\(_3\), OTs-CH\(_3\)); \\
&\text{HRMS: found [M + Na]\(^+\) 317.0455, [C\(_{14}\)H\(_{14}\)O\(_5\)S + Na]\(^+\) requires 317.0454.}
\end{align*}
\]
2-\text{[}(\text{tert-Butyldimethylsilyl})\text{oxy}]\text{methyl}\text{-}3\text{-}(\text{trifluoromethanesulfonyloxy})\text{phenyl 4-methylbenzene-1-sulfonate (309)}

To a stirred solution of alcohol \textbf{305} (100 mg, 0.22 mmol) in dichloromethane at 0 °C was added imidazole (26.0 mg, 0.37 mmol) and \textit{tert}-butyldimethylsilyl chloride (42.0 mg, 0.28 mmol) and stirred at room temperature for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (ethyl acetate\textbackslash hexanes, 1:4) gave the \textit{title compound} (106 mg, 90%) as a yellow oil.

\textbf{Rf}: 0.4 (ethyl acetate\textbackslash hexanes 1:4);

\textbf{IR} \textit{v}_{\text{max}}\text{(neat):} 2931, 2858, 1612, 1598, 1459, 1425, 1382, 1251, 1214, 1191, 1180, 1139, 1086, 1070, 1021, 925, 872, 836, 814, 800, 773, 739, 681, 664 cm\(^{-1}\);

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\(_3\)): \(\delta\) 7.74 (2H, d, \(J = 8.6\) Hz, H-2' and H-6'), 7.37-7.33 (3H, m, H-5, H-3' and H-5'), 7.24 (2H, t, \(J = 9.0\), H-4 and H-6), 4.46 (2H, s, CH\(_2\)), 2.47 (3H, s, OTs-CH\(_3\)), 0.84 (9H, s, SiMe\(_2\)Bu), 0.02 (6H, s, SiMe\(_2\)Bu);

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\(_3\)): \(\delta\) 149.2 (C\(_4\), C-1), 148.7 (C\(_9\), C-3), 146.2 (C\(_9\), C-1'), 132.4(C\(_9\), C-4'), 130.2 (2 × CH, C-2' and C-6'), 129.6 (CH, C-5), 128.5 (2 × CH, C-3' and C-5'), 122.8 (CH, C-4), 120.8 (CH, C-5), 117.0 (C\(_9\), OTs), 111.1 (C\(_9\), C-2), 54.9 (CH\(_2\), CH\(_2\)OSi), 25.9 (3 × CH\(_3\), SiMe\(_2\)Bu), 21.9 (CH\(_3\), OTs-CH\(_3\)), 18.4 (C\(_9\), SiMe\(_2\)Bu), -5.5 (2 × CH\(_3\), SiMe\(_2\)Bu);

\textbf{HRMS}: found [M + Na]\(^+\) 563.0823, [C\(_{21}\)H\(_{27}\)O6F\(_3\)S\(_2\)Si + Na]\(^+\) requires 563.0812.
2-[(tert-Butyldimethylsilyl)oxy]methyl]-3-hydroxyphenyl 4-methylbenzene-1-sulfonate (310)

To a stirred solution of ZnBr$_2$ (28.0 mg, 0.12 mmol) in THF (2 mL) was added DBU (70.0 μL, 0.48 mmol). The reaction mixture was then successively added triflate 309 (56.0 mg, 0.10 mmol) in THF (3 mL), alkyne 306 in THF (0.5 mL) and tetrakis triphenylphosphine palladium (6.00 mg) and stirred for a further 2 h at room temperature. The reaction mixture was filtered through a pad of Celite® and filtrate was washed with sat. aq. NH$_4$Cl (3 × 10 mL), brine (3 × 10 mL) dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (30.0 mg, 75%) as a colourless oil.

R$_f$: 0.25 (ethyl acetate\hexanes 1:4);

IR $\nu_{max}$ (neat): 3296, 2929, 2858, 1623, 1587, 1470, 1374, 1254, 1213, 1190, 1172, 1050, 837, 791, 761 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.76 (1H, s, OH), 7.73 (2H, d, $J = 7.9$ Hz, H-2’ and H-6’), 7.35 (2H, d, $J = 7.9$ Hz, H-3’ and H-5’), 7.05 (1H, t, $J = 8.4$ Hz, H-5), 6.77 (1H, d, $J = 7.9$ Hz, H-4), 6.38 (1H, dd, $J = 8.5$, 1.1 Hz, H-6), 4.80 (2H, s, CH$_2$), 2.46 (3H, s, OTs-CH$_3$), 0.90 (9H, s, SiMe$_2$(Bu)), 0.16 (6H, s, SiMe$_2$(Bu));

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.5 (C$_q$, C-3), 146.4 (C$_q$, C-1), 145.7 (C$_q$, C-8), 132.9 (C$_q$, C-13), 130.0 (2 × CH, C-2’ and C-6’), 128.8 (CH, C-5), 128.6(2 × CH, C-3’ and C-5’), 118.0 (C$_q$, C-2) 115.9 (CH, C-4), 113.6 (CH, C-6), 60.6 (CH$_2$, CH$_2$OTBS), 25.8 (3 × CH$_3$, SiMe$_2$(Bu)), 21.9 (CH$_3$, OTs-CH$_3$), 18.7 (C$_q$, SiMe$_2$(Bu)), -5.6 (2 × CH$_3$, SiMe$_2$(Bu));

HRMS: found [M + Na]$^+$ 431.1323, [C$_{20}$H$_{28}$O$_5$Si + Na]$^+$ requires 431.1319.
(R)-4-[(tert-Butyldimethylsilyl)oxy]pent-1-yn-3-one (306)

To a stirred solution of Weinreb amide 306 (300 mg, 1.20 mmol) in anhydrous THF (5 mL) at 0 °C and was added ethynylmagnesium bromide (10 mL, 0.5 M in THF, 4.90 mmol) dropwise over 30 min. The reaction mixture was then warmed to room temperature and stirred for a further 6 h. The reaction mixture was quenched with sat. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with sat. aq. NH₄Cl (2 × 20 mL), brine (3 × 20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound (200 mg, 78%) as a yellow oil.

[α]D²₀ + 22.2 (c 1.0, CHCl₃);

Rr: 0.15 (ethyl acetate\hexanes 1:19);

IR νmax (neat): 3258, 2955, 2931, 2858, 2093, 1686, 1253, 1127, 1032, 1099, 1074, 936, 830, 776 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 4.29 (1H, q, J = 6.5 Hz, H-4), 3.32 (1H, s, H-1), 1.41 (3H, d, J = 6.6, H-5), 0.93 (9H, s, SiMe₂Bu), 0.12 (3H, s, SiMe₂Bu), 0.08 (3H, s, SiMe₂Bu);

¹³C NMR (125 MHz, CDCl₃): δ 189.8 (C=O), 81.9 (CH, C-1), 80.0 (Cq, C-2), 75.0 (CH, C-4), 25.8 (3 × CH₃, SiMe₂Bu), 20.3 (CH₃, C-5), 18.4 (Cq, SiMe₂Bu), -4.7 (CH₃, SiMe₂Bu), -4.9 (CH₃, SiMe₂Bu);

Methyl 2-ethynyl-6-(propan-2-yloxy)benzoate (315)

To a stirred solution of phenol 300 (916 mg, 5.20 mmol) in DMF (15 mL) was added potassium carbonate (138 mg, 8.30 mmol) followed by 2-bromopropane and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (5 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:20) gave the title compound (1.10 g, 96%) as a yellow oil.

Rf: 0.20 (1:20 ethyl acetate\hexanes);

IR \nu_{\text{max}}(\text{neat}) : 3255, 2954, 2852, 1669, 1598, 1573, 1448, 1434, 1351, 1314, 1293, 1242, 1211, 1173, 1126, 1068, 946, 811, 744, 692, 675 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.29-7.25 (1H, m, H-4), 7.10 (1H, d, J = 8.1 Hz, H-3), 6.95 (1H, d, J = 8.6 Hz, H-5), 4.54 (1H, sep, J = 5.9 Hz, CH(CH₃)₂), 3.92 (3H, s, OCH₃), 3.16 (1H, s, CCH), 1.32 (3H, s, CH(CH₃)₂), 1.37 (3H, s, CH(CH₃)₂);

¹³C NMR (100 MHz, CDCl₃): δ 167.5 (C=O), 154.9 (C₆), 130.4 (CH, C-4), 128.6 (C₆, C-2), 125.0 (CH, C-3), 121.1 (C₆, C-1), 115.3 (CH, C-5), 80.7(CH, CCH), 77.4 (C₆, CCH), 72.0 (CH, C(CH₃)₂), 52.5 (CH₃, OCH₃), 22.1 (2 × CH₃, C(CH₃)₂);

Experimentals

[2-ethynyl-6-(propan-2-yloxy)phenyl]methanol (311)

Method A:
To a solution of ester 315 (350 mg, 1.60 mmol) in dichloromethane (20 mL) at -78 °C was added diisobutylaluminum hydride (3.2 mL, 1.0 M in toluene) dropwise and the mixture was stirred at -78 °C for 3 h. The reaction was quenched with sat. aq. Rochelle salt and stirred for 4 h then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (NaSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (280 mg, 92%) as a yellow oil.

Method B:
To a stirred solution of ester 315 (350 mg, 1.60 mmol) in THF (40 mL) at 0 °C was added lithium aluminium hydride (242.8 mg, 6.40 mmol) portion wise and stirred for 2 h. The reaction mixture was quenched with water (10 mL) and ethyl acetate (50 mL) was added. The mixture was filtered through a pad of Celite® and the filtrate concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound (290 mg, 95%) as a yellow oil.

Rf: 0.25 (1:4 ethyl acetate\hexanes);

IR νmax (neat): 3557, 3281, 2985, 2893, 1733, 1575, 1463, 1393, 1249, 1191, 1149, 1112, 1088, 1034, 972, 789, 734, 644, 605, 574 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.18 (1H, t, J = 8.0, H-4), 7.10 (1H, dd, J = 7.6 Hz, 1.1, H-3), 6.92 (1H, d, J = 8.1 Hz, H-5), 4.90 (2H, s, CH₂OH), 4.62 (1H, sep, J = 6.1 Hz, CH(CH₃)₂), 3.26 (1H, s, CCH), 1.38 (3H, s, CH(CH₃)₂), 1.37 (3H, s, CH(CH₃)₂);

¹³C NMR (100 MHz, CDCl₃): δ 156.2 (C₆, C-2), 132.3 (C₆, C-6), 128.6 (CH, C-4), 125.2 (CH, C-5), 122.6 (C₆, C-1), 114.0 (CH, C-3), 81.4 (C₆, CCH), 81.2 (CH, CCH), 70.9 (CH, CH(CH₃)₂), 59.5 (CH₂, CH₂OH), 22.1 (2 × CH₃, CH(CH₃)₂);
**Experimentals**

**HRMS**: found [M + Na]+ 213.0882, [C_{12}H_{14}O2 + Na]+ requires 213.0886.

**tert-Butyl([2-ethynyl-6-(propan-2-yloxy)phenyl]methoxy)dimethylsilane (316)**

To a stirred solution of alcohol 311 (1.00 g, 5.30 mmol) in dichloromethane (100 mL) at room temperature was added DMAP (64.0 mg, 0.53 mmol), imidazole (721 mg, 10.2 mmol) and tert-butyldimethylsilyl chloride (1.50 g, 10.2 mmol) and the mixture was stirred for 16 h. Sat. aq. NH₄Cl (50 mL) was then added, and the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic layer were washed with brine (3 × 80 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:8) gave the *title compound* (1.60 g, 99%) as a colourless oil.

**Rf**: 0.25 (1:8 ethyl acetate/hexanes)

**IR υ_{max}** (neat): 3313, 2954, 2929, 2885, 2856, 1575, 1462, 1384, 1361, 1315, 1251, 1196, 1117, 1055, 1005, 959, 854, 773, 721 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.15 (1H, t, J = 7.8 Hz, H-4), 7.08 (1H, d, J = 7.2, H-3), 6.89 (1H, d, J = 7.9 Hz, H-5), 4.85 (2H, s, CH₂OTBS), 4.57 (1H, sep, J = 5.9 Hz, CH(CH₃)₂), 3.18 (1H, s, CCH), 1.33 (6H, d, J = 6.7 Hz, CH(CH₃)₂), 0.91 (9H, s, SiMe₂'Bu), 0.09 (6H, s, SiMe₂'Bu);

**¹³C NMR** (100 MHz, CDCl₃): δ 156.5 (Cₗ, C-6), 132.6 (Cₗ, C-2), 128.6 (CH, C-4), 125.4 (CH, C-3), 124.2 (Cₗ, C-1), 114.9 (CH, C-5), 82.3 (Cₗ, CCH), 80.4 (CH, CCH), 70.9 (CH, CH(CH₃)₂), 58.5 (CH₂, CH₂OTBS), 26.2 (3 × Me, SiMe₂'Bu), 22.3 (2 × Me, CH(CH₃)₂), 18.8 (Cₗ, SiMe₂'Bu), -5.1 (2 × Me, SiMe₂'Bu);

**HRMS**: found [M + Na]+ 327.1741, [C_{18}H_{28}O₂Si + Na]+ requires 327.1751.
(4R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(propan-2-yloxy)phenyl)pent-1-yn-3-one (317)

To a solution of alkyne 316 (400 mg, 1.30 mmol) in anhydrous THF (15 mL) at -78 °C was added LiHDMS (2.3 mL, 1.0 M in THF, 2.30 mmol) and stirred at this temperature for 1 h. A solution of Weinreb amide 264b (385.6 mg, 1.60 mmol) in dry THF (3 mL) was then added dropwise and then reaction mixture was warmed to room temperature and stirred for 1 h. Sat. aq. NH₄Cl (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NH₄Cl, brine (3 × 10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the title compound (539 mg, 79%) as a colourless oil.

[α]_D^20 -2.9 (c 1.0, CHCl₃);

Rr: 0.15 (1:19 ethyl acetate\hexanes);

IR υ max (neat): 2955, 2930, 2856, 1575, 1462, 1384, 1373, 1253, 1117, 1055, 1005, 960, 850, 774, 721 cm⁻¹;

^1^H NMR (300 MHz, CDCl₃): δ 7.28 (1H, t, J = 7.8 Hz, H-5), 7.16 (1H, dd, J = 7.8, 1.28 Hz, H-6), 6.98 (1H, d, J = 8.2 Hz, H-4), 4.86 (2H, s, CH₂OTBS), 4.58 (1H, sep, J = 6.2 Hz, CH(CH₃)₂), 4.39 (1H, q, J = 6.8 Hz, H-4'), 1.48 (3H, d, J = 6.7 Hz, H-5'), 1.35 (6H, dd, J = 6.1, 1.3 Hz, CH(CH₃)₂), 0.92 (9H, s, SiMe₂Bu), 0.89 (9H, s, SiMe₂Bu), 0.13-0.09 (12H, m, 2 × SiMe₂Bu);

^1^3^C NMR (100 MHz, CDCl₃): δ 189.8 (C=O), 156.4 (C₆, C-3) 133.5 (C₄, C-1), 128.9 (CH, C-5), 125.9 (CH, C-6), 122.2 (C₆, C-2), 116.3 (CH, C-4), 92.9 (C₆, C-1'), 89.2 (C₆, C-2') 75.5 (CH, C-4'), 70.8 (CH, CH(CH₃)₂), 58.2 (CH₂, CH₂OTBS), 26.1 (3 × CH₃, SiMe₂Bu), 25.9 (3 × CH₃, SiMe₂Bu), 22.2 (2 × CH₃, CH(CH₃)₂), 20.8 (CH₃, C-5'), 18.7 (C₆, SiMe₂Bu), 18.5 (C₆, SiMe₂Bu), -4.5 (CH₃, SiMe₂Bu), -4.9 (CH₃, SiMe₂Bu), -5.1 (2 × CH₃, SiMe₂Bu);
HRMS: found [M + Na]$^+$ 513.2837, [C$_{27}$H$_{46}$O$_3$Si$_2$ + Na]$^+$ requires 513.2827.

{(2-(2-Bromoethyl)-6-(propan-2-yl)phenyl)ethoxy}(tert-butyl)dimethylsilane (323)

To a stirred solution of alkyne 316 (315 mg, 1.00 mmol) in acetone (10 mL) under an atmosphere of argon was added N-bromosuccinimide (202 mg, 1.10 mmol) and silver nitrate (17.6 mg, 0.10 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 h then concentrated in vacuo. The reaction was dissolved in ethyl acetate (20 mL) and filtered through a pad of Celite$^\circledR$ and the filtrate was concentrated in vacuo affording the title compound (419 mg, quant) as yellow oil. Further purification was not required.

Rf: 0.50 (1:19 ethyl acetate\hexanes);

IR $\nu_{\text{max}}$ (neat): 2975, 2928, 1587, 1460, 1372, 1255, 1118, 1057, 1016, 988, 779, 743 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16 (1H, t, $J = 7.8$ Hz, H-4), 7.05 (1H, d, $J = 7.4$ Hz, H-3), 6.89 (1H, d, $J = 8.2$ Hz, H-5), 4.82 (2H, s, CH$_2$OTBS), 4.53 (1H, sep, $J = 6.3$ Hz, CH(CH$_3$)$_2$), 1.34 (6H, d, $J = 6.0$ Hz, CH(CH$_3$)$_2$), 0.93 (9H, s, SiMe$_2$Bu), 0.11 (6H, s, SiMe$_2$Bu);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.5 (C$_q$, C-6), 132.8 (C$_q$, C-2), 128.6 (CH, C-4), 125.3 (CH, C-3), 124.8 (C$_q$, C-1), 115.1 (CH, C-5), 78.9 (C$_q$, C-2'), 71.1 (CH, CH(CH$_3$)$_2$), 58.3 (CH$_2$, CH$_3$OTBS), 52.4 (C$_q$, C-1'), 26.2 (3 $\times$ CH$_3$, SiMe$_2$Bu), 22.3 (2 $\times$ CH$_3$, CH(CH$_3$)$_2$), 18.8 (C$_q$, SiMe$_2$Bu), -5.1 (2 $\times$ CH$_3$, SiMe$_2$Bu);

HRMS: found [M + Na]$^+$ 405.0840, [C$_{18}$H$_{27}$BrO$_2$Si + Na]$^+$ requires 405.0856.
To a stirred solution of alkyne 323 (150 mg, 0.39 mmol) in methanol (10 mL) was added p-toluenesulfonylhydrazine (181.6 mg, 0.98 mmol) and sodium acetate (113.0 mg, 1.37 mmol) at room temperature. The reaction mixture was then refluxed for 12 h then cooled to room temperature and water (10 ml) was added. The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was filtered through a short plug of silica (ethyl acetate) to afford an inseparable mixture title compound (140 mg, 93%) as a yellow oil.

Rf: 0.55 (1:19 ethyl acetate/hexanes);

IR ν_max (neat): 2975, 2928, 1587, 1460, 1372, 1255, 1118, 1057, 1016, 988, 779, 743 cm⁻¹;

¹H NMR (400 MHz, CDCl₃, *denotes product 324): δ 7.44 (1H, d, J = 8.0 Hz, H-2'), 7.23 (2H, d, J = 5.1 Hz, H-5 and H-3), 7.19* (0.3H, t, J = 7.7 Hz, H-4), 6.86 (1H, t, J = 5.3 Hz, H-5), 6.80* (0.3H, m, H-3 and H-5), 6.50 (1H, d, J = 7.8 Hz, H-1'), 4.79* (0.3H, s, CH₂OTBS), 4.72 (2H, s, CH₂OTBS), 4.53 (1H, sep, J = 6.5 Hz, CH(CH₃)₂ and CH(CH₃)₂*), 3.64* (0.3H, t, J = 7.5 Hz, H-1'), 3.28* (0.3H, t, J = 8.1 Hz, H-2'), 1.35 (6H, d, J = 6.2 Hz, CH(CH₃)₂), 1.33* (1.5H, dd, J = 6.0 Hz, CH(CH₃)₂), 0.91* (2H, s, SiMe₂Bu), 0.89 (9H, s, SiMe₂Bu), 0.11* (1.5H, s, SiMe₂Bu) 0.05 (6H, s, SiMe₂Bu);

¹³C NMR (100 MHz, CDCl₃, *denotes product 324): δ 155.6 (C₉, C-6), 137.3 (C₉, C-2), 132.4 (CH, C-1'), 128.2 (C₉, C-1), 128.1 (CH, C-5), 121.5 (CH, C-3), 113.5 (CH, C-5), 108.0 (CH, C-2'), 70.7 (CH, CH(CH₃)₂), 56.8 (CH₂, CH₂OTBS), 26.2* (CH₃, SiMe₂Bu), 26.1 (CH₃, SiMe₂Bu), 22.2 (2 × CH₃, CH(CH₃)₂), 18.4 (C₉, SiMe₂Bu), -5.2 (2 × CH₃, SiMe₂Bu);

**Experimentals**


(1Z,4R)-4-[(tert-butyldimethylsilyl)oxy]-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(propan-2-yloxy)phenyl)pent-1-en-3-one (312)

Method A

To a stirred solution of bromo alkene 322 (60.0 mg, 0.16 mmol) in diethyl ether (7 mL) at -78 °C was added t-BuLi (0.16 mL, 1.5 M in THF, 0.24 mmol) dropwise and stirred for 30 seconds, then a solution of Weinreb amide 264b (59.0 mg, 0.24 mmol) in diethyl ether (1 mL) was added over 10 mins before the reaction mixture was warmed to room temperature slowly over 12 h. Sat. aq. NH₄Cl (10 mL) was added and the aqueous layer was separated and extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (3 × 20 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate\hexanes, 1:19) gave the *title compound* (31.0 mg, 40%) as a yellow oil.

Method B

P-2 nickel was prepared as followed. To a stirred suspension of nickel (II) acetate (60.0 mg, 0.24 mmol) in 95% ethanol (5 mL) was added a solution of sodium borohydride (0.48 mL, 0.50 M in ethanol, 0.24 mmol) and stirred at room temperature. Stirring continued until the gas evolution ceases (30 mins) and a black suspension evolved. The suspension is then placed
under an atmosphere of hydrogen and a solution of alkyne 317 (60.0 mg, 0.12 mmol) in ethanol (1 mL) was added and stirred for 12 h. The reaction mixture was filtered through a pad of Celite® and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (29.0 mg, 50%) as a yellow oil and alkane 318 (29.0 mg, 50%).

**Method C**

To a stirred solution of alkyne 317 (200 mg, 0.47 mmol) in hexanes (30 mL) was added quinoline (0.3 mL, 2.3 mmol) and the mixture was subjected to hydrogenation using an H-cube® flow reactor with the following settings (Lindlar catalyst, 1 mL/min, 10 bar, 20 °C). The reaction mixture was concentrated in vacuo, and purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (185 mg, 80%) as a yellow oil and trace amounts of alkane 318.

\[ [\alpha]_{D}^{20} + 4.80 \text{ (c 0.5, CHCl}_{3} \text{)}; \]

**IR** \( v_{\text{max}} \text{ (neat): } 2955, 2929, 2887, 2857, 1693, 1609, 1575, 1470, 1373, 1384, 1251, 1117, 1065, 1006, 960, 938, 854, 813, 774 \text{ cm}^{-1}; \)

**\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \( \delta \) 7.31 (1H, d, \( J = 12.9 \text{ Hz, H-1}' \)), 7.10 (1H, t, \( J = 7.2 \text{ Hz, H-5} \)), 6.87 (1H, d, 7.6 Hz, H-6), 6.78 (1H, d, \( J = 8.1 \text{ Hz, H-4} \)), 6.57 (1H, d, \( J = 6.6 \text{ Hz, H-2}' \)), 4.67 (2H, s, CH₂OSi), 4.46 (1H, sep, \( J = 6.1 \text{ Hz, } CH(CH_3)_2 \)), 4.12 (1H, q, \( J = 6.9 \text{ Hz, H-4}' \)), 1.28 (6H, d, \( J = 6.8 \text{ Hz, CH(CH}_3)_2 \)), 1.24 (3H, d, \( J = 6.6 \text{ Hz, H-5}' \)), 0.86 (9H, s, SiMe\(_2\)Bu), 0.83 (9H, s, SiMe\(_2\)Bu), 0.018- -0.007 (12H, m, 2 \( \times \) SiMe\(_2\)Bu);

**\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \( \delta \) 203.1 (C=O), 155.4 (C\(_q\), C-3), 142.5 (CH, C-1'), 138.2 (C\(_q\), C-1), 128.1 (CH, C-2'), 127.9 (C\(_q\), C-2), 124.2 (CH, C-5), 121.5 (CH, C-4), 113.8 (CH, C-6), 75.0 (CH, C-4'), 70.6 (CH, CH(CH\(_3\))\(_2\)), 57.1 (CH\(_2\), CH\(_2\)OSi), 26.1 (3 \( \times \) CH\(_3\), SiMe\(_2\)Bu), 25.9 (3 \( \times \) CH\(_3\), SiMe\(_2\)Bu), 22.3 (2 \( \times \) CH\(_3\)), CH(CH\(_3\))\(_2\)), 21.0 (CH\(_3\), C-5'), 18.6 (C\(_q\), SiMe\(_2\)Bu), 18.3 (C\(_q\), SiMe\(_2\)Bu), -4.70 (Me, SiMe\(_2\)Bu), -4.71 (Me, SiMe\(_2\)Bu), -5.1 (2 \( \times \) CH\(_3\), SiMe\(_2\)Bu);

**HRMS**: found [M + Na]\(^+\) 515.2986, [C\(_{27}\)H\(_{48}\)O\(_4\)Si\(_2\) + Na]\(^+\) requires 515.2983.
Experimentals

1-[3-Methoxy-9-(propan-2-yloxy)-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-one (326)

Method A

To a stirred solution of alkene 312 (90.0 mg, 0.18 mmol) in methanol (5 mL) was added trimethyl orthoformate (0.02 mL, 0.18 mmol) and p-toluenesulfonic acid (20.0 mg, 0.095 mmol) and stirred at room temperature for 7 h. Sat. aq. NaHCO$_3$ (20 mL) was then added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with sat. aq. NaHCO$_3$ (3 × 20 mL), brine (3 × 20 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:5) gave the title compound (25.0 mg, 50%) as a yellow oil.

Method B

To a stirred solution of alcohols 228a and 328b (151 mg, 0.60 mmol) in toluene (6 mL) was added DDQ (487 mg, 2.15 mmol) and heated to 100 °C for 4 h. The reaction mixture was quenched with sat. aq. NaHCO$_3$ (5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO$_3$ until aqueous phase was colourless, brine (3 × 10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:5) gave the title compound (99.0 mg, 60%) as a yellow oil.
**Experimentals**

\[ \text{Rf: 0.3 (1:5 ethyl acetate\textbackslash{}hexanes);} \]

**IR** \( \nu_{\text{max}} \) (neat): 3390, 2926, 2888, 1698, 1607, 1574, 1467, 1375, 1267, 1119, 1075, 1070, 1005, 960, 930, 850, 774 cm\(^{-1}\);

**\(^{1}\text{H NMR}\)** (500 MHz, CDCl\(_3\)): \( \delta \) 7.27-7.24 (1H, m, H-7'), 6.96 (1H, d, \( J = 7.6 \) Hz, H-6'), 6.91 (1H, d, \( J = 7.8 \) Hz, H-8'), 6.74 (1H, d, \( J = 12.5 \) Hz, H-5'), 5.80 (1H, d, \( J = 12.3 \) Hz, H-4'), 5.31 (1H, d, \( J = 13.6 \) Hz, H-1'\( \text{ab} \)), 4.57 (1H, sep, \( J = 6.5 \) Hz, CH(CH\(_3\))\(_2\)), 4.15 (1H, d, \( J = 13.3 \) Hz, H-1'\( \text{ab} \)), 3.30 (3H, s, OCH\(_3\)), 2.03 (3H, s, H-2), 1.40 (3H, d, \( J = 6.1 \) Hz, CH(CH\(_3\))\(_2\)), 1.35 (3H, d, \( J = 6.0 \) Hz, CH(CH\(_3\))\(_2\));

**\(^{13}\text{C NMR}\)** (125 MHz, CDCl\(_3\)): \( \delta \) 205.1 (C=O), 154.4 (C\(_q\), C-9'), 136.1 (C\(_q\), C-11'), 133.7 (CH, C-5'), 130.5 (C\(_q\), C-10'), 129.8 (CH, C-7'), 128.3 (CH, C-4'), 123.3 (CH, C-6'), 113.8 (CH, C-8'), 105.4 (C\(_q\), C-3'), 71.5 (CH, CH(CH\(_3\))\(_2\)), 57.9 (CH\(_2\), C-1'), 49.9 (CH\(_3\), OCH\(_3\)), 25.7 (CH\(_3\), C-2), 22.2 (2 \( \times \) CH\(_3\), CH(CH\(_3\))\(_2\));

**HRMS**: found [M + Na]\(^+\) 299.1259. [C\(_{16}\)H\(_{20}\)O\(_4\) + Na]\(^+\) requires 299.1254.
Experimentals

(R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(propan-2-yloxy)phenyl)pentan-3-one (318)

To a stirred solution of ketone 317 (500 mg, 1.0 mmol) in ethyl acetate (25 mL) was added Pd/C (50 mg) and the reaction mixture was placed under an atmosphere of hydrogen for 1 h. The reaction mixture was then filtered through a pad of Celite® and the filtrate concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave the title compound (470 mg, 95%) as a yellow oil.

$[\alpha]_D^{20} +1.90$ (c 1.0, CHCl$_3$);

$R_f$: 0.30 (1:9 ethyl acetate\hexanes);

IR $\nu_{\text{max}}$ (neat): 2955, 2930, 2858, 1719, 1585, 1462, 1384, 1372, 1253, 1118, 1062, 1005, 932, 835, 776 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.09 (1H, t, $J = 7.6$ Hz, H-5), 6.70 (2H, d, $J = 8.4$ Hz, H-4 and H-6), 4.77 (2H, d, $J = 10.8$ Hz, $CH_2ab$), 4.70 (1H, d, $J = 10.8$ Hz, $CH_2ab$), 4.49 (1H, sep, $J = 6.1$ Hz, $CH(CH_3)_2$), 4.10 (1H, q, $J = 6.8$ Hz, H-4'), 2.91-2.76 (4H, m, H-1' and H-2'), 1.28 (6H, d, $J = 6.8$ Hz, $CH(CH_3)_2$), 1.18 (3H, d, $J = 6.8$ Hz, H-5'), 0.83 (9H, s, SiMe$_2$Bu), 0.82 (9H, s, SiMe$_2$Bu), 0.03--0.001 (12H, m, SiMe$_2$Bu);

$^13$C NMR (125 MHz, CDCl$_3$): $\delta$ 213.2 (C=O), 156.0 (C$_q$, C-3), 143.3 (C$_q$, C-1), 128.6 (CH, C-5), 128.3 (C$_q$, C-2), 121.6 (CH, C-6), 111.5 (CH, C-4), 75.1 (CH, C-4'), 70.5 (CH, CH(CH$_3$)$_2$), 56.3 (CH$_2$, CH$_2$OSi), 38.8 (CH$_2$, C-2'), 26.4 (CH$_2$, C-1'), 26.0 (3 $\times$ CH$_3$, SiMe$_2$Bu), 25.9 (3 $\times$ CH$_3$, SiMe$_2$Bu), 22.3 (2 $\times$ CH$_3$, CH(CH$_3$)$_2$), 20.9 (CH$_3$, C-5'), 18.6 (C$_q$, SiMe$_2$Bu), 18.2 (C$_q$, SiMe$_2$Bu), -4.7 (CH$_3$, SiMe$_2$Bu), -4.8 (CH$_3$, SiMe$_2$Bu), -5.1 (2 $\times$ CH$_3$, SiMe$_2$Bu);

HRMS: found [M + Na]$^+$ 517.3151, [C$_{27}$H$_{56}$O$_4$Si$_2$ + Na]$^+$ requires 517.3140.

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(1R)-1-[(3R)-3-Methoxy-9-(propan-2-yloxy)-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (328a) and (1R)-1-[(3S)-3-Methoxy-9-(propan-2-yloxy)-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (328b)

![Chemical structure](image)

To a stirred solution of alkane 318 (500 mg, 1.00 mmol) in methanol (20 mL) was added trimethyl orthoformate (0.10 mL, 1.00 mmol) and p-toluenesulfonic acid (95.0 mg, 0.50 mmol) and stirred at room temperature for 6 h. Sat. aq. NaHCO₃ (50 mL) was added and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 × 20 mL), brine (3 × 20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound 328a (123.4 mg, 44%) as a colourless foam and title compound 328b (100 mg, 36%) as a colourless foam.

\[\alpha\]D\textsuperscript{19.5} -84.27 (c 1.00, CHCl₃);

Rr: 0.30 (1:4 ethyl acetate/hexanes);

IR ν\textsuperscript{max} (neat): 3423, 2965, 2919, 2850, 1589, 1462, 1370, 1250, 1174, 1110, 1079, 1017, 992, 970, 896, 782, 743 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (500 MHz, CDCl₃): δ 7.12 (1H, t, J = 7.2 Hz, H-7'), 6.76 (2H, d, J = 8.6 Hz, H-6' and H-8'), 5.02 (1H, d, J = 13.8 Hz, H-1'ab), 4.71 (1H, d, J = 13.8 Hz, H-1'ab), 4.51 (1H, sep, J = 6.0 Hz, CH(CH₃)₂), 3.99 (1H, q, J = 6.8 Hz, H-1), 3.34 (3H, s, OCH₃), 3.32 (1H, t, J = 13.6 Hz, H-4'ab), 2.66 (1H, dd, J = 15.8, 7.3 Hz, H-4'ab), 2.01 (1H, brs, OH), 1.96 (1H, t, J = 12.6 Hz, H-5'ab), 1.87 (1H, dd, J = 14.0, 7.3 Hz, H-5'ab), 1.37 (3H, d, J = 6.0 Hz, CH(CH₃)₂), 1.32 (3H, d, J = 6.1 Hz, CH(CH₃)₂), 1.27 (3H, d, J = 6.6 Hz, H-2);
**Experimentals**

**13C NMR** (125 MHz, CDCl3): δ 155.3 (Cq, C-6), 145.2 (Cq, C-2), 128.7 (Cq, C-1), 128.5 (CH, C-4), 121.1 (CH, C-3), 112.2 (CH, C-1), 103.3 (Cq, C-13), 71.3 (CH, C-10), 69.2 (CH, C-15), 55.8 (CH2, C-9), 48.3 (OCH3), 29.8 (CH2, C-7), 28.5 (CH2, C-8) 22.5 (CH3, C-11), 22.3 (CH3, C-12), 15.8 (CH3, C-16);


[\(\alpha\)]D\textsuperscript{19.5} +161.25 (c 1.00, CHCl3);

**RI**: 0.25 (1:4 ethyl acetate\hexanes);

**IR** \(\nu_{max}\) (neat): 3463, 2974, 2939, 2850, 1738, 1589, 1462, 1370, 1253, 1174, 1110, 1079, 1017, 992, 970, 896, 778, 744 cm\(^{-1}\);

**1H NMR** (500 MHz, CDCl3): δ 7.11 (1H, t, \(J = 7.7\) Hz, H-7'), 6.76 (2H, d, \(J = 9.4\) Hz, H-7' and H-8'), 5.06 (1H, d, \(J = 13.9\) Hz, H-1\textsubscript{ab}), 4.72 (1H, d, \(J = 13.8\) Hz, H-1\textsubscript{a}), 4.51 (1H, sep, \(J = 6.1\) Hz, CH(CH\textsubscript{3})\textsubscript{2}), 3.89 (1H, q, \(J = 6.8\) Hz, H-1), 3.44 (3H, s, OCH\textsubscript{3}), 3.25 (1H, t, \(J = 12.8\) Hz, H-8\textsubscript{ab}), 2.67 (1H, dd, \(J = 15.1, 8.1\) Hz, H-8\textsubscript{a}), 2.4 (1H, brs, OH), 2.03 (1H, dd, \(J = 14.5, 8.5\) Hz, H-4\textsubscript{a}'), 1.72 (1H, t, \(J = 12.7\) Hz, H-4\textsubscript{a}'), 1.36 (3H, d, \(J = 6.0\) Hz, CH(CH\textsubscript{3})\textsubscript{2}), 1.32 (3H, d, \(J = 6.1\) Hz, CH(CH\textsubscript{3})\textsubscript{2}), 1.17 (3H, d, \(J = 6.3\) Hz, H-2);

**13C NMR** (125 MHz, CDCl3): δ 155.3 (Cq, C-6), 144.8 (Cq, C-2), 128.4 (Cq, C-1), 128.3 (CH, C-4), 121.2 (CH, C-3), 112.1 (CH, C-1), 102.7 (Cq, C-13), 71.2 (CH, C-10), 69.9 (CH, C-15), 56.6 (CH2, C-9), 49.1 (OCH3), 32.2 (CH2, C-7), 28.9 (CH2, C-8) 22.4 (CH3, C-11), 22.3 (CH3, C-12), 16.5 (CH3, C-16);

(3S,3'R,5'S,6'R)-9,9''-diisopropoxy-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (331a) and
(3R,3'R,5'S,6'R)-9,9''-diisopropoxy-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (331b)

To a stirred solution of alcohol 328 (50.0 mg, 0.18 mmol) in dichloromethane (5 mL) at -78 °C and was added trifluoroacetic acid (0.01 mL, 0.18 mmol) and the mixture was stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:9) gave the title compound 331a (17.5 mg, 40%) as a colourless foam and title compound 331b (16.0 mg, 37%) as a colourless foam.

[α]°D⁰ + 141.0 (c 1.2, CHCl₃);

Rr: 0.30 (1:9 ethyl acetate/hexanes);

IR νmax (neat): 2976, 2927, 1586, 1459, 1372, 1253, 1229, 1216, 1107, 1073, 1054, 1014, 987, 972, 720, 690, 666 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.01 (2H, t, J = 7.5 Hz, H-7 and H-7'), 6.76 (4H, d, J = 7.5 Hz, H-6, H-6', H-8 and H-8'), 4.99 (4H, q, J = 13.5 Hz, H-1 and H-1'), 4.50 (2H, sep, J = 5.9 Hz, CH(CH₃)₂), 3.96 (2H, q, J = 6.5 Hz, H-2, 2'), 3.32 (2H, t, J = 13.4 Hz, H-4ab and H-4ab'), 2.67 (2H, dd, J = 14.7, 7.9 Hz, H-4ab and H-4ab'), 2.00 (2H, dd, J = 13.7, 7.8 Hz, H-5ab and H-5
\[ \text{ab} \), 1.8 (2H, t, \( J = 13.0 \) Hz, H-5ab and 5ab'), 1.35 (6H, d, \( J = 6.1 \) Hz, CH(CH\(_3\))\(_2\)), 1.3 (6H, d, \( J = 6.0 \) Hz, CH(CH\(_3\))\(_2\)), 1.19 (6H, d, \( J = 6.5 \) Hz, CHCH\(_3\));

\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 155.4 (C\(_q\), C-9, C-9'), 145.4 (C\(_q\), C-11, C-11'), 129.4, 127.9 (CH, C-7, C-7'), 124.9 (C\(_q\), C-10, C-10'), 121.2 (CH, C-6, C-6'), 112.0 (CH, C-8, C-8'), 101.6 (C\(_q\), C-3, C-3'), 71.1 (CH, CH(CH\(_3\))\(_2\)), 68.9 (CH, C-2, C-2'), 55.7 (CH\(_2\), C-1, C-1'), 33.0 (CH\(_2\), C-4, C-4'), 28.9 (CH\(_2\), C-5, C-5'), 22.4 (CH\(_3\), CH(CH\(_3\))\(_2\)), 22.3 (CH\(_3\), CH(CH\(_3\))\(_2\)), 15.8 (CH\(_3\), CH(CH\(_3\))\(_2\));

\textbf{HRMS}: found [M + Na]+ 519.2709, [C\(_{30}\)H\(_{40}\)O\(_6\)+ Na]+ requires 519.2717.

\[ [\alpha]_{b}^{19.5} + 16.2 \text{ (c 0.9, CHCl\(_3\))}; \]

\textbf{Rr}: 0.2 (1:9 ethyl acetate\hexanes);

\textbf{IR} \( \nu_{\text{max}} \) (neat): 2926, 2122, 1588, 1469, 1373, 1257, 1207, 1142, 1106, 1079, 1034, 1018, 992, 967, 937, 906, 854, 747, 728, 669 cm\(^{-1}\);

\( ^{1}\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.11 (2H, t, \( J = 8.0 \) Hz, H-7 and H-7'), 6.76-6.73 (4H, d, H-6, H-6', H-8 and H-8'), 5.07 (1H, d, \( J = 13.5 \) Hz, H-1ab), 4.93 (2H, s, H-1'), 4.72 (1H, d, \( J = 13.5 \) Hz, H-1ab), 4.51-4.46 (3H, m, CH(CH\(_3\))\(_3\)) 3.94 (1H, q, \( J = 6.3 \) Hz, H-2), 3.82 (1H, q, \( J = 6.3 \) Hz, H-2'), 3.34-3.29 (2H, m, H-4ab, H-4ab'), 2.65-2.54 (2H, m, H-4ab, H-4ab'), 2.11-2.04 (1H, m, H-5ab), 1.94-1.89 (1H, m, H-5ab), 1.71-1.62 (2H, m, H-5ab, H-5ab'), 1.48 (3H, d, \( J = 7.2 \) Hz, CHCH\(_3\)), 1.34-1.30 (6H, m, CH(CH\(_3\))\(_2\)) 1.23 (3H, d, \( J = 6.5 \) Hz, CHCH\(_3\));

\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 155.5 (C\(_q\), C-9), 155.1 (C\(_q\), C-9'), 145.3 (2 \( \times \) C\(_q\), C-11 and C-11'), 129.6 (C\(_q\), C-10), 128.9 (C\(_q\), C-10') 128.1 (CH, C-7), 128.0 (CH, C-7), 120.9 (CH, C-6), 120.8 (CH, C-6'), 112.6 (CH, C-8), 111.5 (CH, C-8'), 99.8 (C\(_q\), C-13), 97.1 (C\(_q\), C-3'), 73.4 (CH, C-2'), 71.4 (CH, CH(CH\(_3\))\(_3\)), 70.5 (CH, CH(CH\(_3\))\(_3\)), 69.8 (CH, C-2), 56.1 (CH\(_2\), C-1') 55.5 (CH\(_2\), C-1), 35.2 (CH\(_2\), C-5'), 34.2 (CH\(_2\), C-5), 28.6 (CH\(_2\), C-4'), 28.4 (CH\(_2\), C-4), 22.4 (4 \( \times \) CH\(_3\), CH(CH\(_3\))\(_3\)), 18.1 (CH\(_3\), CHCH\(_3\)), 15.6 (CH\(_3\), CHCH\(_3\));

\textbf{HRMS}: found [M + Na]+ 519.2736, [C\(_{30}\)H\(_{40}\)O\(_6\)+ Na]+ requires 519.2717.
(±)-1-[3-Methoxy-9-(propan-2-yloxy)-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-ol (313)

To a stirred solution of ketal 326 (40.0 mg, 0.14 mmol) in methanol (10 mL) at 0 °C was added cerium (III) chloride heptahydrate (81.0 mg, 0.22 mmol) and sodium borohyride (8.00 mg, 0.22 mmol) and stirred for 10 min. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by filtering crude product through a short plug of silica (ethyl acetate\hexanes, 1:4) afforded a diastereomeric mixture of title compound (35.0 mg, 90%) as colourless oil that was precluded from being fully characterised due to overlap resonances.

Rf: 0.20 (1:4 ethyl acetate\hexanes);

IR νmax (neat): 3381, 2954, 1730, 1257, 1069, 839, 761 cm⁻¹;

To a stirred solution of alcohol (±)-313 (30.0 mg, 0.09 mmol) in dichloromethane (3 mL) at -78 °C and was added trifluoroacetic acid (1 drop) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:9) gave title compound (±)-314a (13.0 mg, 0.054 mmol, 60%) as a colourless foam and title compound (±)-313b (3.80 mg, 15%) as a colourless foam.

**Rf:** 0.20 (1:9 ethyl acetate/hexanes);

**IR** νmax (neat): 2929, 2956, 2858, 1727, 1579, 1462, 1373, 1260, 1116, 1063, 1022, 987, 838, 806, 778 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.22 (2H, t, J = 8.5 Hz, H-7 and H-7'), 6.93 (2H, d, J = 7.2 Hz, H-6 and H-6') 6.82 (2H, d, J = 8.6 Hz, H-8 and H-8'), 6.69 (2H, d, J = 12.6 Hz, H-4 and H-4'), 5.97 (1H, d, J = 12.6 Hz, H-5 and H-5'), 5.97 (2H, d, J = 12.5 Hz, H-1αb and H-1'αb) 4.59 (2H, d, J = 12.6 Hz, H-1αb and H-1'αb), 4.53 (2H, sep, J = 6.0 Hz, CH(CH₃)₂), 4.15 (2H, q, J = 6.0 Hz, H-2 and H-2'), 1.37 (6H, d, J = 6.1 Hz, CH(CH₃)₂), 1.32 (6H, d, J = 6.0 Hz, CH(CH₃)₂), 1.06 (6H, d, J = 6.5 Hz, CH(CH₃)₂);
**Experimentals**

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.5 (2 × C$_q$, C-9 and C-9$'$), 136.9 (2 × C$_q$, C-11 and C-11$'$), 131.4 (2 × CH, C-4 and C-4$'$), 131.0 (2 × CH, C-5 and C-5$'$), 130.2 (2 × C$_q$, C-10 and C-10$'$), 128.0 (2 × CH, C-7 and C-7$'$), 123.1 (2 × CH, C-6 and C-6$'$), 113.2 (2 × CH, C-8 and C-8$'$), 104.1 (2 × C$_q$, C-3 and C-3$'$), 71.4 (2 × CH, CH(CH$_3$)$_2$), 67.1 (2 × CH, C-2 and C-2$'$), 57.1 (2 × CH$_2$, C-1 and C-1$'$), 22.3 (2 × CH$_3$, CH(CH$_3$)$_2$), 16.3 (2 × CH$_3$, CHCH$_3$);

HRMS: found [M + Na]$^+$ 515.2423, [C$_{30}$H$_{36}$O$_6$+ Na]$^+$ requires 515.2404.

Rr: 0.25 (1:9 ethyl acetate/hexanes);

IR $\nu_{\text{max}}$ (neat): 2929, 2956, 2858, 1727, 1579, 1462, 1373, 1260, 1116, 1063, 1022, 987, 838, 806, 778 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.22 (2H, t, $J = 8.5$ Hz, H-7 and H-7$'$), 6.90 (2H, d, $J = 7.2$ Hz, H-6 and H-6$'$) 6.84 (2H, d, $J = 8.6$ Hz, H-8 and H-8$'$), 6.64 (2H, d, $J = 12.6$ Hz, H-4 and H-4$'$), 5.84 (1H, d, $J = 12.6$ Hz, H-5 and H-5$'$), 5.29 (2H, d, $J = 12.5$ Hz, H-1$'ab$ and H-1$'ab$), 5.1-4.54 (2H, m, H-1$'ab$ and H-1$'ab$ and CH(CH$_3$)$_3$)$_3$, 4.23 (2H, q, $J = 6.0$ Hz, H-2 and H-2$'$), 1.39 (6H, d, $J = 6.1$ Hz, CH(CH$_3$)$_2$), 1.34 (6H, d, $J = 6.0$ Hz, CH(CH$_3$)$_2$), 1.03 (6H, d, $J = 6.5$ Hz, CHCH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.5 (2 × C$_q$, C-9 and C-9$'$), 136.8 (2 × C$_q$, C-11 and C-11$'$), 132.6 (2 × CH, C-4 and C-4$'$), 131.8 (2 × CH, C-5 and C-5$'$), 130.6 (2 × C$_q$, C-10 and C-10$'$), 127.9 (2 × CH, C-7 and C-7$'$), 123.2 (2 × CH, C-6 and C-6$'$), 113.2 (2 × CH, C-8 and C-8$'$), 99.9 (2 × C$_q$, C-3 and C-3$'$), 71.1 (2 × CH, CH(CH$_3$)$_2$), 67.2 (2 × CH, C-2 and C-2$'$), 56.8 (2 × CH$_2$, C-1 and C-1$'$), 22.3 (2 × CH$_3$, CH(CH$_3$)$_2$), 22.2 (2 × CH$_3$, CH(CH$_3$)$_2$), 15.0 (2 × CH$_3$, CHCH$_3$);

HRMS: found [M + Na]$^+$ 515.2423, [C$_{30}$H$_{36}$O$_6$+ Na]$^+$ requires 515.2404.
**Methyl 2-(ethoxymethoxy)-6-ethynylbenzoate (338)**

To a stirred solution of phenol 300 (1.13 g, 6.42 mmol) in dichloromethane (50 mL) was added TBAI (118 mg, 0.32 mmol) and cooled to 0 °C. DIPEA (2.2 mL, 12.8 mmol) was added dropwise, followed by chloromethyl ethyl ether (1.2 mL, 12.8 mmol). The reaction mixture was then warmed to room temperature and stirred 16 h. The reaction was quenched with water (5 mL), washed with brine (3 x 30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:20) gave the *title compound* (1.30 g, 90%) as a yellow oil.

**Rf**: 0.20 (ethyl acetate/hexanes 1:19);

**IR \( \nu_{\text{max}} \) (neat):** 3288, 2977, 2936, 1750, 1736, 1573, 1509, 1467, 1419, 1328, 1299, 1255, 1212, 1134, 1116, 1029, 987, 851, 817, 766, 718, 700, 603, 558 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): \( \delta \) 7.29 (1H, dd, \( J = 8.0, 0.95 \), H-4), 7.20 (1H, dd, \( J = 8.4, 0.91 \) Hz, H-5), 7.17 (1H, dd, \( J = 7.4, 1.1 \) Hz, H-3), 5.23 (2H, s, OCH₂OCH₂CH₃), 3.92 (3H, s, OCH₃), 3.72 (2H, q, \( J = 7.3 \) Hz, OCH₂OCH₂CH₃), 3.18 (1H, s, H-8), 1.20 (3H, t, \( J = 6.7 \) Hz, OCH₂OCH₂CH₃);

**¹³C NMR** (100 MHz, CDCl₃): \( \delta \) 167.1 (C=O), 153.9 (C₆₋₂), 130.5 (CH, C-4), 127.7 (C₆₋₁), 126.0 (CH, C-5), 120.9 (C₆₋₁), 115.9 (CH, C-3), 93.5 (CH₂, OCH₂OCH₂CH₃), 80.7 (CH, C-8), 80.5 (C₆₋₁), 64.6 (CH₂, OCH₂OCH₂CH₃), 52.5 (CH₃, OCH₃), 15.0 (CH₃, OCH₂OCH₂CH₃);

**HRMS**: found [M + Na]⁺ 257.0792, [C₁₃H₁₄O₄ + Na]⁺ requires 257.0784.
Experimentals

[2-(Ethoxymethoxy)-6-ethynylphenyl] methanol (333)

To a stirred solution of ester 338 (2.00 g, 8.50 mmol) in THF (150 mL) at 0 °C was added lithium aluminium hydride (1.30 g, 34.2 mmol) was added in small portion and stirred for 3 h at this temperature. The reaction mixture was quenched with water (10 mL) and ethyl acetate (100 mL) was added. The mixture was then filtered through a pad of Celite® and the filtrate was concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:20) gave the title compound (1.60 g, 90%) as a yellow/reddish oil.

Rf: 0.20 (ethyl acetate/hexanes 1:20)

IR νmax (neat): 3555, 3282, 2984, 2895, 1733, 1575, 1463, 1393, 1249, 1191, 1149, 1112, 1088, 1036, 972, 790, 744, 641, 601, 570 cm⁻¹;

1H NMR (400 MHz, CDCl₃): δ 7.23-7.14 (3H, m, Ar-H), 5.28 (2H, s, OCH₂OCH₂CH₃), 4.91 (2H, br s, CH₂OH), 3.74 (2H, q, J = 7.1 Hz, OCH₂OCH₂CH₃), 3.28 (1H, s, H-8), 2.48 (1H, br s, OH), 1.22 (3H, t, J = 7.1 Hz, OCH₂OCH₂CH₃)

13C NMR (100 MHz, CDCl₃): δ 155.9 (C₆, C-6), 132.3 (C₆, C-2), 129.1 (CH, C-4), 126.7 (CH, C-3), 120.9 (C₆, C-1), 115.8 (CH, C-5), 93.8 (CH₂, C-10), 81.4 (CH, C-8), 77.5 (C₆, C-7), 64.9 (CH₂, C-11), 59.0 (CH₂, C-9), 15.2 (CH₃);

HRMS: found [M + H]⁺ 207.1017, [C₁₂H₁₄O₃ + H]⁺ requires 207.1016.
**Experimentals**

*tert*-Butyl(2-(ethoxymethoxy)-6-ethynylphenyl)methoxy)dimethylsilane (339)

![Chemical Structure](image)

To a stirred solution of alcohol 333 (1.50 g, 7.30 mmol) in dichloromethane (100 mL) at 0 °C was added DMAP (45.0 mg, 0.36 mmol), imidazole (745 mg, 10.9 mmol) and *tert*-butyldimethylsilyl chloride (1.60 g, 10.9 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. Sat. aq. NH₄Cl (50 mL) was then added and the aqueous layer was separated and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (3 × 80 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the *title compound* (2.30 g, quant) as a colourless oil.

Rf: 0.2 (ethyl acetate/hexanes 1:19)

**IR** ν<sub>max</sub> (neat): 3675, 2952, 2929, 2856, 1757, 1576, 1462, 1390, 1248, 1195, 1149, 1113, 1046, 988, 833, 774, 722, 663, 602, 547 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (500 MHz, CDCl₃): δ 7.20-7.12 (3H, m, Ar-H), 5.25 (2H, s, OCH₂OC₂H₅), 4.90 (2H, s, CH₂OTBS), 3.75 (2H, q, J = 7.2 Hz, OCH₂OC₂H₅), 2.32 (1H, s, H-8), 1.24 (3H, t, J = 7.1 Hz, OCH₂OC₂H₅), 0.91 (9H, s, SiMe₂'Bu), 0.09 (6H, s, SiMe₂'Bu);

**<sup>13</sup>C NMR** (125 MHz, CDCl₃): δ 156.1 (C₉, C-2), 132.0 (C₉, C-6), 128.7 (CH, C-4), 126.5, (CH, C-5), 123.7 (C₉, C-1), 115.9, (CH, C-3), 93.5 (CH₂, OCH₂OC₂H₅), 81.4 (C₉, C-7), 80.5 (CH, C-8), 64.3 (CH₂, OCH₂OC₂H₅), 58.6 (CH₂, CH₂OTBS), 26.0 (3 x CH₃, SiMe₂'Bu), 18.6 (C₉, SiMe₂'Bu) 15.1 (CH₃, OCH₂OC₂H₅);

**HRMS**: found [M + Na]<sup>+</sup> 343.1713, [C<sub>18</sub>H₂₈O₃Si + Na]<sup>+</sup> requires 343.1700.
Experimentals

(R)-1-2-[(tert-butyldimethylsilyl)oxy]methyl]-3-(ethoxymethoxy)phenyl)-4-hydroxypent-1-yn-3-one (340)

To a stirred solution of alkyne 339 (400 mg, 0.98 mmol) in anhydrous THF (15 mL) at -78 °C was added LiHDMS (1.9 mL, 1 M in THF, 1.90 mmol) and stirred for 1 h. A solution of Weinreb amide 264b (385.6 mg, 1.50 mmol) in anhydrous THF (3 mL) was then added dropwise and the reaction mixture was warmed to room temperature and stirred for a further 1 h. Sat. aq. NH₄Cl (10 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with sat. aq. NH₄Cl (3 × 10 mL), brine (3 × 10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (397 mg, 80%) as a colourless oil.

\[ \alpha \]²⁰ +14.2 (c 0.38, CHCH₃)

Rf: 0.20 (ethyl acetate/hexanes 1:19);

IR \( \nu_{\text{max}} \) (neat): 2977, 2955, 2930, 2887, 2857, 2197, 1193, 1005, 925, 902, 832, 813, 794, 775, 725, 630 cm⁻¹;

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.28-7.24 (3H, m, Ar-H), 5.27 (2H, s, OCH₂OCH₂CH₃), 4.90 (2H, d, J = 10.6 Hz, CH₂OTBS), 4.38 (1H, q, J = 6.7 Hz, H-4''), 3.71 (2H, q, J = 7.6 Hz, OCH₂OCH₂CH₃), 1.50 (3H, d, J = 7.0 Hz, H-5''), 1.23 (3H, t, J = 6.8 Hz, OCH₂OCH₂CH₃), 0.94 (9H, s, SiMe₂/But), 0.90 (9H, s, SiMe₂/But), 0.14 (3H, s, SiMe₂/But), 0.11 (9H, s, SiMe₂/But);

\(^1^3\)C NMR (100 MHz, CDCl₃): \( \delta \) 189.7 (C=O), 156.2 (C₆q, C-6), 133.2 (C₆q, C-2), 129.1 (CH, C-4), 127.2 (CH, C-3), 127.2 (C₆q, C-1), 117.7 (CH, C-5), 93.6 (CH₂, OCH₂OCH₂CH₃), 92.6 (C₆q, C-1''), 89.3 (C₆q, C-2''), 75.5 (CH, C-4''), 64.6 (CH₂, OCH₂OCH₂CH₃), 58.5 (CH₂, CH₂OSi), 26.1 (3 x CH₃, SiMe₂/But), 25.9 (3 x CH₃, SiMe₂/But), 20.8 (CH₃, C-15), 18.5 (C₆q, SiMe₂/But), 18.3
(C<sub>q</sub>, SiMe<sub>2</sub>^tBu), 15.2 (CH<sub>3</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), -4.7 (CH<sub>3</sub>, SiMe<sub>2</sub>^tBu), -5.05 (CH<sub>3</sub>, SiMe<sub>2</sub>^tBu), -5.21 (2 x CH<sub>3</sub>, SiMe<sub>2</sub>^tBu);

**HRMS**: found [M + Na]<sup>+</sup> 529.2776, [C<sub>27</sub>H<sub>46</sub>O<sub>5</sub>Si<sub>2</sub> + Na]<sup>+</sup> requires 529.2768.

(R)-1-(2-[[tert-butyldimethylsilyl]oxy]methyl)-3-(ethoxymethoxy)phenyl)-4-hydroxypentan-3-one (341)

To a stirred solution of alkynyl ketone 340 (500 mg, 0.98 mmol) in ethyl acetate (25 mL) was added Pd/C (50.0 mg) and the reaction mixture was placed under an atmosphere of hydrogen for 1 h. The hydrogen source was removed and the reaction mixture was filtered through a pad of Celite® and the filtrate were concentrated in vacuo. Purification by flash chromatography (ethyl acetate hexanes, 1:9) gave the title compound (489 mg, 95%) as a pale yellow oil.

[α]<sup>20</sup> <sub>D</sub> +27.2 (c 1.00, CHCl<sub>3</sub>);

**Rf**: 0.30 (ethyl acetate hexanes 5:95);

**IR** ν<sub>max</sub> (neat): 2951, 2929, 2900, 2855, 1589, 1471, 1462, 1443, 1389, 1370, 1275, 1245, 1174, 1146, 1116, 1102, 1038, 1030, 1003, 941, 916, 900, 831, 812, 775, 742, 702, 681, 665 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.15 (1H, t, J = 7.8 Hz, H-5), 6.98 (1H, d, J = 8.1 Hz, H-6), 6.83 (1H, d, J = 7.8 Hz, H-4), 5.22 (2H, s, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 4.79 (2H, q, J = 10.0 Hz, CH<sub>2</sub>OTBS), 4.15 (1H, q, J = 6.6 Hz, H-4'), 3.72 (2H, q, J = 7.1 Hz, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 3.01-2.82 (4H, m, H-1', H-2'), 1.26-1.21 (6H, m, H-5' and OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 0.88 (18H, s, 2 × SiMe<sub>2</sub>^tBu), 0.08 (6H, s, SiMe<sub>2</sub>^tBu), 0.05 (6H, s, SiMe<sub>2</sub>^tBu);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 213.1 (C=O), 155.8 (C<sub>q</sub>, C-3), 143.0 (C<sub>q</sub>, C-2), 128.8 (CH, C-5), 127.9 (C<sub>q</sub>, C-1), 122.9 (CH, C-6), 112.6 (CH, C-4), 93.7 (CH<sub>2</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 75.1 (CH,
C-4'), 64.4 (CH₂, CH₂OTBS), 56.3 (CH₂OCH₂OCH₂CH₃), 38.8 (CH₂ C-1'), 26.4 (CH₂, C-2'), 26.2 (3 x CH₃, SiMe₂'Bu), 25.9 (3 x CH₃, SiMe₂'Bu), 20.9 (CH₃, C-5'), 18.6 (C₉, SiMe₂'Bu), 18.2 (C₉, SiMe₂'Bu), 15.2 (CH₃, OCH₂OCH₂CH₃), -4.6 (CH₃, SiMe₂'Bu), -4.8 (CH₃, SiMe₂'Bu), -5.1 (2 x CH₃, SiMe₂'Bu);

**HRMS**: found [M + Na]⁺ 533.3097, [C₂₇H₅₀O₅Si₂ + Na]⁺ requires 533.3089.
(R)-1-[(R)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (343a) and (R)-1-[(S)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (343b)

To a stirred solution of saturated ketone 341 (500 mg, 0.98 mmol) in anhydrous methanol (60 mL) was added trimethyl orthoformate (0.1 mL, 1.00 mmol) and 10-camphorsulfonic acid (68.0 mg, 0.30 mmol) and stirred at room temperature for 24 h. A further portion of camphorsulfonic acid (23.0 mg, 0.10 mmol) was added and stirred for further 30 h. Sat. aq. NaHCO$_3$ (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with sat. aq. NaHCO$_3$ (2 × 50 mL), brine (3 × 50 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:4) gave the title compound 343a (85 mg, 30%) as a colourless oil and title compound 343b (100 mg, 35%).

$[\alpha]^{24}_D -51.5$ (c 1.00, CHCl$_3$);

$R_f$: 0.30 (1:3 ethyl acetate\hexanes);

$\text{IR } \nu_{\text{max}}$ (neat): 3459, 2942, 1716, 1588, 1471, 1371, 1245, 1151, 1105, 1058, 1037, 997, 900, 835, 782, 745, 638, 594 cm$^{-1}$;

$^1\text{H NMR}$ (400 MHz, CDCl$_3$): $\delta$ 7.12 (1H, t, $J = 7.7$ Hz, H-7'), 6.97 (1H, d, $J = 8.0$ Hz, H-6'), 6.81 (1H, d, $J = 7.7$ Hz, H-8'), 5.23 (2H, q, $J = 6.9$ Hz, OCH$_2$OCH$_2$CH$_3$), 5.01 (1H, d, $J = 13.3$ Hz, H-1'a'b), 4.72 (1H, d, $J = 13.3$ Hz, H-1'a'b), 3.97 (1H, q, $J = 6.7$ Hz, H-1), 3.75 (2H, q, $J =$
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7.0 Hz, OCH₂OCH₂CH₃, 3.34 (3H, s, OCH₃), 3.32-3.27 (1H, m, H-5′ab), 2.68-2.62 (1H, m, H-5′ab), 2.06 (1H, brs, OH), 1.94-1.83 (2H, m, H-4′), 1.25 (3H, t, J = 7.3 Hz, OCH₂OCH₂CH₃), 1.12 (3H, d, J = 6.4 Hz, H-2′);

¹³C NMR (100 MHz, CDCl₃): δ 154.8 (C_q, C-9′), 145.2 (C_q, C-1′), 128.7 (CH, C-7′), 128.2 (C_q, C-10′), 122.7 (CH, C-6′), 112.7 (CH, C-8′), 103.4 (C_q, C-3′), 94.0 (CH₂, OCH₂OCH₂CH₃), 69.2 (CH, C-1), 64.6 (CH₂, OCH₂OCH₂CH₃), 55.7 (CH₂, C-1′), 48.3 (CH₃, OCH₃), 29.8 (CH₂, C-4′), 28.5 (CH₂, C-5′), 15.8 (CH, C-2), 15.3 (CH₃, OCH₂OCH₂CH₃);


[α]₂⁴° +49.7 (c 1.00, CHCl₃);

Rf: 0.20 (1:3 ethyl acetate/hexanes);

IR v_max (neat): 3459, 2942, 1716, 1588, 1471, 1371, 1245, 1151, 1105, 1058, 1037, 997, 900, 835, 782, 745, 638, 594 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.12 (1H, t, J = 7.8 Hz, H-7′), 6.98 (1H, d, J = 8.0 Hz, H-6′), 6.82 (1H, d, J = 7.5 Hz, H-8′), 5.23 (2H, s, OCH₂OCH₂CH₃), 5.02 (1H, d, J = 14.0 Hz, H-1′ab), 4.74 (1H, d, J = 14.0 Hz, H-1′ab), 3.87 (3H, q, J = 6.4 Hz, H-1), 3.74 (2H, q, J = 7.0 Hz, OCH₂OCH₂CH₃), 3.23 (1H, t, J = 12.4 Hz, H-5′ab), 2.69-2.63 (1H, ddd J = 15.4, 8.0, 1.4 Hz, H-5′ab), 2.37 (1H, brs, OH), 2.03-1.97 (1H, ddd, J = 14.5, 8.0, 1.6 Hz, H-4′ab), 1.70 (1H, td, J = 12.6, 1.8 Hz, H-4′ab), 1.23 (3H, t, J = 7.2 Hz, OCH₂OCH₂CH₃), 1.17 (3H, d, J = 6.5 Hz, H-2);

¹³C NMR (100 MHz, CDCl₃): δ 154.8 (C_q, C-9′), 144.8 (C_q, C-11′), 128.5 (CH, C-1′), 127.9 (C_q, C-10′), 122.2 (CH, C-6′), 112.7 (CH, C-8′), 102.8 (C_q, C-3′), 93.9 (CH₂, OCH₂OCH₂CH₃), 69.9 (CH, C-1), 64.6 (CH₂, OCH₂OCH₂CH₃), 56.4 (CH₂, C-1′), 49.2 (CH₃, OCH₃), 32.2 (CH₂, C-4′), 28.9 (CH₂, C-5′), 16.5 (CH₃, C-2), 15.3 (CH₃, OCH₂OCH₂CH₃);

(R)-3-[(R)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benoxepin-9-ol (344a) and (S)-3-[(R)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benoxepin-9-ol (344b)

To a stirred solution of saturated ketone 341 (500 mg, 0.98 mmol) in methanol (60 mL) was added trimethyl orthoformate (0.1 mL, 1.0 mmol) and camphorsulfonic acid (68.0 mg, 0.30 mmol) and stirred at room temperature for 24 h. A further portion of camphorsulfonic acid (23.0 mg, 0.10 mmol) was then added and stirred for another 5 h. Sat. aq. NaHCO₃ (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 × 50 mL), brine (3 × 50 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound 344a (79.0 mg, 34%) as a colourless foam and title compound 344b (82 mg, 35%) as colourless foam.

[\alpha]_D^{24} -44.80 (c 1.00, CHCl₃);

Rr: 0.2 (1:1 ethyl acetate/hexanes);

IR ν_max (neat): 3513, 3430, 3381, 3222, 2942, 1609, 1466, 1364, 1329, 1277, 1255, 1182, 1161, 1135, 1071, 1035, 1002, 970, 935, 902, 846, 830, 784, 745, 725, 679;

¹H NMR (500 MHz, CDCl₃): δ 7.01 (1H, t, J = 7.6 Hz, H-7), 6.75 (1H, d, J = 7.7 Hz, H-6), 6.60 (1H, d, J = 7.7 Hz, H-8), 4.92 (1H, d, J = 13.8 Hz, H-1ab), 4.88 (1H, brs, OH), 4.76 (1H, d, J = 13.9 Hz, H-1ab), 3.99 (1H, q, J = 6.5 Hz, H-1'), 3.43 (3H, s, OCH₃), 3.30 (1H, td, J = 14.5, 2.0 Hz, H-5ab), 2.64 (1H, ddd, J = 15.1, 8.0, 2.4 Hz, H-5ab), 2.16 (1H, brs, OH), 1.96-1.84 (2H, m, H-4), 1.13 (3H, d, J = 6.7 Hz, H-2');
**Experimentals**

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.8 (C\(_q\), C-9), 145.8 (C\(_q\), C-11), 128.7 (CH, C-7), 125.6 (C\(_q\), C-10), 121.5 (CH, C-6), 113.7 (CH, C-8), 103.4 (C\(_q\), C-3), 69.3 (CH, C-1'), 55.5 (CH\(_2\), C-1), 48.3 (CH\(_3\), OCH\(_3\)), 29.8 (CH\(_2\), C-4), 28.4 (CH\(_2\), C-5), 15.8 (CH\(_3\), C-2');

**HRMS:** found [M + Na]\(^+\) 261.1098, \([\text{C}_{13}\text{H}_{18}\text{O}_4 + \text{Na}]^+\) requires 261.1097.

\([\alpha]_D^{24}\) +46.07 (c 0.382, CHCl\(_3\));

**Rf:** 0.15 (1:1 ethyl acetate\(\)/hexanes);

**IR** \(\nu_{\text{max}}\) (neat): 3513, 3430, 3381, 3222, 2942, 1609, 1466, 1364, 1329, 1277, 1255, 1182, 1161, 1135, 1071, 1035, 1002, 970, 935, 902, 846, 830, 784, 745, 725, 679 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.03 (1H, t, \(J = 8.0\) Hz, H-7), 6.73 (1H, d, \(J = 7.2\) Hz, H-6), 6.60 (1H, d, \(J = 8.0\) Hz, H-8), 4.99 (1H, d, \(J = 13.9\) Hz, H-1\(\alpha\)), 4.91 (1H, brs, OH), 4.76 (1H, d, \(J = 13.9\) Hz, H-1\(\beta\)), 3.89 (1H, q, \(J = 6.5\) Hz, H-1'), 3.45 (3H, s, OCH\(_3\)), 3.25 (1H, \(t, J = 13.4\) Hz, H-5\(\alpha\)), 2.64 (1H, ddd, \(J = 15.1, 8.0, 2.4\) Hz, H-5\(\beta\)), 2.42 (1H, brs, OH), 2.03 (1H, dd, \(J = 13.1, 8.0\) Hz, H-4\(\alpha\)), 1.69 (1H, t, \(J = 13.5\) Hz, H-4\(\beta\)), 1.18 (3H, d, \(J = 6.5\) Hz, H-2');

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 152.9 (C\(_q\), C-9), 145.4 (C\(_q\), C-11), 128.5 (CH, C-7), 125.4 (C\(_q\), C-10), 121.4 (CH, C-6), 113.6 (CH, C-8), 102.7 (C\(_q\), C-3), 70.0 (CH, C-1'), 56.2 (CH\(_2\), C-1), 49.2 (CH\(_3\), OCH\(_3\)), 32.3 (CH\(_2\), C-4), 28.8 (CH\(_2\), C-5), 16.5 (CH\(_3\), C-2');

**HRMS:** found [M + Na]\(^+\) 261.1098, \([\text{C}_{13}\text{H}_{18}\text{O}_4 + \text{Na}]^+\) requires 261.1097.
1-[9-(ethoxymethoxy)-3-methoxy-1,3-dihydro-2-benoxepin-3-yl]ethan-1-one (335)

![Chemical structure](image)

To a stirred solution of alcohol 343 (120 mg, 0.40 mmol) in anhydrous acetonitrile (6 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (487 mg, 1.60 mmol) and the mixture was heated at 100 °C for 1 h. The reaction mixture was cooled to room temperature and then quenched with sat. aq. NaHCO₃ (5 mL) and dichloromethane (5 mL) was then added and stirred for 20 min. The aqueous phase was separated and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ until aqueous phase was colourless, brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate\hexanes, 1:9) gave the title compound (60.0 mg, 50%) as a peachy oil.

Rᵣ: 0.25 (1:9 ethyl acetate\hexanes);

IR νₘₐₓ (neat): 2918, 2850, 1730, 1579, 1464, 1352, 1243, 1155, 1060, 1032, 992, 940, 807 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.26 (1H, d, J = 8.0 Hz, H-7'), 7.16 (1H, d, J = 8.0 Hz, H-6'), 7.03 (1H, d, J = 7.6 Hz, H-8'), 6.76 (1H, d, J = 12.4 Hz, H-4'), 5.80 (1H, d, J = 12.3 Hz, H-5'), 5.31-5.26 (3H, m, H-1'ab and OCH₂OCH₂CH₃), 4.47 (1H, d, J = 13.3 Hz, H-1'ab), 3.77 (2H, q, J = 6.9 Hz, OCH₂OCH₂CH₃), 3.29 (3H, s, OCH₃), 2.03 (3H, s, H-2'), 1.25 (3H, t, J = 6.9 Hz, OCH₂OCH₂CH₃);

¹³C NMR (100 MHz, CDCl₃): δ 205.1 (C₉, C=O), 154.1 (C₉, C-9'), 136.2 (C₉, C-11'), 133.7 (CH, C-5'), 130.0 (CH, C-4' and C₉, C-10'), 128.7 (CH, C-7'), 124.5 (CH, C-6'), 114.5 (CH, C-8'), 105.6 (C₉, C-3'), 94.1 (CH₂, OCH₂OCH₂CH₃), 64.7 (CH₂, C-1'), 57.9 (CH₂, OCH₂OCH₂CH₃), 50.0 (CH₃, OCH₃), 25.9 (CH₃, C-2), 15.3 (CH₃, OCH₂OCH₂CH₃);

1-(9-hydroxy-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl)ethan-1-one (342)

To a stirred solution of alcohol 344 (160 mg, 0.67 mmol) in anhydrous acetonitrile (6 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (305 mg, 1.30 mmol) and the mixture was heated to 57 °C for 4 h. The reaction mixture was cooled to room temperature and then quenched with sat. aq. NaHCO₃ (5 mL) and dichloromethane (5 mL) was added and stirred for 20 min. The aqueous phase was separated and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with sat. aq. NaHCO₃ until aqueous phase was colourless, brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:4) gave the title compound (40 mg, 25%) as a peachy solid.

M.p.: 119.3-125.4 °C;

Rf: 0.20 (1:4 ethyl acetate/hexanes);

IR νₘₐₓ (neat): 3381, 2924, 2854, 1715, 1645, 1455, 1348, 1333, 1299, 1268, 1224, 1204, 1186, 1158, 1087, 1026, 982, 949, 935, 840, 730, 694;

¹H NMR (400 MHz, CDCl₃): δ 7.18 (1H, d, J = 7.6 Hz, H-7'), 6.95 (1H, d, J = 8.0 Hz, H-6'), 6.76 (1H, d, J = 8.0 Hz, H-8'), 6.73 (1H, d, J = 12.4 Hz, H-4'), 5.81 (1H, d, J = 12.3 Hz, H-5'), 5.25 (1H, d, J = 13.4 Hz, H-1'ab), 4.45 (1H, d, J = 13.3 Hz, H-1'ab), 3.30 (3H, s, OCH₃), 2.04 (3H, s, H-2);

¹³C NMR (100 MHz, CDCl₃): δ 205.3 (C=O), 152.3 (C₉, C-9'), 136.5 (C₄, C-11'), 133.8 (CH, C-5'), 129.8 (CH, C-7'), 128.5 (CH, C-4'), 127.4 (C₉, C-10'), 123.6 (CH, C-6'), 115.3 (CH, C-8'), 105.5 (C₉, C-3'), 57.8 (CH₂, C-1'), 50.0 (CH₃, OCH₃), 25.9 (CH₃, C-2);

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\[ (\pm)-1-[9-(\text{ethoxymethoxy})-3\text{-methoxy}-1,3\text{-dihydro}-2\text{-benzoxepin}-3\text{-yl}]\text{ethan}-1\text{-ol} \ (336a) \]
and

\[ (\pm)-1-[9-(\text{ethoxymethoxy})-3\text{-methoxy}-1,3\text{-dihydro}-2\text{-benzoxepin}-3\text{-yl}]\text{ethan}-1\text{-ol} \ (336b) \]

To a stirred solution of ketal 335 (30.0 mg, 0.10 mmol) in methanol (8 mL) at 0 °C was added cerium (III) chloride heptahydrate (49.0 mg, 0.15 mmol) and sodium borohydride (6.00 mg, 0.15 mmol) and stirred at this temperature for 10 min. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (3 \times 10 mL). The combined organic layers were washed with brine (3 \times 10 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification by filtering crude through short plug of silica (ethyl acetate\hexanes, 1:9) afforded the title compound (±)-336a (6.01 mg, 30%) as colourless oil and title compound (±)-336b (12.0 mg, 51%).

**Rr**: 0.30 (1:9 ethyl acetate\hexanes);

\[ \text{IR } \nu_{\text{max}} \text{ (neat)}: 3443, 2977, 2927, 1711, 1579, 1465, 1393, 1363, 1312, 1241, 1150, 1111, 1014, 984, 833, 806, 745, 713 \text{ cm}^{-1}; \]

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 7.26 \ (1\text{H, t, } J = 8.0 \text{ Hz, H-7'}), \ 7.08 \ (1\text{H, d, } J = 8.4 \text{ Hz, H-6'}), \ 7.01 \ (1\text{H, d, } J = 7.7 \text{ Hz, H-8'}), \ 6.77 \ (1\text{H, d, } J = 12.6 \text{ Hz, H-5'}), \ 5.93 \ (1\text{H, d, } J = 12.7 \text{ Hz, H-4'}), \ 5.25 \ (2\text{H, q, } J = 7.7 \text{ Hz, OCH}_2\text{OCH}_2\text{CH}_3), \ 5.23 \ (1\text{H, d, } J = 13.0 \text{ Hz, H-1ab}), \ 5.47 \ (1\text{H, d, } J = 13.1 \text{ Hz, H-1ab}), \ 3.38 \ (3\text{H, s, OCH}_3), \ 1.88 \ (1\text{H, brs, OH}), \ 1.25 \ (3\text{H, t, } J = 6.8 \text{ Hz, H-10}), \ 1.20 \ (3\text{H, d, } J = 6.6 \text{ Hz, H-2}); \]

\[ ^{13}\text{C NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 152.3 \ (C_q, \ C-9'), \ 137.1 \ (C_q, \ C-11'), \ 132.9 \ (\text{CH, C-5'}), \ 130.4 \ (\text{CH, C-4'}), \ 129.0 \ (C_q, \ C-10'), \ 128.7 \ (\text{CH, C-7'}), \ 124.2 \ (\text{CH, C-6'}), \ 114.0 \ (\text{CH, C-8'}), \ 105.3 \ (C_q, \ C-
C-3'), 94.1 (CH₂, OCH₂OCH₂CH₃), 69.7 (CH, C-1), 64.6 (CH₂, OCH₂OCH₂CH₃), 58.0 (CH₂, C-1'), 49.0 (CH₃, OCH₃), 17.0 (CH₃, C-2), 15.3 (CH₃, OCH₂OCH₂CH₃);


Rf: 0.2 (1:9 ethyl acetate/hexanes);

**IR** νₘₐₓ (neat): 3454, 2976, 2925, 1709, 1579, 1393, 1355, 1240, 1149, 1109, 1014, 984, 920, 832, 805, 745, 684 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃); δ 7.21 (1H, t, J = 7.9 Hz, H-7'), 7.08 (1H, d, J = 8.1 Hz, H-6'), 6.97 (1H, d, J = 7.8 Hz, H-8'), 6.71 (1H, d, J = 12.1 Hz, H-5'), 5.96 (1H, d, J = 12.1 Hz, H-4'), 5.25 (2H, q, J = 6.7 Hz, OCH₂OCH₂CH₃), 5.18 (1H, d, J = 13.5 Hz, H-1ab), 5.48 (1H, d, J = 13.5 Hz, H-1ab), 3.92 (1H, q, J = 6.4 Hz, H-1), 3.73 (2H, q, J = 7.18 Hz, OCH₂OCH₂CH₃), 3.40 (3H, s, OCH₃), 1.88 (1H, brs, OH), 1.22 (3H, t, J = 6.8 Hz, OCH₂OCH₂CH₃), 0.98 (3H, d, J = 6.6 Hz, H-2);

**¹³C NMR** (100 MHz, CDCl₃); δ 154.0 (C₉, C-9'), 137.0 (C₉, C-11'), 131.8 (CH, C-5'), 130.5 (CH, C-4'), 128.9 (C₉, C-10'), 128.5 (CH, C-7), 124.0 (CH, C-6'), 114.0 (CH, C-8'), 105.4 (C₉, C-3'), 94.1 (CH₂, OCH₂OCH₂CH₃), 68.4 (CH, C-1), 64.6 (CH₂, OCH₂OCH₂CH₃), 57.8 (CH₂, C-1), 48.3 (CH₃, OCH₃), 16.6 (CH₃, C-2), 15.2 (CH₃, OCH₂OCH₂CH₃);

Bis((Z,R)-4-[(tert-butyldimethylsilyl)oxy]-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(ethoxymethoxy)phenyl)pent-1-en-3-one (334)

To a stirred solution of ketone 340 (200 mg, 0.39 mmol) in hexanes (25 mL) was added quinoline (0.3 mL, 2.30 mmol) and subjected to hydrogenation using a H-cube® flow reactor with the following settings (Lindlar catalyst, 1mL/min, 10 bar, 20 °C). The reaction mixture was concentrated in vacuo and purification by flash chromatography (ethyl acetate/hexanes, 1:19) gave the title compound (159 mg, 80%) as a yellow oil and trace amounts of alkane 341. 

$\alpha_D^{20}$ -14.4 (c 1.00, CHCl₃);

Rr: 0.35 (1:19 ethyl acetate/hexanes);

IR $\nu_{\text{max}}$(neat): 2955, 2929, 2857, 2887, 1698, 1576, 1471, 1390, 1362, 1152, 1114, 1043, 1005, 989, 936, 883, 813, 725, 666 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl₃): δ 7.34 (1H, d, $J = 12.4$ Hz, H-1'), 7.14 (1H, t, $J = 8.5$ Hz, H-5'), 7.08 (1H, d, $J = 8.5$ Hz, H-6), 6.98 (1H, d, $J = 8.5$ Hz, H-4), 6.65 (1H, d, $J = 12.4$ Hz, H-2'), 5.22 (2H, s, OCH₂OCH₂CH₃), 4.74 (2H, s, CH₂OTBS), 4.17 (1H, q, $J = 6.9$ Hz, H-4'), 3.72 (2H, q, $J = 7.0$ Hz, OCH₂OCH₂CH₃), 1.29 (3H, d, $J = 6.9$ Hz, H-5'), 1.22 (3H, t, $J = 7.2$ Hz, OCH₂OCH₂CH₃), 0.91 (18H, d, 2 × SiMe₂'Bu), 0.07 (12H, d, SiMe₂'Bu);

$^{13}$C NMR (100 MHz, CDCl₃): δ 203.0 (C=O), 155.3 (C₉, C-3'), 142.4 (CH, C-1'), 138.0 (C₉, C-1), 128.3 (CH, C-5), 127.5 (C₉, C-2), 124.3 (CH, C-6), 122.7 (CH, C-2'), 114.9 (CH, C-4), 93.8 (CH₂, OCH₂OCH₂CH₃), 75.0 (CH, C-4'), 64.4 (CH₂, OCH₂OCH₂CH₃), 57.2 (CH₂, CH₂OTBS), 26.1 (3 x CH₃, SiMe₂'Bu), 25.9 (3 x CH₃, SiMe₂'Bu), 21.0 (CH₃, C-5'), 18.6 (C₉, SiMe₂'Bu), 18.3 (C₉, SiMe₂'Bu), 15.2 (CH₃, OCH₂OCH₂CH₃), -4.6 (CH₃, SiMe₂'Bu), -4.7 (CH₃, SiMe₂'Bu), -5.2 (2 x CH₃, SiMe₂'Bu);

To a stirred solution of alcohol \((\pm)-336\) (30.0 mg, 0.10 mmol) in dichloromethane (3 mL) at -78 °C and was added trifluoroacetic acid (1 drop) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated \textit{in vacuo}. Purification by flash chromatography (ethyl acetate\hexanes, 2:3) gave the \textit{title compound} \((\pm)-346\text{a}\) (15.0 mg, 60%) as a colourless solid and \textit{title compound} \((\pm)-346\text{b}\) (2.50 mg, 10%) as a colourless solid.

**Rf**: 0.35 (2:3 ethyl acetate\hexanes);

**IR** \(\nu_{\text{max}}\) (neat): 2924, 2854, 2166, 1737, 1670, 1460, 1377, 1259, 1216, 1017, 797, 740 cm\(^{-1}\);

\(^1\text{H NMR}\) (400 MHz, CDCl₃): \(\delta\) 7.22 (2H, \(t, J = 8.0\) Hz, H-7 and H-7'), 7.07 (2H, \(d, J = 8.4\) Hz, H-6 and H-6'), 6.99 (2H, \(d, J = 7.7\) Hz, H-8 and H-8'), 6.70 (2H, \(d, J = 12.7\) Hz, H-5 and H-5'), 5.98 (2H, \(d, J = 12.5\) Hz, H-4 and H-4'), 5.25 (4H, \(q, J = 6.8\) Hz, 2 × OCH₂OCH₂CH₃), 5.17 (2H, \(d, J = 13.7\) Hz, H-1'ab and H-1'ab), 4.62 (2H, \(d, J = 13.7\) Hz, H-1'ab and H-1'ab), 4.14 (2H, \(q, J = 6.5\) Hz, H-2 and H-2'), 3.73 (4H, \(q, J = 7.5\) Hz, 2 × OCH₂OCH₂CH₃), 1.23 (6H, \(t, J = 6.8\) Hz, 2 × OCH₂OCH₂CH₃), 1.06 (6H, \(d, J = 6.4\) Hz, 2 × CHCH₃);
**13C NMR** (100 MHz, CDCl3): δ 154.1 (2 × C<sub>q</sub>, C-9 and C-9'), 136.8 (2 × C<sub>q</sub>, C-11 and C-11'), 131.3 (2 × CH<sub>2</sub>, C-5 and C-5'), 131.1 (2 × CH<sub>2</sub>, C-4 and C-4'), 129.5 (2 × C<sub>q</sub>, C-10 and C-10') 128.2 (2 × CH, C-7 and C-7'), 124.2 (2 × CH, C-6 and C-6'), 113.9 (2 × CH, C-8 and C-8'), 104.1 (2 × C<sub>q</sub>, C-2 and C-2'), 94.1 (2 × CH<sub>2</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 67.0 (2 × CH, C-3 and C-3'), 64.6 (2 × CH<sub>2</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 57.0 (2 × CH<sub>2</sub>, C-1 and C-1'), 16.3 (2 × CH<sub>3</sub>, CH(CH<sub>3</sub>)), 15.2 (2 × CH<sub>3</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>);

**HRMS**: found [M + Na]<sup>+</sup> 547.2299, [C<sub>30</sub>H<sub>36</sub>O<sub>8</sub> + Na]<sup>+</sup> requires 547.2302.

**Rr**: 0.4 (2:3 ethyl acetate\hexanes);

**IR** <sub>ν<sub>max</sub></sub> (neat): 2924, 2854, 2166, 1978, 1737, 1670, 1460, 1377, 1259, 1216, 1017, 797, 740 cm<sup>-1</sup>;

**1H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.24 (2H, t, J = 7.7 Hz, H-7 and H-7'), 7.11 (2H, d, J = 8.2 Hz, H-6 and H-6'), 6.98 (2H, d, J = 7.5 Hz, H-8 and H-8'), 6.65 (2H, d, J = 12.7 Hz, H-5 and H-5'), 5.84 (2H, d, J = 12.5 Hz, H-4 and H-4'), 5.28-5.23 (6H, m, 2 × OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, H-1<sub>ab</sub> and H-1'<sub>ab</sub>), 4.57 (2H, d, J = 13.7 Hz, H-1<sub>ab</sub> and H-1'<sub>ab</sub>), 4.22 (2H, q, J = 6.5 Hz, H-3 and H-3'), 3.77 (4H, m, 2 × OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 1.23 (6H, t, J = 6.8 Hz, 2 × OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 1.04 (6H, d, J = 6.6 Hz, 2 × CHCH<sub>3</sub>);

**13C NMR** (100 MHz, CDCl<sub>3</sub>): δ 154.2 (2 × C<sub>q</sub>, C-9 and C-9'), 136.7 (2 × C<sub>q</sub>, C-11 and C-11'), 132.5 (2 × CH<sub>2</sub>, C-5 and C-5'), 131.8 (2 × CH<sub>2</sub>, C-4 and C-4'), 130.1 (2 × C<sub>q</sub>, C-10 and C-10') 128.2 (2 × CH, C-7 and C-7'), 124.3 (2 × CH, C-6 and C-6'), 114.1 (2 × CH, C-8 and C-8'), 100.0 (2 × C<sub>q</sub>, C-2 and C-2'), 94.2 (2 × CH<sub>2</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 67.2 (2 × CH, C-3 and C-3'), 64.6 (2 × CH<sub>2</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>), 56.8 (2 × CH<sub>2</sub>, C-1 and C-1'), 15.3 (2 × CH<sub>3</sub>, CHCH<sub>3</sub>), 15.0 (2 × CH<sub>3</sub>, OCH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>);

**HRMS**: found [M + Na]<sup>+</sup> 547.2292, [C<sub>30</sub>H<sub>36</sub>O<sub>8</sub> + Na]<sup>+</sup> requires 547.2302.
Method A

To a stirred solution of ketal 342 (20.0 mg, 0.08 mmol) in methanol (5 mL) at 0 °C was added cerium (III) chloride heptahydrate (63.5 mg, 0.17 mmol) and sodium borohydride (7.00 mg, 0.17 mmol) and stirred for 10 min. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), filtered and concentrated in vacuo affording (±)-alcohol 345 which was subjected to dimerisation conditions immediately.

To a stirred solution of crude (±)-alcohol 345 (20.0 mg, 0.08 mmol) in dichloromethane (5 mL) at -78 °C and was added trifluoroacetic acid (1 drop) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate:hexanes, 2:3) gave a mixture of title compound (±)-3 (13.0 mg, 80%) as a colourless solid and along with trace quantities of (±)-2 and (±)-3a.

Method B

To a stirred solution of (S)-(−)-2-methyl-CBS-oxazaborolidine (70 μL, 1.0 M in THF, 0.07 mmol) was added borane N,N-diethylaniline complex (50 μL, 0.25 mmol) in THF (1.5 mL)
and the mixture was stirred for 20 min at -10 °C. A solution of ketal 342 (58.0 mg, 0.25 mmol) in THF (6 mL) was then added drop wise over 30 min. The reaction mixture was stirred for 30 mins at -10 °C then methanol (2 mL) was added and the mixture was concentrated in vacuo. The crude residue was filtered through a pad of silica to afford alcohols (R)-345 which was subjected to dimerisation conditions immediately.

To a stirred solution of (R)-alcohol (R)-345 (55.0 mg) in dichloromethane (5 mL) at -78 °C was added trifluoroacetic acid (25 μL) and the mixture was stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 2:3) gave a mixture of title compounds (30.0 mg, 60% over two steps) as a colourless solid and along with trace quantities of (+)-2 and (+)-3a.

\[ \alpha \] D 27.5 +6.3 (c 0.27, CHCl₃);

Rf: 0.20 (3:10 ethyl acetate/hexanes);

IR ν max (neat): 3361, 2924, 2854, 1738, 1661, 1584, 1466, 1352, 1260, 1081, 1058, 1015, 802, 760, 733, 692;


For chiral HPLC

To a stirred solution of (+)-3 (3.00 mg, 7.00 μmol) in dichloromethane (2 mL) at 0 °C was added DIPEA (0.15 mL, 8.00 μmol) dropwise, followed by chloromethyl ethyl ether (55 μL, 7 μmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (1 mL), washed with brine (3 x 2 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by preparatory TLC (ethyl acetate/hexanes,
2:3) gave the *title compound* (2.30 mg, 40%) as a colourless solid e.e = 97% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (1:10), t₁ (R) = 8.87 min, t₂ (S) = 9.63 min; [α]$_D^{27.5}$ +25.2 (c 0.25, CHCl$_3$). The $^1$HNMR data obtained was in agreement with that described previously (±)-346a.
(-)-Pestalospirane B ((-)-3)

To a stirred solution of (R)-(−)-2-methyl-CBS-oxazaborolidine (70 μL, 1.0 M in THF, 0.07 mmol) was added borane N,N-diethylaniline complex (50 μL, 0.25 mmol) in THF (1.5 mL) and the mixture was stirred for 20 min at -10 °C. A solution of ketal 342 (58.0 mg, 0.25 mmol) in THF (6 mL) was then added drop wise over 30 min. The reaction mixture was stirred for 30 mins at -10 °C then methanol (2 mL) was added and the mixture was concentrated in vacuo. The crude residue was filtered through a pad of silica to afford alcohols (S)-345 which was subjected to dimerisation conditions immediately.

To a stirred solution of (S)-alcohol (S)-345 (55.0 mg) in dichloromethane (5 mL) at -78 °C was added trifluoroacetic acid (25 μL) and stirred at this temperature for 1 h. The reaction was quenched with trimethylamine (0.03 mL) and warmed to room temperature. Water (5 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 2:3) gave a mixture of title compounds (30.0 mg, 60% over two steps) as a colourless solid and along with trace quantities of (−)-2 and (−)-3a.

\[ \alpha \]D²⁷.⁵ -5.7 (c 0.25, CHCl₃);

Rf: 0.20 (3:10 ethyl acetate\hexanes);

For chiral HPLC

To a stirred solution of (-)-3 (3.00 mg, 7.00 μmol) in dichloromethane (2 mL) at 0 °C was added DIPEA (0.15 mL, 8 μmol) dropwise, followed by chloromethyl ethyl ether (55 μL, 7 μmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (1 mL), washed with brine (3 x 2 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by preparatory TLC (ethyl acetate:hexanes, 2:3) gave the title compound (2.30 mg, 40%) as a colourless solid e.e = 98% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (4:40), t₁ (R) = 8.53 min, t₂ (S) = 9.23 min; [α]²⁷.⁵° -24.0 (c 0.25, CHCl₃). The ¹HNMR data obtained was in agreement with that described previously (±)-346a.
### (-)-Pestalospirane B

![Structural Diagram](image)

### Experimental Data

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### (-)-Pestalospirane A

![Structural Diagram]

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3-[(S)-1-Hydroxyethyl]-1,3-dihydro-2-benzoxepin-9-ol (3535)

To a stirred solution of (R)-(−)-2-methyl-CBS-oxazaborolidine (30 µL, 1.0 M in THF, 0.03 mmol) was added borane N,N-diethylaniline complex (50 µL, 0.25 mmol) in THF (1.5 mL) and the mixture was stirred for 20 min at -10 °C. A solution of ketal 342 (58.0 mg, 0.25 mmol) in THF (6 mL) was then added drop wise over 30 min. The reaction mixture was stirred for 7 h at 0 ºC then methanol (2 mL) was added and the mixture was concentrated in vacuo. The crude residue was filtered through a pad of silica to afford title compound (41.0 mg, 80%) as a colourless foam.

Rf: 0.30 (3:10 ethyl acetate\hexanes);

IR ν_{max} (neat): 3361, 2970, 2950, 2853, 1738, 1583, 1463, 1365, 1230, 1217, 1083, 1033, 907, 843, 803, 727 668 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.07 (2H, t, J = 7.4 Hz, H-6 and H-6*), 6.82 (2H, d, J = 7.7 Hz, H-5 and H-5*), 6.65 (2H, dd, J = 7.9, 2.9 Hz, H-7 and H-7*), 6.60 – 6.53 (2H, m, H-4 and H-4*), 5.85 (2H, td, J = 12.8, 2.9 Hz, H-3 and H-3*), 5.24 (2H, t, J = 13.8 Hz, H-1αb and H-1*αb), 4.53-4.45 (3H, m, H-1αb, H-1*αb and H-2), 4.31- 4.29 (1H, m, H-2*), 4.02 – 4.3.97 (1H, m, CHOH), 3.80 (1H, q, J = 7.1 Hz, CHOH *), 1.28 (3H, d, J = 6.6 Hz, CHCH₂3);

¹³C NMR (100 MHz, CDCl₃): δ 152.38 (C₉, C-8), 153.36 (C₉, C-8*), 138.2 (C₉, C-10), 137.9 (C₉, C-10*), 132.1 (CH, C-4), 131.6 (CH, C-4*), 131.4 (CH, C-5), 131.2 (CH, C-5*), 128.42 (CH, C-6), 128.40 (CH, C-6*), 125.92 (C₉, C-9), 125.90 (C₉, C-9*), 123.6 (CH, C-5), 123.5 (CH, C-5*), 114.9 (CH, C-7), 114.8 (CH, C-7*), 86.5 (CH, C-2), 85.4 (CH, C-12*), 70.1 (CH, CHOH), 69.8 (CH, CHOH*), 63.7 (CH₂, C-1), 63.4 (CH₂, C-1*), 19.1 (CH₃, CHCH₃), 18.2 (CH₃, CHCH₃*);

(3R,3'S,5'R,6'S)-9''-(4-bromobenzoyloxy)-3',6'-dimethyl-1H,1''H-dispiro[2-benzoxepine-3,2'-[1,4]dioxane-5',3''-[2]benzoxepine]-9-yl 4-bromobenzoate ((-)\textsuperscript{-}356)

To a stirred solution of (-)-3 (15 mg, 0.04 mmol) in dichloromethane (5 mL) at 0 °C was added DMAP (1 mg, 8 μmmol), triethylamine (22 μL, 0.16 mmol) and p-bromobenzoyl chloride (35 mg, 0.16 mmol) and stirred for 1.5 h. The reaction mixture was then quenched with water (2 mL) and the aqueous layer was separated and extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes, 1:9) gave title compound which was recrystallized from methanol/dichloromethane/hexanes (1:1:1) at -4 °C to give the title compound (24 mg, 80%) as a colourless crystal.

[\textgreek{a}]\textsubscript{D}\textsuperscript{27.5} \textgreek{D} 39.0 (c 0.30, CHCl\textsubscript{3})

M.p: 252-255 °C

R\textsubscript{r}: 0.40 (1:4 ethyl acetate/hexanes);

IR \nu\textsubscript{max} (neat): 2923, 2853, 2157, 2034, 1704, 1416, 1263, 1226, 1071, 1049, 1009, 804, 751 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.09 (4H, d, J = 8.5 Hz, Ar-H), 7.68 (4H, d, J = 8.5 Hz, Ar-H), 7.35 (2H, t, J = 7.7 Hz, H-7 and H-7'), 7.28 (2H, m, H-6 and H-6'), 7.01 (2H, d, J = 7.7 Hz, H-8 and H-8'), 6.76 (2H, d, J = 12.5 Hz, H-5 and H-5'), 6.00 (2H, d, J = 12.5 H-4 and H-4'), 4.67 (2H, s, H-1 and H-1'), 4.06 (2H, q, J = 6.6 Hz, H-3 and H-3'), 1.03 (6H, d, J = 6.8 Hz, CH(CH\textsubscript{3}));

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 164.6 (2 × C\textsubscript{q}, C=O), 147.4 (2 × C\textsubscript{q}, C-9 and C-9'), 137.1 (2 × C\textsubscript{q}, C-11 and C-11'), 132.3 (2 × CH, Ar-C), 131.9 (4 × CH, Ar-C), 131.5 (2 × CH, C-4 and C-4'), 130.7 (2 × CH, C-5 and C-5'), 129.3 (2 × C\textsubscript{q}, Ar-C), 128.8 (2 × CH, C-7), 128.3 (2 × CH,
C-6 and C-6'), 128.1 (2 × C_q, Ar-C), 121.3 (2 × CH, C-8 and C-8'), 104.1 (2 × C_q, C-2 and C-2'), 67.1 (2 × CH, C-3 and C-3'), 57.5 (2 × CH_2, C-1 and C-1'), 16.1 (2 × CH_3, CH(CH_3));

**HRMS:** found [M + Na]^+ 795.0210. [C_{38}H_{30}Br_2O_8+ Na]^+ requires 795.0200.
Appendices
5.1 NMR Spectra of Novel Compounds

(R)-But-3-yne-1,2-diyl bis(4-methylbenzenesulfonate) (177)
(R)-5-Ethynyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (188)
1-{2-[(tert-Butyldimethylsilyl)oxy]ethoxy}but-3-yn-2-ol (204)
1-{2-[(tert-Butyldimethylsilyl)oxy]ethoxy}but-3-yn-2-yl 4-methylbenzene-1-sulfonate (200)
2-\((2\text{-}[4\text{-methylbenzenesulfonyl}oxy]but-3\text{-yn-1-yl}oxy)\)ethan-1-ol (205)
1-(2-hydroxyethoxy)but-3-yn-2-ol (206)
1-[(Ethoxymethoxy)methyl]-2-iodobenzene (210)
1-{[\textit{tert}-Butyldimethylsilyl]oxy}ethoxy\}-4-{\textit{tert}-[\textit{ethoxymethoxy}]methyl}phenyl]but-3-yn-2-ol (213)
1-\{(tert-Butyldimethylsilyl)oxy\}ethoxy\}-4-\{(ethoxymethoxy)methyl\}phenyl\]but-3-yn-2-yl 4-methylbenzene-1-sulfonate (209)
2-(2-[(Ethoxymethoxy)methyl]phenyl)ethynyl)-1,4-dioxane (214)
2-(2-[((Ethoxymethoxy)methyl]phenyl)ethyl)-1,4-dioxane (228)
(2-(2-(1,4-dioxan-2-yl)ethyl)phenyl)methanol
4,5-Dihydro-1H-spiro[2-benzoxepine-3,2'-[1,4]dioxane] (227)
2-(2-(1,4-dioxan-2-yl)ethyl)benzaldehyde (229)
(Z)-(2-(2-(1,4-dioxan-2-yl)vinyl)phenyl)methanol (208)
1H-spiro[2-benzoxepine-3,2'-[1,4]dioxane] (207)
Appendices

(2-((Trimethylsilyl)ethynyl)phenyl)methanol (260)
(S)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[(tert-butyldiphenylsilyl)oxy]methyl)phenyl)pent-1-yn-3-one (265)
(S)-5-(2-[(tert-Butyldiphenylsilyl)oxy]methyl)phenyl)-3,3-dimethoxypent-4-yn-2-ol (266)
Appendices

(S)-1-(2-[[tert-butyldiphenylsilyl]oxy)methyl]phenyl)-4-hydroxypentan-3-one (267)
(S)-5-(2-[(tert-Butyldiphenylsilyl)oxy]methyl)phenyl)-3,3-dimethoxypentan-2-ol (268)
(S)-1-(2-[[tert-Butyldiphenylsilyl]oxy]methyl)phenyl)-4-hydroxypentan-3-one (269)
(S)-1-[(R)-3-Methoxy-1,3,4,5-tetrahydro-2-benzoepin-3-yl]ethan-1-ol (273b)
(S)-1-[(S)-3-Methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (273a)
(3R,3'S,5'R,6'S)-3',6'-dimethyl-4''',5''''-tetrahydro-1H,1''''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3'''-benzo[c]oxepine] (275a)
(3R,3'R,5'S,6'R)-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2''-[1,4]dioxane-5',3''-benzo[c]oxepine] (275b)
(R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2,2-dimethyl-2,4-dihydro-1,3-benzodioxin-5-yl)pent-1-yn-3-one hydrate (290)
$(Z,R)-4-[(\text{tert-butyl} \text{dimethylsilyl})\text{oxy}] - 1-(2,2\text{-dimethyl}-2,4\text{-dihydro-1,3-benzodioxin-5-yl})\text{pent-1-en-3-one (289a)}$ and $(E,R)-4-[(\text{tert-butyl} \text{dimethylsilyl})\text{oxy}] - 1-(2,2\text{-dimethyl}-2,4\text{-dihydro-1,3-benzodioxin-5-yl})\text{pent-1-en-3-one (289b)*}$
(R)-4-((tert-Butyldimethylsilyloxy)-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-5-yl)pentan-3-one (291)
(R)-4-Hydroxy-1-[3-hydroxy-2-(methoxymethyl)phenyl]pentan-3-one (293)
(R)-4-Hydroxy-1-[3-hydroxy-2-(hydroxymethyl)phenyl]pentan-3-one (294)
Methyl 2-ethynyl-6-hydroxybenzoate (300)
Methyl 2-ethynyl-6-[(4-methylbenzenesulfonyl)oxy]benzoate (301)
3-Ethynyl-2-(hydroxymethyl)phenyl 4-methylbenzene-1-sulfonate (302)
2-[[\textit{tert}-Butyldimethylsilyl]oxy]methyl]-3-ethynylphenyl 4-methylbenzene-1-sulfonate (303)
Methyl 2-[(4-methylbenzenesulfonyloxy)-6-(trifluoromethanesulfonyloxy)benzoate (308)
2-(Hydroxymethyl)-3-(trifluoromethanesulfonyloxy)phenyl 4-methylbenzene-1-sulfonate (305)
3-Hydroxy-2-(hydroxymethyl)phenyl 4-methylbenzenesulfonate (358)
2-[[tert-Butyldimethylsilyl]oxy]methyl]-3-(trifluoromethanesulfonyloxy)phenyl 4-methylbenzene-1-sulfonate (309)
2-[(\textit{tert}-Butyldimethylsilyl)oxy]methyl]-3-hydroxyphenyl 4-methylbenzene-1-sulfonate (310)
(R)-4-[(tert-Butyldimethylsilyl)oxy]pent-1-yn-3-one (306)
Methyl 2-ethynyl-6-(propan-2-yloxy)benzoate (315)
[2-ethynyl-6-(propan-2-yloxy)phenyl]methanol (311)
tert-Butyl(2-ethyl-6-(propan-2-yloxy)phenyl)methoxy)dimethylsilane (316)
(4R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[[((tert-butyldimethylsilyl)oxy)methyl]-3-(propan-2-yloxy)phenyl)pent-1-yn-3-one (317)
{(2-(2-Bromoethyl)yl)-6-(propan-2-yl)phenyl)methoxy}(tert-butyl)dimethylsilane (323)
{[2-([Z]-2-Bromoethenyl)-6-(propan-2-yl)phenylmethoxy)(tert-butyl)dimethylsilane (322) and {[2-(2-bromoethyl)-6-(propan-2-yloxy)phenyl]methoxy}(tert-butyl)dimethylsilane (324)*}
(1Z,4R)-4-[(tert-butyldimethylsilyl)oxy]-1-(2-[[tert-butyldimethylsilyl]oxy]methyl)-3-(propan-2-yloxy)phenyl)pent-1-en-3-one (312)
1-[3-Methoxy-9-(propan-2-yloxy)-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-one (326)
(R)-4-[(tert-Butyldimethylsilyl)oxy]-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(propan-2-yloxy)phenyl)pentan-3-one (318)
(1R)-1-[(3R)-3-Methoxy-9-(propan-2-yloxy)-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (328a)
(1R)-1-[(35)-3-Methoxy-9-(propan-2-yloxy)-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (328b)
(3S,3'R,5'S,6'R)-9,9''-diisopropoxy-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-
dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (331a)
(3R,3'R,5'S,6'R)-9,9''-diisopropoxy-3',6'-dimethyl-4,4'',5,5''-tetrahydro-1H,1''H-dispiro[benzo[c]oxepine-3,2'-[1,4]dioxane-5',3''-benzo[c]oxepine] (331b)
(±)-1-[3-Methoxy-9-(propan-2-yloxy)-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-ol (313)
Appendices

Methyl 2-(ethoxymethoxy)-6-ethynylbenzoate (338)
[2-(Ethoxymethoxy)-6-ethynylphenyl] methanol (333)
tert-Butyl([2-(ethoxymethoxy)-6-ethynylphenyl]methoxy)dimethylsilane (339)
(R)-1-(2-[[tert-butyldimethylsilyl]oxy]methyl)-3-(ethoxymethoxy)phenyl)-4-hydroxypent-1-yn-3-one (340)
(R)-1-(2-[(tert-butyldimethylsilyl)oxy]methyl)-3-(ethoxymethoxy)phenyl)-4-hydroxypentan-3-one
(R)-1-[(R)-9-(ethoxymethoxy)-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-3-yl]ethan-1-ol (343a)
(S)-3-[(R)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benoxepin-9-ol (343b)
(R)-3-[(R)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (344a)
(S)-3-[(R)-1-hydroxyethyl]-3-methoxy-1,3,4,5-tetrahydro-2-benzoxepin-9-ol (344b)
Appendices

1-[9-(ethoxymethoxy)-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-one (335)
1-(9-hydroxy-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl)ethan-1-one (342)
Bis((Z,R)-4-[[({tert-butyl(dimethyl)silyl)oxy]-1-(2-[[({tert-butyl(dimethyl)silyl)oxy]methyl]-3-(ethoxymethoxy)phenyl]pent-1-en-3-one) (334)
(±)-1-[9-(ethoxymethoxy)-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-ol (±-336a)
(±)-1-[9-(ethoxymethoxy)-3-methoxy-1,3-dihydro-2-benzoxepin-3-yl]ethan-1-ol (±-336b)
(±)-9,9''-bis(Ethoxymethoxy)-3',6'-dimethyl-1H,1''H-dispiro[2-benzoxepine-3,5'-
(±)-9,9''-bis(Ethoxymethoxy)-3',6'-dimethyl-1'H,1''H-dispiro[2-benzoxepine-3,5'-'[1,4]dioxane-2',3''-[2]benzoxepine] (±-346b)
No NOE correlation
Appendices

(-)-Pestalospirane B ((-)-3)
[(S)-1-Hydroxyethyl]-1,3-dihydro-2-benzoxepin-9-ol (353)
(-)-(3R,3'S,5'R,6'S)-9''-(4-bromobenzoyloxy)-3',6'-dimethyl-1'H,1''H-dispiro[2-
benzoxepine-3,2'-[1,4]dioxane-5',3''-[2]benzoxepine]-9-yl 4-bromobenzoate ((-)\textsuperscript{-356})
5.2 Crystal Structural Data

5.2.1 Crystal Structural Data for bromo-dimer 275b

**General Information**

X-ray crystallographic data were collected from a single crystal sample, which was mounted on a loop fiber. Data were collected using a Bruker AXS Smart diffractometer equipped with a APEX II CCD Detector and a Kappa goniometer. The crystal-to-detector distance was 5.9 cm, and the data collection was carried out in 1024 x 1024 pixel mode. Single crystals were kept at 99 K during data collection. Using WInGX v1.80.03 software the structure was solved with the SHELXS-97 structure solution with Direct Methods and refined with the SHELXL-97 refinement using Least Squares minimization. The SADABS program was used for Absorption Correction.
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5.2.2 Crystal Structural Data for bromo-dimer (-)-356

General Information

Thin needles of compound (-)-356 were passed through Paratone-N oil and were mounted in nylon loops for flash cooling in liquid nitrogen. Crystals were transported frozen to the Australian Synchrotron where data were collected on the MX1 beamline at 100K and at a wavelength of 0.71073 Å using the Blu-Ice software package. Oscillation data were processed using XDS to a theta max value of 27.16°. Unmerged intensity data from XDS were converted to SHEXL hkl format using XDSCONV. The structure was solved using SHELXT and atoms visualised using shelXle. One molecule of compound (-)-356 was located in the structure. Additionally, an extended chain of N-hexane molecules fills a channel in the crystal the N-hexane is modelled as three carbon atoms with crystal symmetry producing the remainder of the molecule. The C-C distance of the N-hexane was restrained to 1.50 Å for stable refinement in SHELXL. Heavy atoms were fully refined by least squares refinement in SHELXL before anisotropic refinement and the subsequent additional of hydrogen atoms in idealised positions.
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References
References


References


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